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EFECTO DE LA DESHIDROEPIANDROSTERONA SOBRE EL METABOLISMO CEREBRAL DE LA DOPAMINA

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PRESENTA

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Efecto de la deshidroepiandrosterona sobre el Metabolismo cerebral de la Dopamina

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El futuro está aquí. Idea original: José Luis Bueno; Fotografía: José Luis Bueno; Edición: Enrique Chávez Esparza.

El Visionario, óleo. Mauricio Soltero.

Niño perdido, óleo sobre tela. Mauricio Soltero.

Pensar que compites contra los demás es un error muy grande, cada quien gana y pierde consigo mismo. De este modo, no importa si eres mejor que unos o que otros, lo que realmente importa es si tú mismo eres mejor que ayer, y si serás mejor mañana.

-Iván Pérez-Neri-

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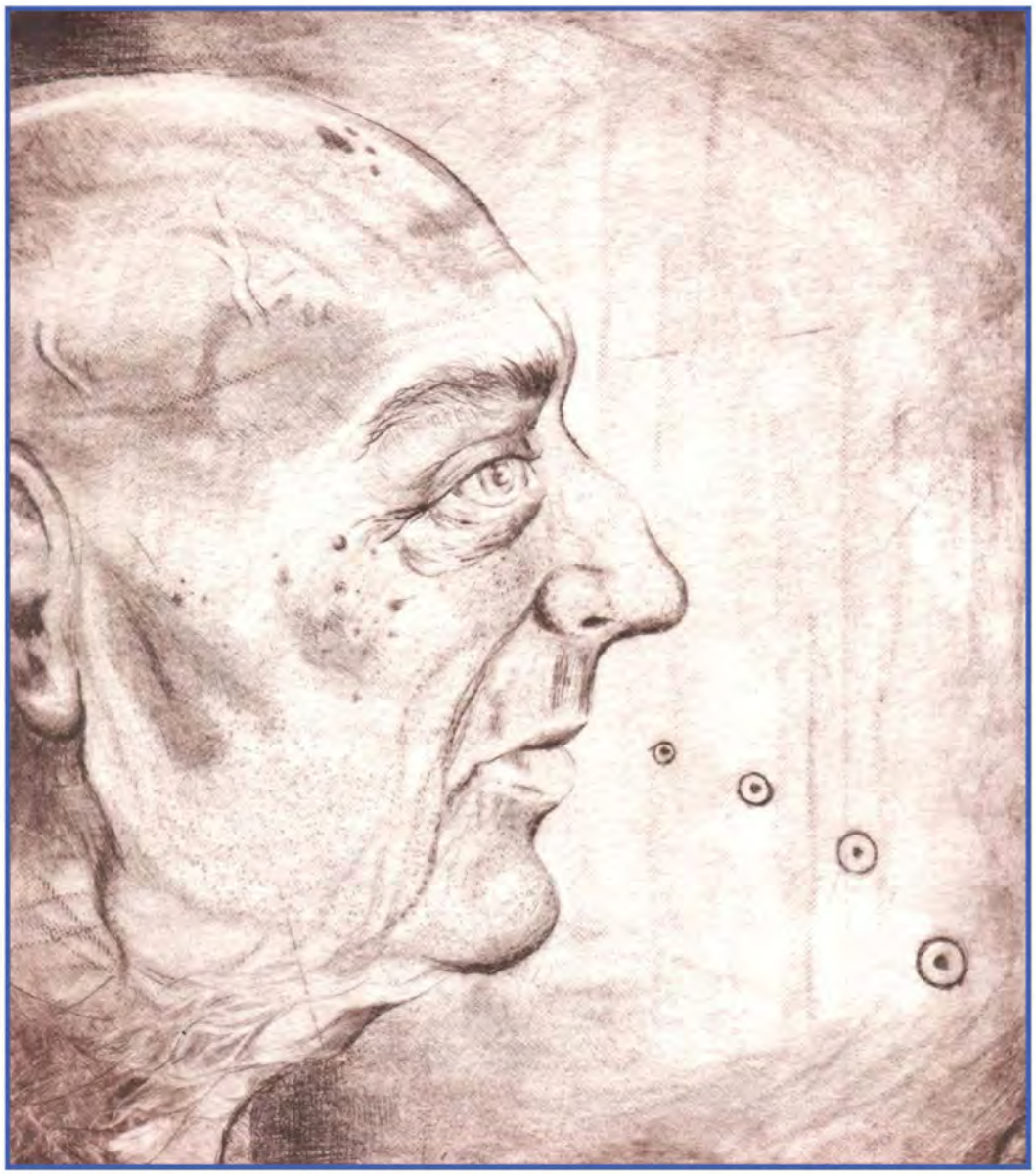

Mi viejo interior, grabado. Mauricio Soltero.

Yo alterado, dibujo y tinta. Mauricio Soltero.

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Abreviaturas

3β-HSD	Deshidrogenasa de 3β-hidroxiesteroides
3-MT	3-Metoxitiramina
5-HIAA	Ácido 5-hidroxi-indolacético
5-HT	Serotonina
7OH-DHEA	7-Hidroxideshidroepiandrosterona
16OH-DHEA	16-Hidroxideshidroepiandrosterona
17β-HSD	Deshidrogenasa de 17β-hidroxiesteroides
17OH-PREG	17-Hidroxipregnenolona
17OH-PROG	17-Hidroxiprogesterona
ACTH	Hormona adrenocorticotrópica
ALDH	Aldehído deshidrogenasa
Amg	Amígdala
COMT	Catecol-*O*-metiltransferasa
Crb	Cerebelo
CS	Cuerpo estriado
Cx	Corteza cerebral
CxF	Corteza frontal
DA	Dopamina
DAT	Transportador de dopamina
DHEA	Deshidroepiandrosterona
DHEAS	Deshidroepiandrosterona sulfato
DOPAC	Ácido dihidroxifenilacético
E1	Estrona
E2	17β-Estradiol
Hic	Hipocampo
HVA	Ácido homovanílico
KO	Knock out
L-DOPA	L-Dihidroxifenilalanina
MAO	Monoamino oxidasa
NA	Noradrenalina
NAc	Núcleo accumbens
NET	Transportador de noradrenalina
NO	Óxido nítrico
OR	P450 oxidorreductasa
PBR	Receptor de benzodiazepinas periférico
PD	Enfermedad de Parkinson
PREG	Pregnenolona
PROG	Progesterona
ROS	Especias reactivas de oxígeno
SN	Substantia nigra
SNC	Sistema nervioso central
StAR	Proteína reguladora aguda de la esteroidogénesis
Test	Testosterona
TH	Tirosina hidroxilasa
VMAT	Transportador vesicular de monoaminas
VTA	Área tegmental ventral

Resumen

La deshidroepiandrosterona (DHEA) es un esteroide que modula a algunos sistemas de neurotransmisión, además de ser neuroprotector y antidepresivo. Tiene efecto sobre la dopamina (DA), involucrada junto con serotonina (5-HT) y noradrenalina (NA), en la enfermedad de Parkinson (PD) y la depresión. Hasta 75% de los pacientes con PD presentan depresión, de modo que estas dos enfermedades pueden presentarse simultáneamente complicando su tratamiento. No se conocen con detalle los cambios que causa la DHEA en el metabolismo de la DA, los cuales pueden reflejar su influencia sobre la neurotransmisión dopaminérgica.

En este estudio, analizamos el efecto de la DHEA sobre el metabolismo de la DA en el cuerpo estriado (CS) y el núcleo accumbens (NAc), en ratas. El recambio del neurotransmisor se redujo en el CS pero no en el NAc, sugiriendo que el esteroide reduce la liberación o la degradación del neurotransmisor. Analizamos la actividad de la principal enzima que cataboliza a la DA, la monoamino oxidasa (MAO). La DHEA redujo la actividad de la MAO en el NAc, pero no en el CS, sugiriendo que el efecto sobre el recambio de DA en el CS no está mediado por la inhibición de la MAO, por lo que podría entonces reflejar una menor liberación de DA. In vitro, el esteroide inhibió a MAO A y B en homogenados del CS y el NAc.

En el caso del NAc, nuestros resultados muestran que la inhibición de MAO no afecta a la DA, por lo que podría involucrar a otros neurotransmisores. Para probar esta hipótesis, se evaluaron los efectos de la DHEA sobre otras monoaminas. El esteroide aumentó el recambio de serotonina en el NAc y el CS, y tendió a aumentar el contenido de noradrenalina en el NAc, pero no en el CS; esto sugiere que el efecto de la DHEA sobre MAO en el NAc, modula al sistema noradrenérgico.

Los resultados sugieren que el esteroide reduce la liberación de DA en el CS, la cuál en exceso es neurotóxica; esto podría reducir el catabolismo del neurotransmisor y la generación de especies reactivas de oxígeno por la MAO. En el NAc, el esteroide podría estimular al sistema noradrenérgico inhibiendo a la MAO A; esto podría estar involucrado en el efecto antidepresivo del esteroide, mientras que la inhibición de MAO B podría también ser parte de su mecanismo neuroprotector. Ninguno de los tratamientos que se utilizan actualmente en la práctica clínica para la PD es al mismo tiempo neuroprotector y antidepresivo. La DHEA podría ser una alternativa terapéutica para reducir la neurodegeneración y la depresión en la PD.

Prólogo

Una imagen da inicio al texto de Iván Pérez Neri, titulado *Efecto de la deshidroepiandrosterona sobre el metabolismo cerebral de la dopamina*: se trata del retrato de un rostro, la imagen de un niño cuya mirada evoca las palabras del pensador mexicano Roger Bartra: "la melancolía se convierte en una red mediadora que comunica entre sí a seres que sufren o intentan comprender la soledad y el aislamiento, la incomprensión y la dislocación, la transición y la separación."[1] Iván Pérez Neri nos muestra, en el óleo sobre tela que ha elegido para dar inicio a esta obra científica, que la vocación de la ciencia biomédica –en este caso, de la biología cerebral y la neuroquímica- no es solamente el desarrollo de estructuras intelectuales interesadas en modelar la naturaleza, sino que consiste también en un trabajo comprometido con el entendimiento y el alivio del sufrimiento humano. El óleo se titula *Niño perdido*, y al igual que la melancolía descrita por Roger Bartra, "se refiere también a las consecuencias trágicas de la soledad, la incomunicación y la angustia, ocasionadas por la siempre renovada diversificación de las experiencias humanas."[1]

Ahora bien, la historia conceptual de la melancolía nos ha mostrado que este concepto, tan antiguo como la medicina occidental, presente desde los trabajos de Hipócrates en su teoría de los humores –un producto del exceso de la bilis negra-, se ha transformado durante los siglos XIX y XX para dar lugar a un nuevo concepto: lo que conocemos hoy en día como "depresión" apareció inicialmente con el término "depresión mental". Hacia 1860 apareció en los diccionarios médicos, con una definición según la cual el término depresión "se aplica al abatimiento anímico de las personas que sufren alguna enfermedad."[2] El historiador Germán Berrios nos informa en su excepcional *Historia de los síntomas de los trastornos mentales* que los médicos del siglo XIX prefirieron la palabra depresión a la de melancolía porque sugería una explicación fisiológica para el problema. Emil Kraepelin, el padre de la taxonomía psiquiátrica contemporánea, legitimó el término melancolía y lo relacionó de forma definitiva con la enfermedad mental designada por él con el nombre "psicosis maniaco-depresiva", y conocida en la actualidad como "trastorno bipolar".

Durante el siglo XX, la psiquiatría (y en particular la psiquiatría de los trastornos afectivos como la depresión y el trastorno bipolar) experimentó una transformación conceptual radical como consecuencia del nacimiento y el desarrollo dinámico de la neurobioquímica y, en general, de la

1. Bartra R. Cultura y melancolía. Las enfermedades del alma en la España del Siglo de Oro. Anagrama, Barcelona, 2001. 2. Berrios G. La historia de los síntomas de los trastornos mentales. Fondo de Cultura Económica. Ciudad de México, 2008.

biomedicina. La circunstancia específica que propició la reescritura de la psiquiatría fue el descubrimiento de psicofármacos con efectos terapéuticos bien demostrados, y con efectos medibles en diversos sistemas de neurotransmisión:

1. El descubrimiento de Crane y Kline de los efectos antidepresivos del agente antituberculoso iproniazida mediante la inhibición de la enzima monoaminooxidasa.
2. El descubrimiento de Roland Kuhn de los efectos antidepresivos del agente G22355, posteriormente nombrado imipramina, mediante efectos en los sistemas aminérgicos del sistema nervioso central. Específicamente, mediante la recaptación de serotonina y norepinefrina, como se demostraría muchos años después.

La investigación neuroquímica del sistema nervioso transformó el rostro de la psiquiatría clínica y sentó las bases para una nueva concepción biológica de los trastornos afectivos; la antigua figura teórica de la melancolía y la bilis negra encontró un nuevo lenguaje y una nueva ecuación. Sin embargo, pronto fue evidente que la heterogeneidad de los estados depresivos requería una teoría más compleja, para su explicación, que el reduccionismo simple según el cual la depresión resultaba de un déficit de norepinefrina o serotonina; la variedad de contextos en que la depresión aparece obliga a la re-evaluación de la hipótesis inicial.

El estudio de la depresión en contextos neurológicos como la enfermedad cerebrovascular y las neoplasias cerebrales facilitó el desarrollo de hipótesis neuroanatómicas relacionadas con el procesamiento emocional. Las investigaciones de Paul Yakovlev, Paul Bucy y Heinrich Klüver pusieron de relieve el papel de la amígdala y el así llamado circuito basolateral de la amígdala; investigaciones ulteriores de Robinson, Strakstein y Alexopoulos mostraron la relevancia de la lateralización hemisférica del procesamiento emocional y de la así llamada "depresión vascular".

Por otra parte, el estudio de la depresión en pacientes con esclerosis múltiple y enfermedades de los ganglios basales mostró la importancia de los circuitos fronto-subcorticales en el desempeño de tareas relacionadas con el procesamiento central y la expresión de las emociones. Es en este contexto donde se inscribe la matriz que da origen al trabajo de Iván Pérez Neri. En efecto, uno de los problemas clínicos fundacionales en el terreno de la neurología se refiere al control neural del movimiento, y en particular, a las enfermedades capaces de alterar este control motor. En 1817, el neurólogo inglés James Parkinson publicó los trabajos más importantes de su carrera: en ellos describió la existencia de "movimientos temblorosos involuntarios con fuerza muscular disminuida, falta de acción en algunas partes, aun cuando se les preste apoyo, con una propensión a inclinar el tronco hacia delante..."[3]. Un fascinante debate se desarrolló en las décadas posteriores –por más de un

3. Parkinson J. An Essay on the Shaking Palsy. Sherwod, Neely and Jonas, Londres, 1817.

siglo y medio. Si bien las descripciones originales de Parkinson no contenían información relacionada con alguna posible alteración de las funciones mentales o del procesamiento emocional, en 1881 Benjamin Ball presentó un ensayo titulado *On the relations between Insanity and Paralysis Agitants*, donde inició un conjunto de comunicaciones clínicas dedicadas a estudiar la relación entre la enfermedad de Parkinson (el epónimo había sido acuñado ya por Charcot en 1862) y las alteraciones mentales. Afirmó la existencia de pacientes con enfermedad de Parkinson y problemas clínicos como alucinaciones, irritabilidad, depresión y deterioro cognoscitivo. A partir de entonces, un conjunto de autores europeos como Parant, Régis, Luys, Rogers y Bechet, confirmaron la observación de Ball. Al inicio de la década siguiente, las numerosas observaciones clínicas de Von Economo sobre la epidemia de influenza en España, y el subsecuente parkinsonismo postencefalítico, aportaron nuevos argumentos para enlazar en una hipótesis neural compleja el control motor, la regulación emocional y aún el desempeño intelectual. El concepto de los circuitos fronto-estriato-tálamo-corticales proporcionó a finales del siglo XX una herramienta teórica capaz de unificar estos conceptos en forma coherente, y los trabajos de Arvid Carlsson, a la cabeza de una corriente internacional de neuropsicofarmacólogos, proporcionaron el lenguaje preciso para modelar los códigos de interacción en los circuitos fronto-subcorticales, mediante el recurso de la dopamina y las estructuras y procesos químicos relacionados. En 1944, Carlsson trabajó en la Universidad de Lund proporcionando atención clínica a un gran conjunto de personas judías que habían escapado de los campos de concentración del ejército Nazi, enfermos de desnutrición y tuberculosis; lo que más impresionó a Carlsson fue el estado mental perturbador de estas personas, caracterizado por suspicacia, desconfianza y angustia;[4] estas experiencias sensibilizaron a Carlsson en el asunto de la experiencia humana bajo condiciones de excepción; años más tarde sus investigaciones neurofarmacológicas darían luz no sólo a la relación entre dopamina y enfermedad de Parkinson (sus trabajos abrieron el campo clínico al uso de levo-dopa, la cual es aún el estándar de atención en esta población neurológica), sino también a la relación entre dopamina y psicosis, al mostrar que los medicamentos antipsicóticos recién descubiertos son capaces de ejercer un efecto antipsicótico (es decir, alucinolítico y antidelirante) mediante el control de la neurotransmisión dopaminérgica. El día de hoy, las teorías más aceptadas acerca de los mecanismos neuroquímicos de las psicosis aún validan la hipótesis de Carlsson, aunque establecen una interesante relación entre la experiencia de los pacientes psicóticos y el efecto de la dopamina sobre los así llamados "circuitos de castigo y recompensa" cerebrales: en forma más específica, los trabajos de Shitij Kapur y colaboradores han mostrado que la disregulación de la dopamina en el estriado dorsal y ventral produce una asignación de relevancia aberrante relacionada con estímulos que

4. Carlsson A. Autobiography. Tomado de la página web: Nobelprize.org. The Official Website of the Nobel Prize. Consultado el 14 de Diciembre del 2013.

habitualmente son irrelevantes en la esfera psicológica.[5] Este mecanismo, que subyace al fenómeno de las alucinaciones y las ideas delirantes en el esquema de Kapur, enlaza la experiencia de la psicosis con el procesamiento emocional, mediante un código de interacción regulado por la dopamina producida en la sustancia nigra y el área tegmental ventral.

Tal es el horizonte histórico, científico y clínico donde aparece la tesis de Iván Pérez Neri. Junto a un equipo de investigadores del Instituto Nacional de Neurología y Neurocirugía de México, donde destaca su tutor, el Doctor Camilo Ríos Castañeda, reconocido líder de la neuroquímica mexicana, así como el Doctor Sergio Montes López, experto en neurofarmacología, Iván Pérez Neri ha construido un ambicioso proyecto de investigación básica que analiza el efecto de un esteroide, la deshidroepiandrosterona, sobre el metabolismo de la dopamina en el cuerpo estriado y el núcleo accumbens en ratas, y sobre la actividad de la monoaminooxidasa. Los resultados obtenidos sugieren que el esteroide reduce la liberación o la degradación del neurotransmisor en el cuerpo estriado, lo cual podría reducir el catabolismo del neurotransmisor y la generación de especies reactivas de oxígeno por la monoaminooxidasa. Esto podría conferir un efecto neuroprotector en pacientes con enfermedad de Parkinson; ahora bien, la hipótesis de Pérez Neri es dual, ya que enfatiza los posibles efectos antidepresivos de la DHEA, mediados por una estimulación del sistema noradrenérgico en el núcleo accumbens y una subsecuente inhibición de la monoaminooxidasa A. Se trata de una hipótesis plausible y que amerita una cadena entusiasta de investigación por venir. Estoy seguro de que en los próximos años veremos la labor científica de Pérez Neri impulsando el diseño y la realización de experimentos de ciencia básica con un robusto valor heurístico, lo cual podría retroalimentar en forma creativa la circulación de conocimientos que subyace a toda innovación clínica.

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Sistema Nacional de Investigadores, Nivel II. CONACyT.

5. Kapur S. Psychosis as a state of aberrant salience: A framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry 2003; 160: 13-23.

I.I. Deshidroepiandrosterona

La deshidroepiandrosterona (DHEA) y su éster sulfato (DHEAS) son los productos de mayor secreción de la corteza de las glándulas adrenales [1-3] y son los esteroides más abundantes en el plasma humano [4,5].

El esteroide fue aislado de la orina por primera vez en 1934, pero hasta 1954 fue obtenido del plasma [2].

Se han atribuido a la DHEA efectos benéficos en la obesidad, el metabolismo de lípidos, la aterosclerosis, la diabetes, la memoria, la osteoporosis y el envejecimiento, entre otros (Fig. 1) [1,2,4,6,7].

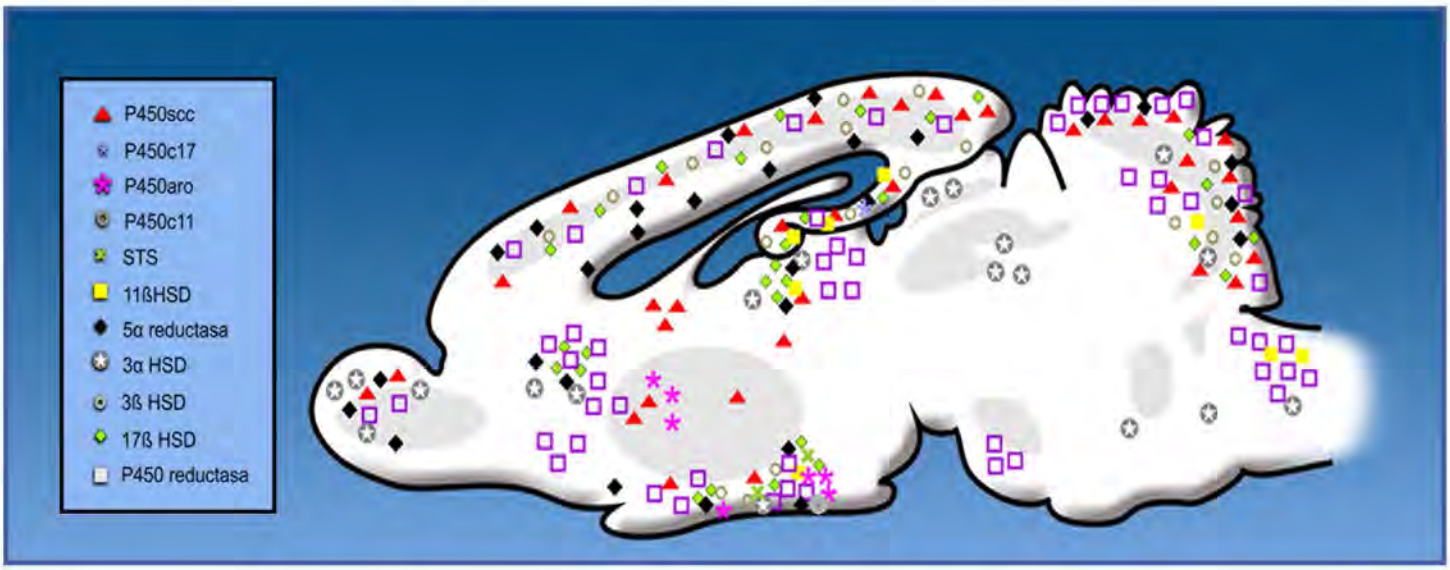
Figura 1. Algunos efectos benéficos reportados para la DHEA. DHEA, deshidroepiandrosterona; DHEA-S, deshidroepiandrosterona sulfato.

Por este motivo, se distribuye sin prescripción médica en los Estados Unidos, donde se considera un complemento alimenticio que se encuentra aprobado por la Food and Drug Administration desde 1994 [2,4].

La DHEA es sintetizada principalmente en la zona *reticularis* de la corteza de las glándulas adrenales, pero se encuentra presente en el cerebro independientemente de su origen periférico [1,8-13], lo que sugiere que el esteroide también se sintetiza dentro del sistema nervioso central (SNC).

Las enzimas que participan en la biosíntesis de la DHEA han sido encontradas a nivel cerebral en alguna etapa del desarrollo, así como en el cerebro adulto de diferentes especies animales (Fig. 2) [1,9,10,13-17]; dichas enzimas se encuentran tanto en los astrocitos [18-20]

Figura 2. Expresión regional de enzimas esteroidogénicas en el cerebro adulto de rata. 3αHSD, deshidrogenasa de 3α-hidroxiesteroides; 3βHSD, deshidrogenasa de 3β-hidroxiesteroides; 11βHSD, deshidrogenasa de 11β-hidroxiesteroides; 17βHSD, deshidrogenasa de 17β-hidroxiesteroides; P450aro, aromatasa; P450c11, 11β-hidroxilasa; P450c17, 17α-hidroxilasa; P450scc, desmolasa; STS, sulfotransferasa de esteroides.



como en las neuronas [13,19-21], aunque su actividad es mayor en los primeros [20].

El contenido cerebral de la DHEA se ha estimado en 0.42 y 0.12 ng/g de tejido en el cerebro anterior y posterior de la rata, respectivamente [8], o hasta 12 ng/g de tejido en el cerebro completo, dependiendo de la técnica de cuantificación utilizada [22].

En el cerebro humano, su contenido, de mayor a menor, se encuentra en: hipotálamo (Hip), cuerpo estriado (CS), corteza frontal (CxF), cerebelo (Crb), hipocampo (Hic) y amígdala (Amg); aproximadamente entre 30 y 100 nmol/kg de tejido en estas regiones (0.10-0.35 pg/g de tejido) [23].

El contenido de la DHEAS es menor al de la DHEA en esas mismas regiones del cerebro humano (aproximadamente 5-50 nmol/kg de tejido) [23].

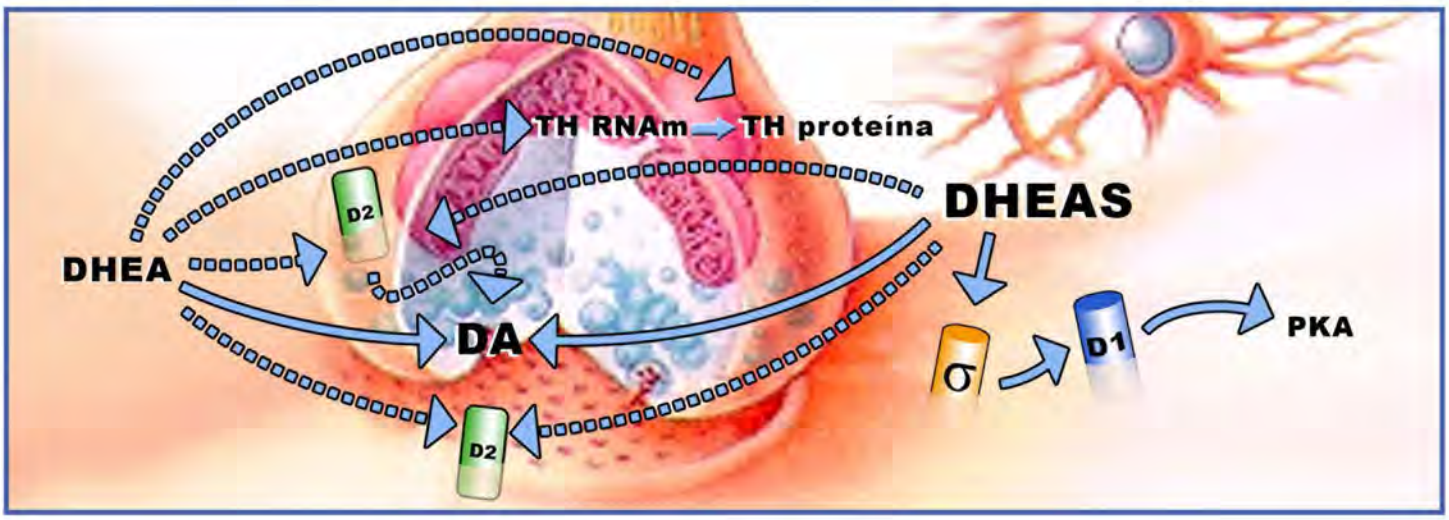
Por esto, puede sugerirse que la DHEA cumple funciones importantes en el SNC; de hecho, se ha reportado que el esteroide y su éster DHEAS modulan la supervivencia y la muerte neuronales [25-29], el desarrollo del SNC [30], la cognición [31-33], la conducta [34-39] y están asociados con varios trastornos psiquiátricos: en ocasiones con su fisiopatología, y en otras, como posible agente terapéutico [40].

La DHEA modula diferentes sistemas de neurotransmisión, lo que podría estar involucrado en sus efectos conductuales [11,24].

Con respecto a los sistemas monoaminérgicos, la DHEA y la DHEAS modulan la liberación [41-43] y el metabolismo de las monoaminas [44-48], así como la activación de receptores dopaminérgicos (Fig. 3) [49-52].

La DHEA podría ejercer sus efectos a través de mecanismos genómicos o no-genómicos, mediados por el esteroide mismo o por alguno de sus metabolitos (Fig. 4).

Figura 3. Efecto de la DHEA y la DHEAS sobre la neurotransmisiòn dopaminèrgica; las flechas continuas y discontinuas representan mecanismos estimuladores e inhibidores, respectivamente. DA, dopamina; D1, receptor D1; D2, receptor D2; DHEA, deshidroepiandrosterona; DHEAS, deshidroepiandrosterona sulfato; PKA, protein cinasa A; σ, receptor σ; TH, tirosina hidroxilasa.



I.I.I. Biosíntesis de la Deshidroepiandrosterona

La DHEA se sintetiza a partir del colesterol (Fig. 4), el cuál es transportado por la proteína reguladora aguda de la esteroidogénesis (StAR) hacia el interior de las mitocondrias, donde es convertido en pregnenolona (PREG) por acción de la desmolasa (P450scc, CYP11A1) (Figs. 4,5) [2,9,13,53,54].

Posteriormente, la PREG es metabolizada en el retículo endoplásmico por la P450c17 para ser convertida en progesterona (*PROG*) o en DHEA (*Fig. 4,5*) [*2,9,13*].

I.I.I.I Proteína Reguladora Aguda de la Esteroidogénesis

La StAR es una proteína de 37 kDa sintetizada *de novo* en respuesta al AMPc producido por activación del receptor para la hormona adrenocorticotrópica (ACTH); esto puede observarse en los astrocitos [18]. Su vida media es de 1-2 min [55].

En la corteza cerebral (Cx), el ácido ascórbico aumenta el contenido, tanto de PREG como de la DHEA, por un mecanismo dependiente de serotonina (5-HT) y AMPc [56] que podría involucrar la activación de la StAR; esta proteína puede unir una sola molécula de colesterol y requiere de un cambio conformacional para liberarla [54].

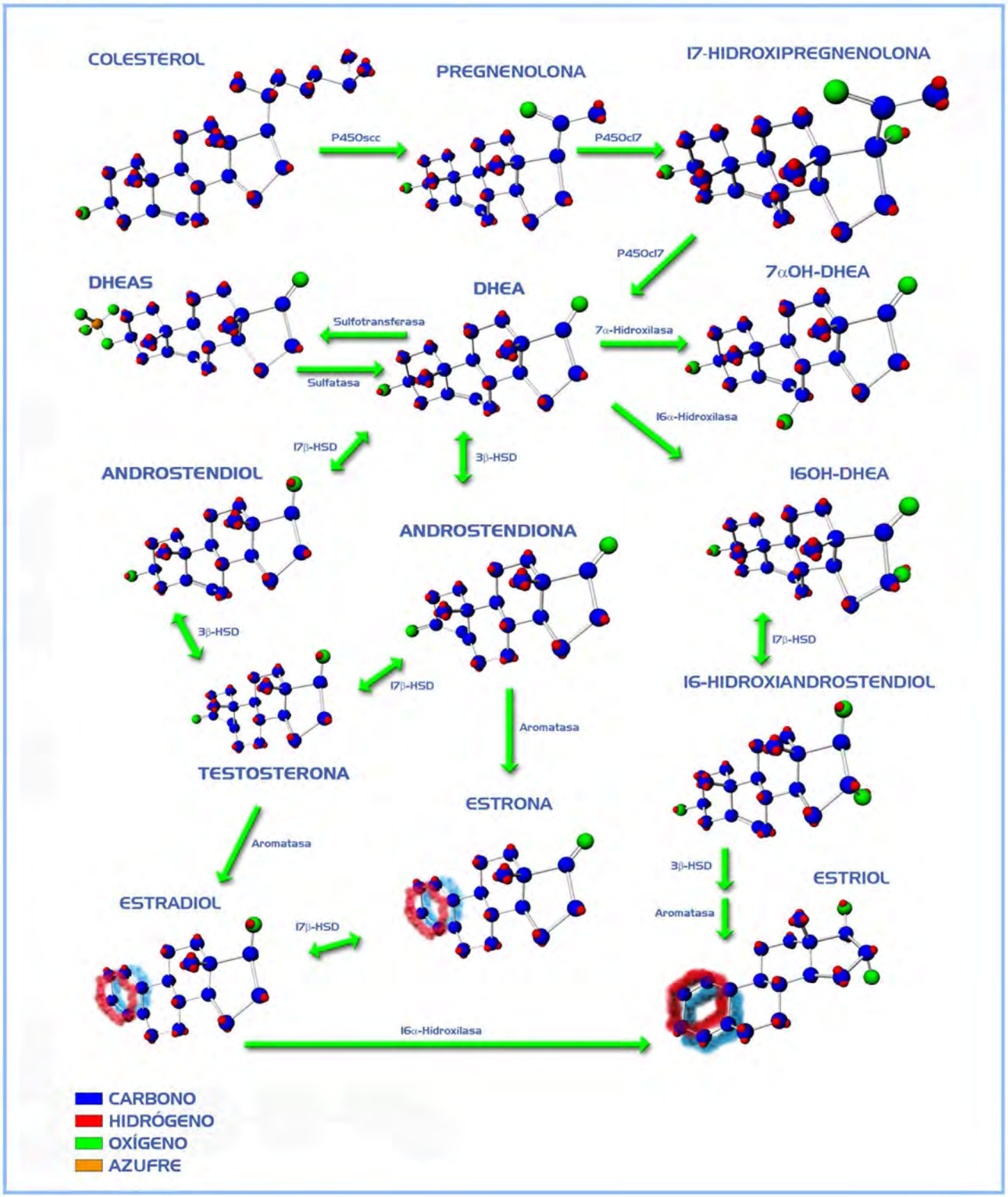
La StAR se expresa en el cerebro, en las neuronas o en la glía de regiones como el puente, el CS, el Crb, el Hic, la Cx, los bulbos olfatorios y el tálamo [9,13,18].

Esta proteína es fosforilada por PKA durante su traducción, para ser convertida en una forma de menor peso molecular (30 kDa) que se localiza en la membrana mitocondrial interna [55].

La StAR participa en el transporte de colesterol de la membrana mitocondrial externa a la interna, regulando así su metabolismo por la desmolasa (Fig. 4).

Esto es de suma importancia, dado que la membrana mitocondrial interna tiene un bajo

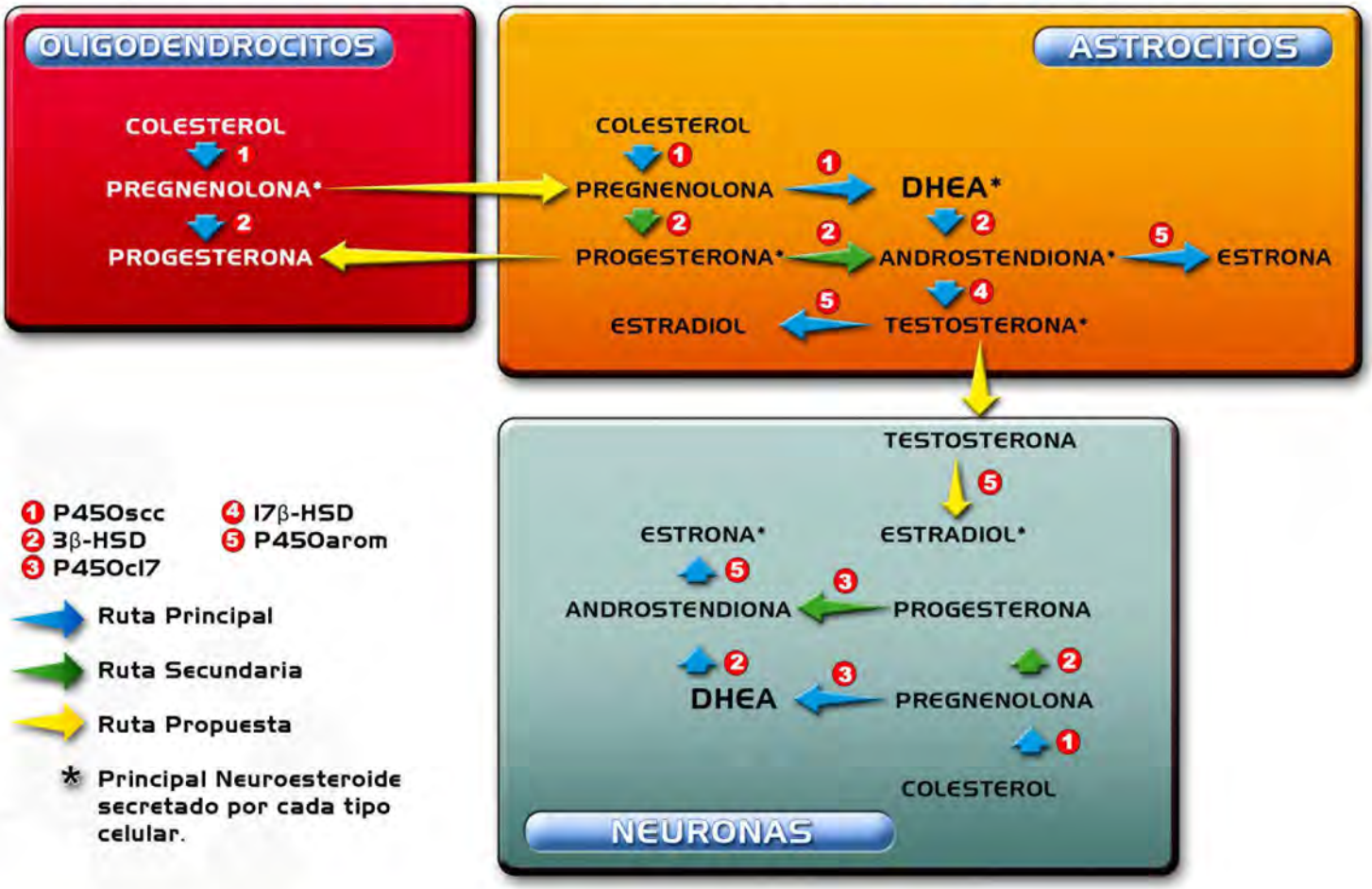
Figura 4. Síntesis y metabolismo de la DHEA. 3β-HSD, deshidrogenasa de 3β-hidroxiesteroides; 7αOH-DHEA, 7α-hidroxideshidroepiandrosterona; 16OH-DHEA, 16-hidroxideshidroepiandrosterona; 17β-HSD, deshidrogenasa de 17β-hidroxiesteroides; DHEA, deshidroepiandrosterona; DHEAS, deshidroepiandrosterona sulfato; P450c17, 17α-hidroxilasa; P450scc, desmolasa.



contenido de colesterol, ya que su presencia a este nivel podría afectar la respiración mitocondrial [55], por lo que la actividad de esta proteína es relevante para el metabolismo energético y el estrés oxidante.

La activación de receptores NMDA favorece la conversión del péptido completo de StAR en su forma activa (30 kDa) y aumenta dos o tres veces el contenido basal de PREG, por un mecanismo dependiente de calcio [9,13]; por lo que la neurotransmisión glutamatérgica podría regular la síntesis de esteroides.

Figura 5. Esteroidogénesis en los tres principales tipos celulares en el sistema nervioso. 3β-HSD, deshidrogenasa de 3β-hidroxiesteroides; 17β-HSD, deshidrogenasa de 17β-hidroxiesteroides; DHEA, deshidroepiandrosterona; P450arom, aromatasa; P450c17, 17α-hidroxilasa; P450scc, desmolasa.



I.1.1.2 Receptor de Benzodiazepinas Periférico

El receptor de benzodiazepinas periférico (PBR) favorece el transporte de colesterol de la membrana mitocondrial externa a la interna; el AMPc aumenta su actividad [57,58].

El PBR se expresa en muchos tejidos, incluyendo al SNC [57,58].

Se localiza en la membrana externa de la mitocondria, aunque algunos estudios han sugerido que también se encuentra en otros organelos e incluso en la membrana plasmática [58].

Las especies reactivas de oxígeno (ROS) causan la oligomerización del PBR en la membrana mitocondrial, aumentando su

actividad [57], lo que podría incrementar la síntesis de esteroides en condiciones de estrés oxidante.

I.I.I.3 Desmolasa

La desmolasa cataliza el paso limitante en la síntesis de esteroides (Fig. 4,5) [5,10,16,54].

Está codificada en el cromosoma 15 [5,10,11,16,54] y su actividad consiste en una serie de tres reacciones a través de las cuáles el colesterol se convierte en PREG y ácido isocapróico (Fig. 4,5): hidroxilación en posición 20α, hidroxilación en el carbono 22 y ruptura del enlace c20c22 [10,11,16,54].

Esto requiere el flujo de electrones a través de adrenodoxina (ferredoxina) y adrenodoxina reductasa (ferredoxina reductasa) [16,54], las cuáles han sido encontradas en la Cx, el Crb y el tallo cerebral de ratas y ratones [17].

A nivel cerebral, la desmolasa puede localizarse tanto en neuronas como en astrocitos y oligodendrocitos (Fig. 5) [19], en regiones como el Crb, el puente, el CS, el Hic, la Amg, el mesencéfalo, la región preóptica del Hip y la corteza piriforme [9,13,15,17,18]; colocaliza con StAR [18].

Su actividad es mayor en oligodendrocitos que en los otros tipos celulares [19].

En el tejido cerebral humano, esta enzima ha sido detectada en las cortezas frontal y temporal, la materia blanca subcortical y el Hic de niños y adultos [5].

I.I.I.4. 17α-Hidroxilasa/17,20-liasa

La 17α-hidroxilasa/17,20-liasa (P450c17) se localiza en los microsomas de las gónadas y las glándulas adrenales.

Es producto de un solo gen codificado en el cromosoma 10 [54], el cuál es activado por PKA e inhibido por PKC.

Se encuentra en astrocitos y neuronas (Fig. 5) [19,20] de diferentes regiones cerebrales, incluyendo el Hic, el Hip, el Crb, la corteza y el tallo cerebrales [13,17,19,20] y algunas neuronas inmunopositivas para tirosina hidroxilasa (TH) [14,16].

La actividad de la P450c17 en cultivos celulares es mayor en los astrocitos que en las neuronas (Fig. 5) [19,20].

Sin embargo, la síntesis de la DHEA es menor en cultivos mixtos de astrocitos y microglía comparada con la que se observa en cultivos astrocíticos puros [20], probablemente porque las citocinas y el óxido nítrico (NO), que pueden ser secretados por la microglía, inhiben la expresión de la enzima.

La P450c17 tiene actividad de 17α-hidroxilasa y 17,20-liasa, ambas reacciones ocurren en un mismo sitio activo y son necesarias para la conversión de PREG en DHEA (Figs. 4,5) [5,10,11,16,54].

La primera reacción resulta en la síntesis de glucocorticoides, mientras que cuando ocurren ambas se favorece la formación de hormonas sexuales, y su ausencia resulta en la síntesis de mineralocorticoides [10,16,54].

Es por esto que la actividad de 17,20-liasa es fundamental para la biosíntesis de la DHEA y las hormonas sexuales (Figs. 4,5).

La P450-oxidorreductasa (OR) aumenta las dos actividades enzimáticas de la P450c17, favoreciendo la síntesis de todos los esteroides.

El citocromo *b5* aumenta la actividad 17,20-liasa [16,54,60-62] sin modificar la de 17α-hidroxilasa, cuando se encuentra en presencia de la OR, probablemente al estabilizar el acoplamiento entre las dos proteínas [16,60], favoreciendo así la síntesis de la DHEA.

Sin embargo, el citocromo *b5* también puede aumentar la actividad de 17α-hidroxilasa en ausencia de OR [61].

La administración de dosis de DHEA mayores a 50 mg/kg aumenta la expresión de la OR [3].

El residuo de ser106 es necesario para las dos actividades enzimáticas de la P450c17 [63].

La fosforilación en serina puede aumentar selectivamente la actividad 17,20-liasa [54,62,64].

P450c17 es fosforilada por un mecanismo dependiente de AMPc [64], probablemente mediado por PKA.

En ausencia del citocromo *b5*, la P450c17 presenta más actividad sobre PROG para la 17α-hidroxilación [61].

Sin embargo, la adición del citocromo *b5* aumenta en más de 100% la actividad de 17α-hidroxilasa sobre PREG y solo aumenta ligeramente la misma actividad sobre PROG [61], lo que sugiere que el citocromo *b5* también modula la selectividad de la enzima por cada sustrato.

La enzima de algunas especies animales utiliza tanto a 17-hidroxipregnenolona (17OH-PREG) como a 17-hidroxi-progesterona (17OH-PROG) como sustrato de la actividad 17,20-liasa.

La enzima en los humanos utiliza principalmente al primero de ellos [54,61], aunque su actividad sobre 17OH-PROG puede aumentar en presencia del citocromo *b5* [61].

La enzima proveniente de otras especies puede tener un comportamiento distinto respecto de la regulación de sus dos actividades enzimáticas [63].

En cualquiera de los casos, P450c17 es inhibida competitivamente por su producto 17OH-PREG [54].

La tasa de actividades 17,20-liasa/ 17α-hidroxilasa aumenta gradualmente a partir de la adrenarquia, a los 8-10 años de edad, alcanza su máximo entre los 20 y 30 años y se reduce en el envejecimiento durante la adrenopausia en los humanos; este fenómeno ocurre también en otros primates.

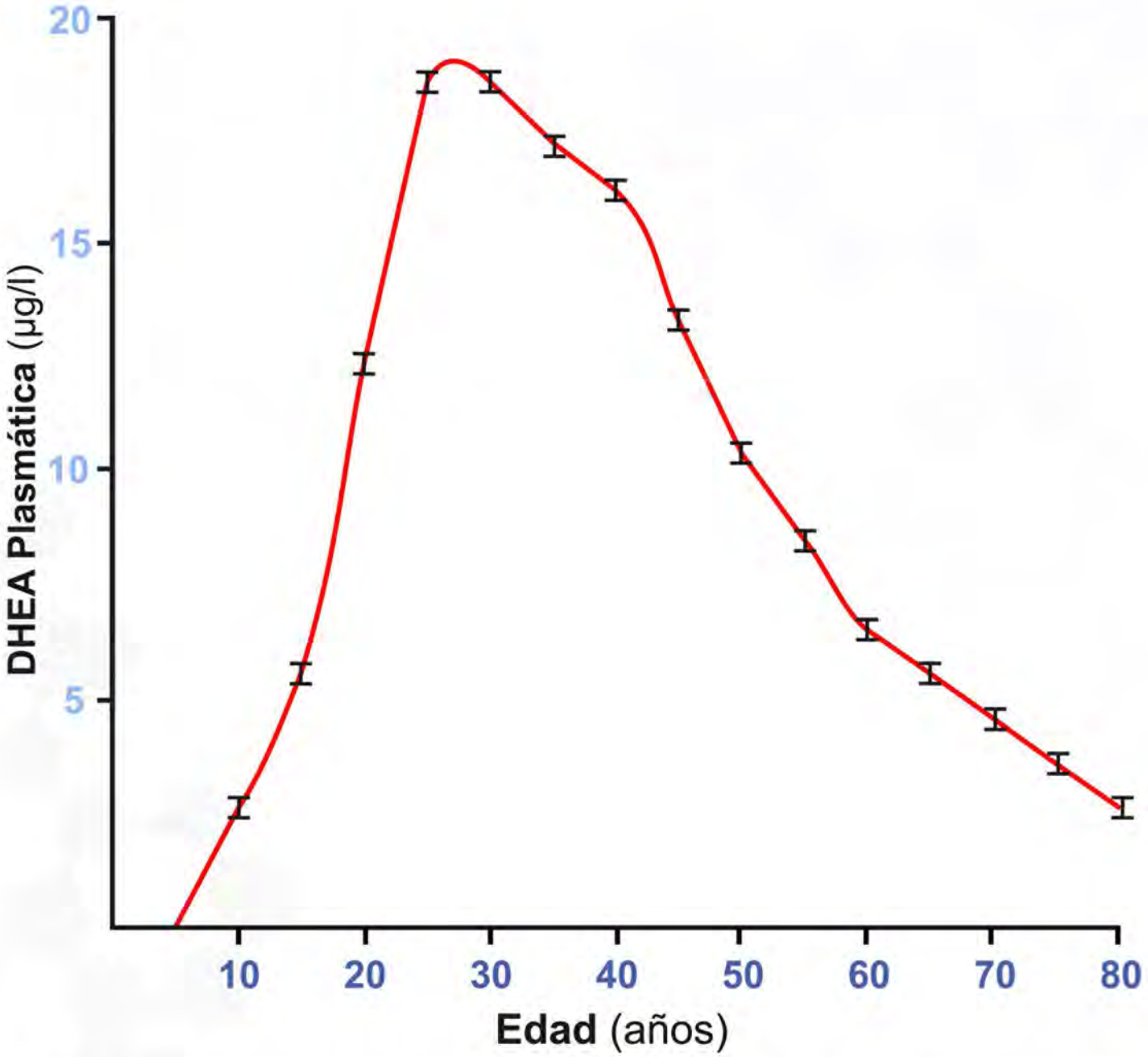
A consecuencia de esto, la concentración plasmática de la DHEA varía a lo largo de la vida de acuerdo con el mismo patrón (Fig. 6) [2-4,6,7,54,62,65,66].

La concentración plasmática de la DHEA puede haberse reducido, hasta en 95% de su valor máximo en la juventud, a los 85-90 años de edad (Fig. 6) [7].

El aumento en la síntesis de la DHEA después de la adrenarquia está asociado con un aumento en la expresión del citocromo *b5* [62] mientras que la disminución de su síntesis en el envejecimiento está asociada con la disminución de la expresión de la OR, en las glándulas adrenales [6].

Una ruta adicional para la síntesis de la DHEA es la actividad de la deshidrogenasa de 17β-hidroxiesteroides (17β-HSD) sobre androstendiol (Figs. 4,5) o la hidrólisis del grupo éster en la DHEAS por la sulfatasa de esteroides (Fig. 4) [16].

Figura 6. Concentración plasmática de la DHEA a lo largo de la vida en los humanos. DHEA, deshidroepiandrosterona.

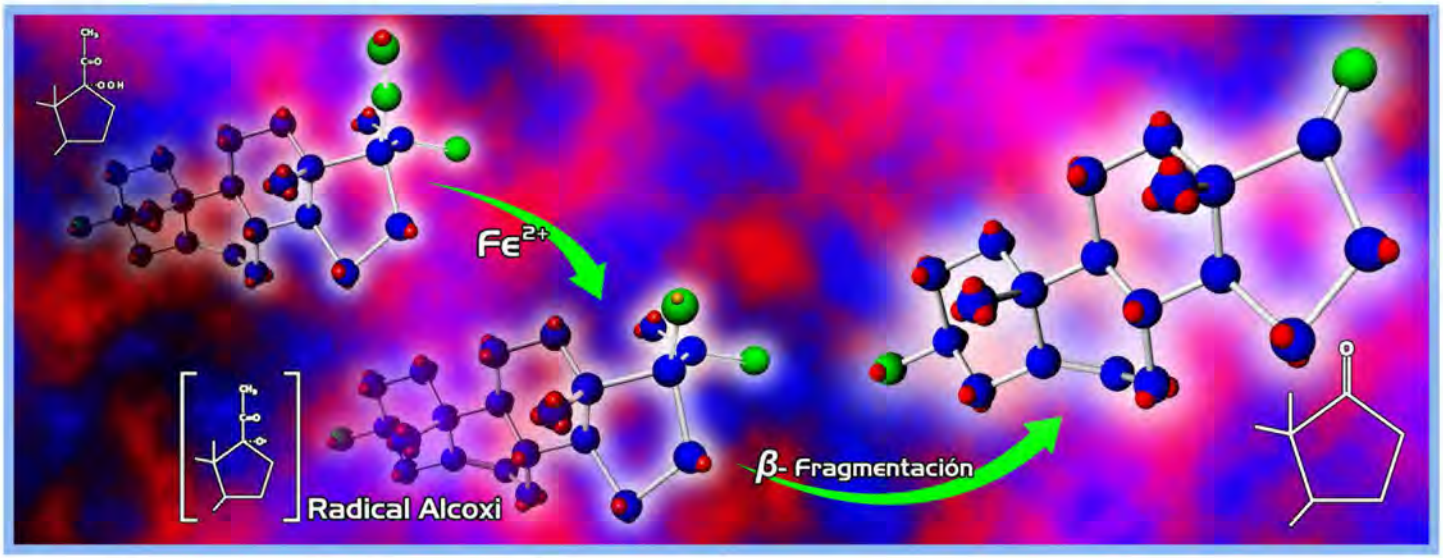


y actividad de la P450c17 en el cerebro adulto no han sido consistentes, algunos estudios han sugerido que la DHEA se sintetiza en el SNC por una ruta alternativa.

La incubación de células de glioma C6 con H_2O_2, $FeSO_4$ o $FeCl_3$ (10 mM) aumenta el contenido de PREG y DHEA (pero no el de PROG) de 2 a 5 veces, por un mecanismo que no depende de desmolasa, de la deshidrogenasa de 3β-hidroxiesteroides (3β-HSD) ni de P450c17, pero que podría involucrar alguna otra proteína (Fig. 7) [67].

Esto sugiere que, más allá de la expresión y actividad de enzimas esteroidogénicas a nivel cerebral, la DHEA podría ser sintetizada en este órgano por un mecanismo no-enzimático.

Figura 7. Propuesta de mecanismo alternativo para la síntesis de DHEA a partir de PREG mediado por Fe^{2+}.



I.I.2. Metabolismo de la Deshidroepiandrosterona

La DHEA puede ser convertida en DHEAS por la sulfotransferasa SULT2A1 (Fig. 4) [13,16], cuya expresión y actividad en las glándulas adrenales es estimulada por AMPc e inhibida por citocinas como los factores de crecimiento transformante β y de necrosis tumoral α [63].

Se ha detectado a esta enzima en el Hic de rata [13].

La DHEAS es convertida en DHEA por acción de la sulfatasa de esteroides (Fig. 4), la cual está codificada en el brazo corto del cromosoma X [68].

La DHEA puede formar androstendiona por actividad de la 3β-HSD, la cuál a su vez, es convertida en testosterona (Test) por actividad de la 17β-HSD, y posteriormente a 17β-estradiol (E2) por actividad de aromatasa (Figs. 4,5) [1,9].

Androstendiona también puede ser convertida en estrona (E1) por acción de aromatasa y posteriormente en E2 por la 17-β-HSD (Fig. 4,5) [9].

La reductasa de 17-cetoesteroides se encuentra en el retículo endoplásmico y convierte de forma reversible a la DHEA en androstendiol (Fig. 4) [16].

Se ha sugerido que, en el cerebro humano, la expresión de esta enzima es glial [69]; ha sido encontrada en cultivos de astrocitos pero no en neuronas ni oligodendrocitos (Fig. 5) [16,19].

En el tejido cerebral humano y el de rata, la enzima ha sido detectada en el Hic, la Cx y la materia blanca subcortical [5,13].

Esta misma enzima también puede convertir androstendiona en Test y E1 en E2 (Fig. 4,5) [7,13,16]; se denomina 17β-HSD cuando cataliza la reacción inversa [16].

Existen 5 isoformas de esta enzima, de las que el tipo I cataliza preferentemente la conversión de E1 en E2 y de DHEA en androstendiol.

El tipo II convierte preferentemente a Test en androstendiona, androstendiol en DHEA y E2 en E1 (Fig. 4,5) [16].

En el tejido cerebral humano, la síntesis de androstendiol a partir de la DHEA es mayor en el Crb y el CS que en la CxF, el Hic o la Amg [70].

La 3β-HSD convierte a la DHEA en androstendiona (Fig. 4,5) [7,13].

Esta enzima cataliza dos reacciones, que son 3β-hidroxilación e isomerización del doble enlace c5c6 a c4c5 [16].

Existen varias isoformas de esta enzima, todas codificadas en el cromosoma 1 [16].

Su expresión y actividad han sido encontradas tanto en las neuronas como en los astrocitos y los oligodendrocitos (Fig. 5) [19] en regiones como la Amg, el Hic y el Crb [13,16].

Su actividad es mayor en los astrocitos que en los otros tipos celulares [19].

La DHEA puede metabolizarse a androstendiona, Test y E2 en el Hic, el Hip y la Cx [9,13,20].

También se ha descrito que la DHEA puede ser metabolizada por la 7α-hidroxilasa en el Hic (Fig. 4) [16].

La 7-hidroxideshidroepiandrosterona (7OH-DHEA) es prácticamente el único metabolito formado a partir de la DHEA en esta región cerebral en el ratón (neonato y adulto) y en cultivos primarios de rata [69,71].

En el tejido cerebral humano obtenido *post mortem*, puede detectarse la formación de 7OH-DHEA y androstendiol a partir de la DHEA, en la CxF (Fig. 4) [70]; la síntesis de 7OH-DHEA es mayor en esta región cerebral que en el Crb, CS, Hic y Amg, y es inhibida por el E2 [70].

De las tres isoformas de la enzima (CYP7A1, CYP7B1 y CYP39A1), CYP7B1 es la que participa en el metabolismo de la DHEA a nivel cerebral [69].

La expresión de esta enzima es principalmente neuronal [69].

En ratas neonatas y adultas, además de 7OH-DHEA, se detectan cantidades apreciables de androstendiol [69].

En biopsias del lóbulo temporal humano, la DHEA se metaboliza a 7OH-DHEA y androstendiol (Fig. 4) [69].

Aún cuando el androstendiol puede ser metabolizado a Test y posteriormente a E2 (Fig. 4), no se detectó la formación de ninguno de estos dos metabolitos en el lóbulo temporal humano [69].

Se ha descrito la formación de 7αOH-DHEA, 7βOH-DHEA y 16α-hidroxi-deshidroepiandrosterona (16OH-DHEA) por microsomas hepáticos mediada por CYP3A4 y CYP3A5 [3,72].

CYP3A7 puede sintetizar 16OH-DHEA y 7βOH-DHEA pero no 7αOH-DHEA, mientras que CYP2D1, CYP2B1 y CYP2C11 sintetizan principalmente 16OH-DHEA; CYP3A23 contribuye a la síntesis de 7αOH-DHEA en las ratas [3,72].

Por su parte, la DHEA aumenta la expresión de CYP3A23 y reduce la de CYP2C11 en hepatocitos de rata [3].

Algunas de las enzimas que metabolizan a la DHEA también son moduladas por mediadores inflamatorios.

La expresión de CYP2B y CYP2C11 se reduce en hepatocitos de rata tratados con lipopolisacárido [3].

Las interleucinas 1 y 6 también reducen la expresión de CYP2C11 [3].

Para ser metabolizada dentro del SNC, la DHEA debe ser sintetizada en dicho sistema o transportada desde el torrente sanguíneo.

Esto último ocurre ya que la DHEA circula en el plasma unida débilmente a albúmina [2], lo que le permite difundir hacia el SNC, a diferencia de los esteroides que circulan unidos fuertemente a globulinas, como la de unión a hormonas sexuales [16].

Ya sea sintetizada en el SNC o transportada desde otros órganos, su contenido cerebral se estima de 4 a 6 veces mayor a su concentración plasmática, aunque su nivel en el líquido cefalorraquídeo representa solo el 5% del que se observa en el plasma [2].

Diferentes estudios muestran que la DHEA puede ser sintetizada y metabolizada por diferentes vías, enzimáticas y no-enzimáticas, dentro del SNC.

Adicionalmente, puede acceder a dicho sistema al cruzar la barrera hemato-encefálica.

Esto le permite modular diferentes mecanismos implicados en la fisiopatología de trastornos psiquiátricos y neurológicos, como es el caso del sistema dopaminérgico.

I.2. Sistema Dopaminérgico

El estudio de la dopamina (DA) en el SNC se remonta a finales de los años 50's, cuando se obtuvieron evidencias que sugerían su papel como neurotransmisor, lo cuál llevo a Arvid Carlsson a obtener, junto con Paul Greengard, el premio Nobel de Medicina en el año 2000 por contribuir, entre otras aportaciones, a establecer que la transmisión sináptica está mediada por compuestos químicos, y no sólamente por impulsos eléctricos [73].

Desde entonces, se han caracterizado con mucho detalle los mecanismos de señalización utilizados por la DA, así como su relación con procesos fisiológicos relacionados con la motivación [74], la atención [75], la memoria [76], el aprendizaje [77], el control del movimiento voluntario [78]; y fisiopatológicos como la esquizofrenia [79,80], la enfermedad de Parkinson (PD) [78], el abuso de sustancias [81] y los trastornos del estado de ánimo [82], entre otros.

La mayor parte de los núcleos dopaminérgicos se encuentran en el tallo cerebral y proyectan axones hacia muchas regiones cerebrales, principalmente entre los núcleos de la base y el sistema límbico: el CS y el núcleo accumbens (NAc) [83].

I.2.1. Síntesis de Dopamina

La TH representa el paso limitante en la síntesis de catecolaminas (Fig. 8) [84].

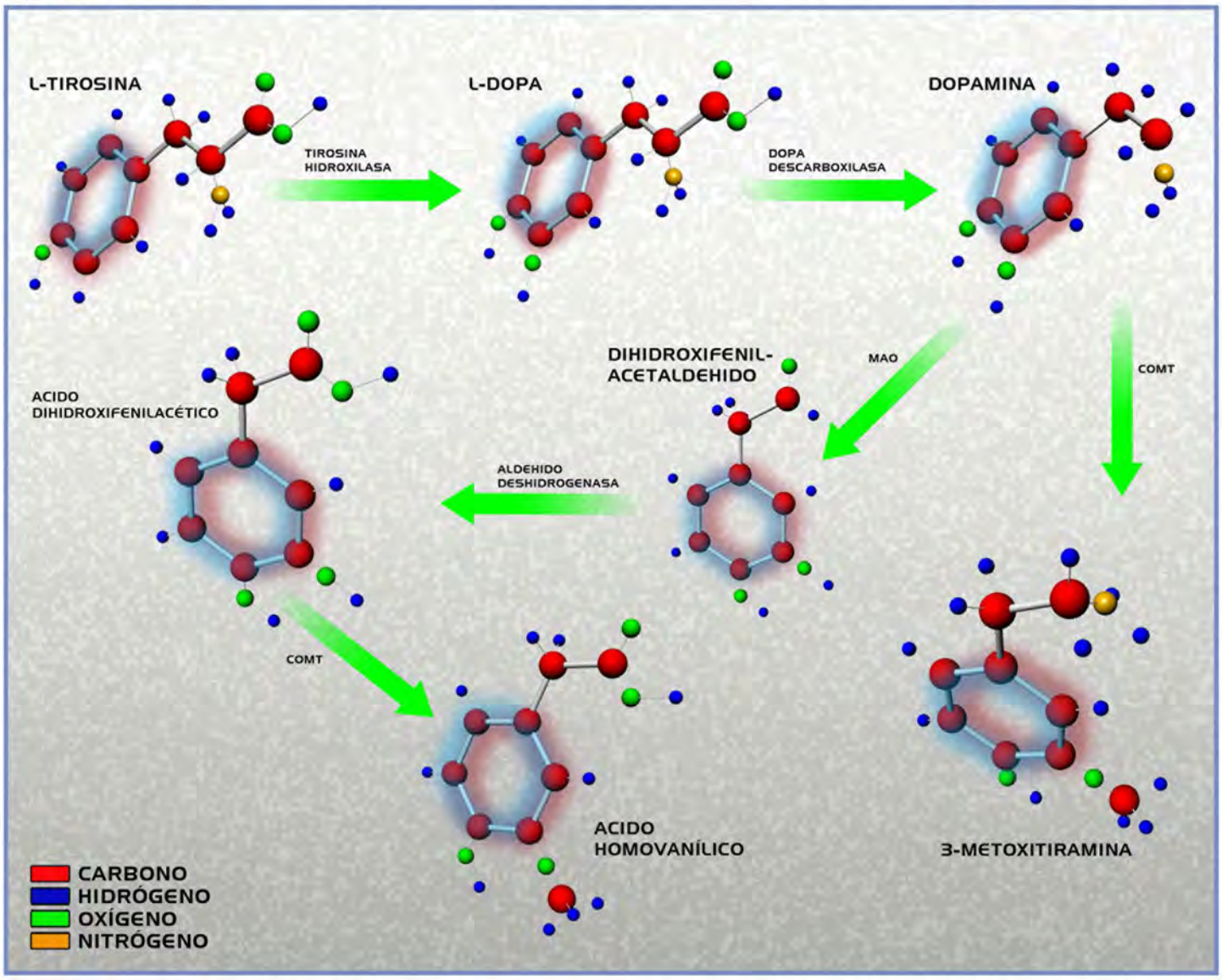
La enzima utiliza O_2 y BH_4 para catalizar la conversión de tirosina en 3,4-dihidroxi-fenilalanina (L-DOPA, Fig. 8), que posteriormente es convertida en DA por acción de la descarboxilasa de aminoácidos aromáticos, también conocida como DOPA descarboxilasa [84].

TH también requiere de Fe^{2+}, el cual se encuentra unido mediante enlaces de coordinación con los residuos de His331 e His336 [84].

El orden de unión de los cofactores y substratos es: BH_4, O_2 y tirosina [84].

El dominio N-terminal de la enzima es regulador, mientras que el dominio C-terminal es catalítico [84].

Figura 8. Metabolismo de la dopamina. COMT, catecol-O-metiltransferasa; L-DOPA, L-dihidroxifenilalanina; MAO, monoamino oxidasa; TH, tirosina hidroxilasa.



El cofactor BH_4 se une al sitio activo de la enzima en su extremo C-terminal.

La actividad de la enzima se encuentra regulada por mecanismos de fosforilación y desfosforilación.

El dominio N-terminal de TH contiene cuatro residuos de serina que pueden ser fosforilados por diferentes cinasas, como PKA, CaM PKII, PKG y PKC, entre otras [84,85].

PKC fosforila el residuo de Ser31, probablemente a través de la activación de la MAPK, aumentando la actividad de la enzima [84].

CaM PKII fosforila a TH en el residuo de Ser19 [84]; por su parte, Ser40 puede ser fosforilada por PKA, PKC y CaM PKII [84,86].

La fosforilación de Ser40 por PKA reduce la K_m de la enzima por BH_4 y aumenta la K_i para las catecolaminas (dado que inhiben a la enzima por ser sus productos finales), aumentando la actividad de la TH [84-86].

Este efecto no ocurre cuando TH es

fosforilada por PKC o CaM PKII, aún cuando ambas pueden fosforilar, entre otros, el mismo residuo de serina que PKA [84,85].

Ser40 es desfosforilada por la fosfatasa de proteínas tipo 2A [84,87].

La activación de TH por CaM PKII requiere de las proteínas 14-3-3, probablemente para estabilizar a la enzima fosforilada y reducir su desfosforilación [84,87].

Las proteínas 14-3-3 se unen a TH cuando se encuentra fosforilada, en Ser19 o también en Ser40, pero no en Ser31 [87].

Aún cuando las proteínas 14-3-3 se unen a TH fosforilada en Ser40, esta unión no modifica la actividad de la enzima [87].

La expresión de TH aumenta por actividad de la proteína de unión al elemento de respuesta al AMPc [84], el cuál puede ser regulado por los receptores para DA.

La forma activa de la proteína es un tetrámero, cada subunidad tiene un peso molecular aparente de 60-61 kDa [84].

El dominio C-terminal media la interacción entre las subunidades de la proteína [84].

Se han descrito en los humanos cuatro variantes de procesamiento alternativo del gen que codifica para TH; todas se han encontrado en el tejido cerebral, pero hTH1 y hTH2 son las más abundantes [84].

Estas variantes difieren en un segmento de 71 aminoácidos en el extremo N-terminal, pero su actividad catalítica es similar [84].

La isoforma hTH1 no se expresa en la médula adrenal de rata, pero sí en la de los humanos y otras especies de mamíferos [88].

La isoforma hTH2 se expresa en la médula adrenal humana y la de los monos Rhesus pero no en la de otras especies animales [88].

Las isoformas hTH3 y hTH4 han sido encontradas solamente en los humanos [88].

Tanto hTH1 como hTH2 tienen una afinidad similar por BH_4 (73-95 µM), pero la de hTH2 por tirosina (K_m=17 µM) es mayor que la de hTH1 (K_m=37 µM) [85].

Todas las catecolaminas inhiben la actividad de TH, posiblemente al competir con la unión de BH_4 o uniéndose al Fe^{3+} en el sitio activo de la enzima [84,89].

DA se une al Fe^{3+} con una K_D de 1 µM [84].

Otros estudios han estimado la constante de inhibición de TH por DA en 30 µM [89].

TH también puede ser inhibida por su propio substrato (tirosina) en concentraciones elevadas (mayores a 60 µM) [85].

La fosforilación de TH reduce la inhibición de la enzima [84,89].

La activación de autorreceptores D2 reduce la fosforilación de TH en Ser40 [90] e inhibe la actividad de la enzima [86,90], la cuál, por otro lado, aumenta tras la inhibición de monoamino oxidasa (MAO) [91].

I.2.2. Catabolismo de la Dopamina

I.2.2.1. Monoamino oxidasa

MAO es una enzima que se encuentra localizada en la membrana mitocondrial externa y que cataliza la desaminación

oxidativa de las monoaminas, dando lugar a la formación de los aldehídos correspondientes, amonio y peróxido de hidrógeno (Fig. 8) [92-97].

El catabolismo de la DA por esta enzima requiere de O_2, por lo que se ve disminuido en condiciones de asfixia [98].

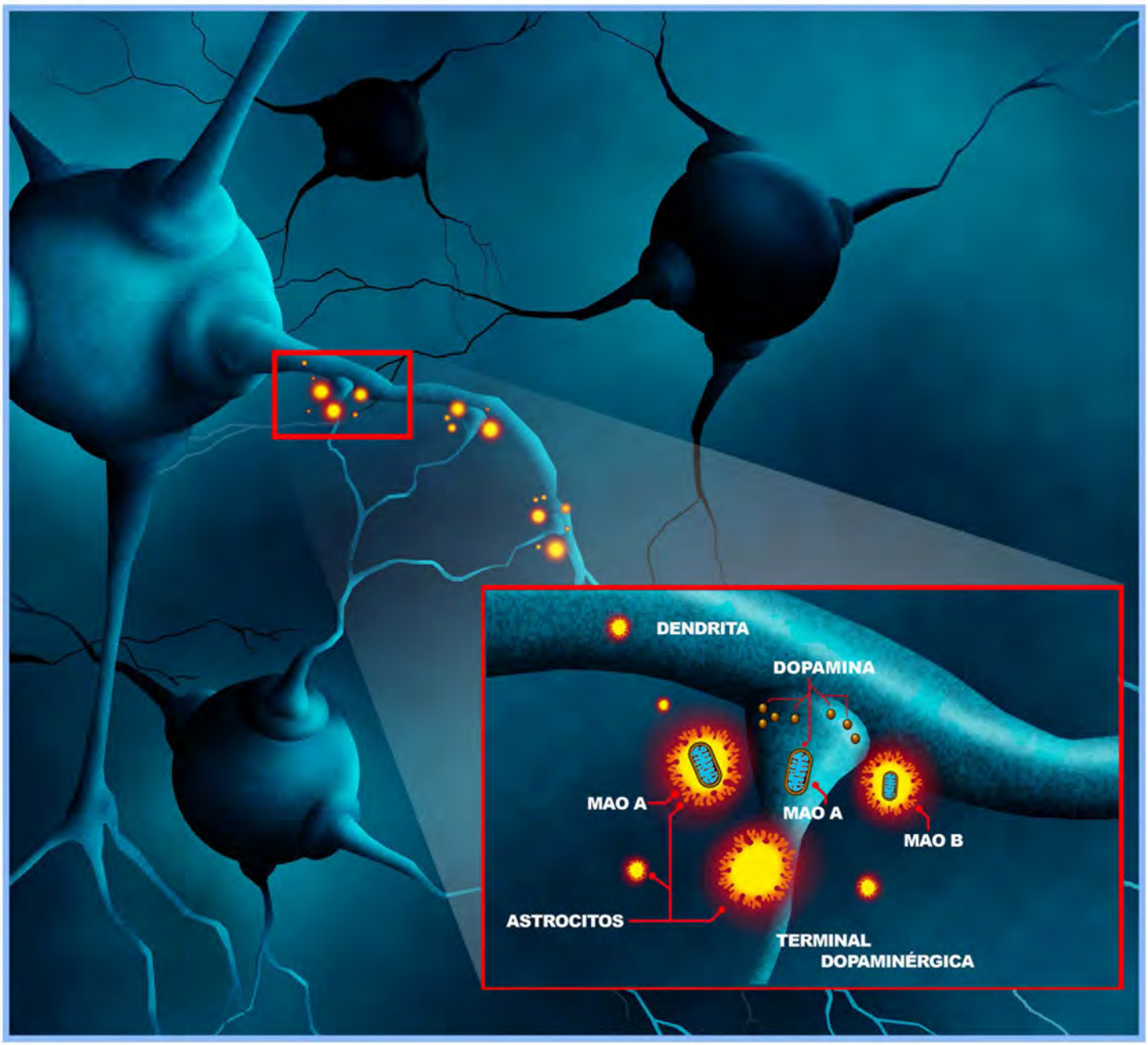
La forma activa de la proteína es un dímero [99].

Su actividad está aumentada en la esclerosis lateral amiotrófica [100].

Existen dos isoformas de MAO (Fig. 9) [92,93,96].

MAO A se encuentra en las neuronas catecolaminérgicas y tiene mayor afinidad por noradrenalina (NA) y 5-HT, mientras que MAO B se encuentra en los astrocitos, las interneuronas y las neuronas serotonérgicas,

Figura 9. Localización de las dos isoformas de MAO en los diferentes tipos celulares del tejido nervioso. MAO, monoamino oxidasa.



pero no en oligodendrocitos (Fig. 9) [101], y tiene mayor afinidad por feniletilamina [92,94-96,101].

La DA tiene una afinidad similar por ambas isoformas de MAO pero, en los roedores, el neurotransmisor es metabolizado por MAO A principalmente, de acuerdo con algunos estudios [92,94-96,102,103].

Los genes que codifican para las dos isoformas de MAO contienen secuencias similares a elementos de respuesta a AMPc [104], por lo que podrían ser regulados por los receptores para DA, los cuales usan dicho mecanismo de señalización.

Los ionóforos de calcio aumentan la actividad de las dos isoformas de MAO [105], lo que sugiere que la actividad neuronal podría aumentar el catabolismo de la DA.

Aún cuando la actividad de MAO puede contribuir al estrés oxidante, ambas isoformas de la enzima son inhibidas por las ROS [106].

MAO B es la principal isoforma que se expresa en el cerebro [93].

Las dos isoformas de MAO son idénticas en aproximadamente el 70% de su secuencia de aminoácidos [92,94,107]; son producto de dos genes distintos localizados en el cromosoma X [92,94,95].

La actividad de MAO B, pero no la de MAO A, aumenta durante el envejecimiento, mientras que la actividad de las dos isoformas aumenta por tratamiento con el glucocorticoide sintético dexametasona [108].

Es por esto que MAO B está asociada con los trastornos que acompañan al envejecimiento, como las enfermedades neurodegenerativas, en especial la PD.

Diferentes estudios han ayudado a mostrar el impacto de la actividad de esta enzima para la conducta y los sistemas de neurotransmisión monoaminérgicos.

Los ratones knock out (KO) para MAO A presentan un aumento en el flujo sanguíneo cerebral [94] y en el contenido de 5-HT y NA en el mismo órgano, además de un ligero aumento en el contenido de DA [92,94,95,109,110]; a nivel conductual, presentan agresividad y un menor tiempo de inmovilidad en nado forzado, lo que sugiere un efecto antidepresivo [92,94,95,110].

Los animales KO para MAO B presentan un aumento en el contenido cerebral de feniletilamina, pero no en el de 5-HT, NA o DA [92,94,95,102,111]; de forma similar a los KOs para MAO A, los de MAO B presentan un menor tiempo de inmovilidad en nado forzado [92,94].

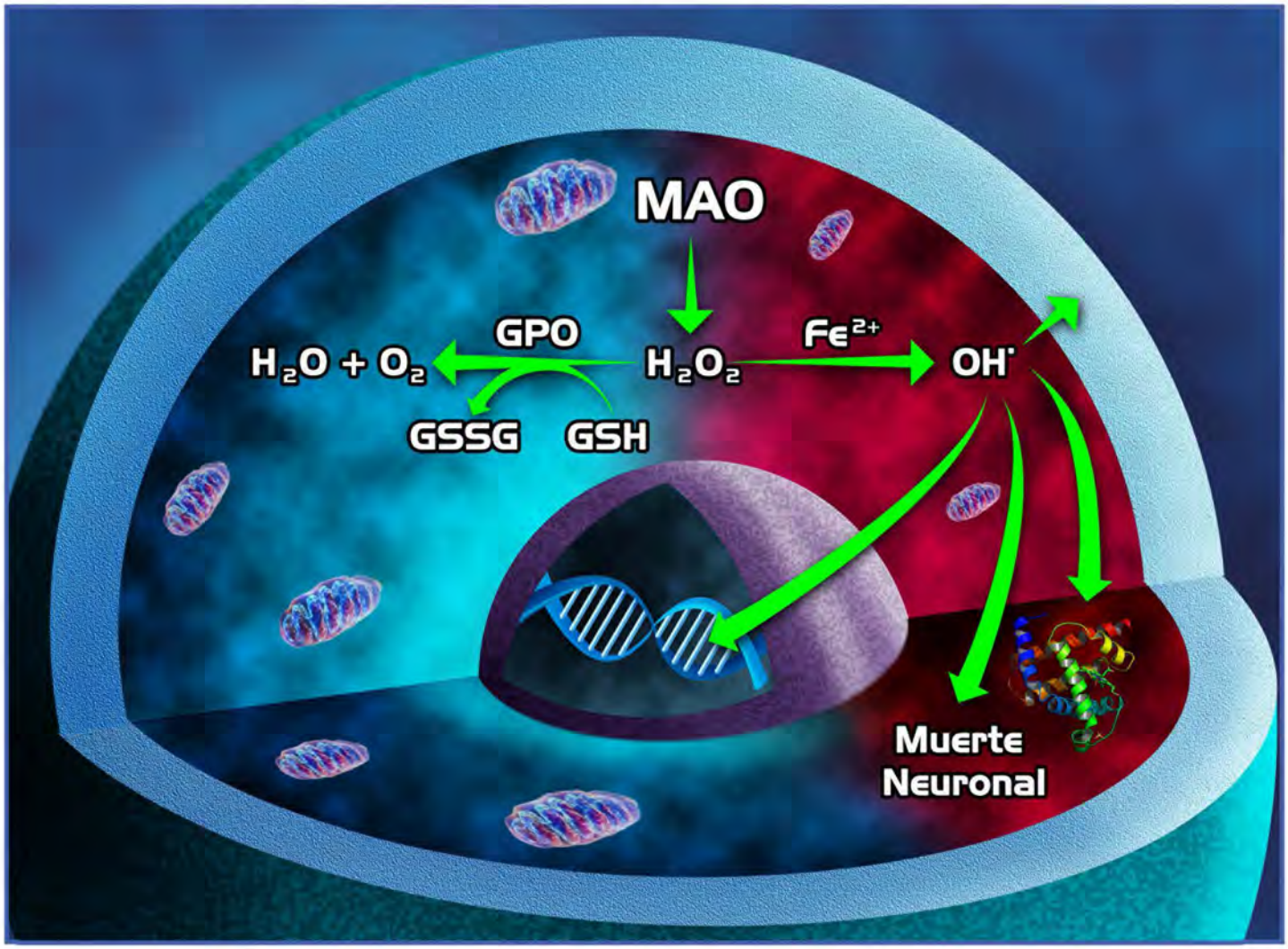
El efecto antidepresivo de la deficiencia en la actividad de ambas isoformas de MAO, sugiere que la enzima modula los sistemas de neurotransmisión involucrados en las regiones cerebrales relacionadas con el estado de ánimo, como es el caso del NAc.

Algunos estudios en ratones, sugieren que la principal isoforma de MAO que se expresa en el NAc es MAO B, y que su expresión es mayor en el NAc que en el CS [112,113], aunque los inhibidores que tienen efecto antidepresivo, son los de MAO A [92,96].

El H_2O_2 producido por la actividad de MAO puede reaccionar con Fe^{2+} formando ROS, las cuales están involucradas en mecanismos de muerte neuronal, particularmente en la PD (Fig. 10) [92-94,96,97,114].

La inhibición de MAO es relevante para la neuroprotección y el estado de ánimo, ya que los inhibidores selectivos de MAO tienen un efecto benéfico en la PD

Figura 10. Participación de MAO en mecanismos de neurodegeneración mediados por la reacción de Fenton. GPO, glutatión peroxidasa; GSH, glutatión reducido; GSSG, glutatión oxidado; MAO, monoamino oxidasa.



[92,93,96,114,115] y en la depresión [92,96,116,117].

Tanto la inhibición de MAO A como la de MAO B tiene un efecto neuroprotector en algunos modelos de daño nigroestriatal [92].

I.2.2.2. Aldehído Deshidrogenasa

La actividad de MAO da lugar a la formación de aldehídos, cuya oxidación por aldehído deshidrogenasa (ALDH) forma ácidos carboxílicos (Fig. 8) [92].

Esta enzima está presente en una gran variedad de tejidos y se localiza en las mitocondrias, los microsomas y el citosol de las células [118].

Aislada del hígado de conejo, tiene un peso molecular estimado de 194 kDa mientras que el de sus subunidades se estima en 48 kDa [119], de donde puede inferirse que la forma activa es un tetrámero.

ALDH contiene Zn^{2+} y, en solución (amortiguador de fosfato de sodio/potasio 100 nM, pH 7.4), fluoresce a 280 nm de excitación y 340 nm de emisión [119].

Los glucocorticoides reducen la expresión de esta enzima, inducida por hidrocarburos

en hepatocitos, a través de un elemento de respuesta a glucocorticoides que está presente en la región 5' del gen de ALDH [120].

En los seres humanos, se han descrito 12 genes que codifican para la enzima; ALDH1 y ALDH2 se expresan en el hígado [118].

Algunos esteroides y compuestos relacionados modifican la actividad de ALDH.

El dietilestilbestrol aumenta tanto la K_m como la V_{max} de la enzima por acetaldehído [119,121]; en cambio, PROG aumenta la K_m y reduce la V_{max} por el mismo sustrato [119]; ambas sustancias compiten entre sí y su efecto es reversible [119].

Algunos estudios muestran que PROG no modifica la actividad de ALDH [122], lo que podría deberse al análisis de diferentes isoformas de la enzima en cada estudio.

ALDH es inhibida por disulfiram [118,121,122] y por hormonas tiroideas [122] pero no por Test, androsterona, DHEA, E2, cortisona ni 11-desoxicortisona [122].

1.2.2.3. Catecol-O-metiltransferasa

Catecol-*O*-metiltransferasa (COMT) cataliza la *O*-metilación de las catecolaminas (Fig. 8), utilizando S-adenosil-L-metionina como co-substrato y Mg^{2+} como cofactor [100].

Además, puede reconocer como substratos a L-DOPA, metabolitos de la melanina y de las catecolaminas, catecolestrógenos y ácido ascórbico [97,100,123].

Los ratones KO para la COMT son viables y muestran solo cambios menores en el contenido cerebral de monoaminas [97,100].

Sin embargo, los machos KO presentan un aumento de 3 veces en el contenido de DA en la CxF, pero no en el CS [97,100,123].

La inhibición de la COMT reduce el contenido cerebral de 3-metoxitiramina (3-MT) y del ácido homovanílico (HVA), pero aumenta el de el ácido dihidroxifenilacético (DOPAC) sin alterar el de DA [100].

De acuerdo con algunos estudios, el efecto de la COMT sobre la neurotransmisión dopaminérgica parece ser más evidente en la CxF que en el CS [123].

El HVA, que se forma por actividad secuencial de MAO y COMT a partir de la DA (Fig. 8), está presente en los animales KO para la COMT, lo que sugiere la existencia de una vía metabólica alternativa para la síntesis del metabolito [97,100].

La 6-nitronorepinefrina, formada por interacción entre el NO y la NA, es un inhibidor endógeno de esta enzima [100]; de forma similar, el Ca^{2+} y la S-adenosilhomocisteína, formada por actividad de la COMT sobre S-adenosilmetionina, inhiben la actividad de la enzima [97].

La COMT se encuentra codificada en un solo gen en el cromosoma 22, que da lugar a una isoforma soluble y a otra que se une a la membrana celular; la segunda de ellas es la que predomina en el tejido cerebral, a diferencia de otros tejidos en los que la forma soluble es la más abundante [97,100,123].

La enzima está presente en diferentes órganos, principalmente en el hígado, el riñón y en el tracto gastrointestinal [97,100].

Las isoformas soluble y de membrana de la COMT tienen un peso molecular estimado de 24 y 29 kDa, respectivamente [100].

La forma membranal se localiza hacia el lado citosólico de la membrana celular [100,123].

Con respecto a las propiedades cinéticas de las dos isoformas de COMT, la forma soluble tiene una K_m más alta para DA y una mayor V_{max} que la forma membranal de la enzima [97,100,123].

Sin embargo, por su abundancia y su mayor afinidad por los substratos, es más probable que la forma membranal sea la principal involucrada en el metabolismo de las catecolaminas en el tejido cerebral [100,123].

Existen en los humanos tres variantes polimórficas de la COMT que producen enzimas de baja, media y alta actividad; su baja actividad se ha asociado con la esquizofrenia, la depresión mayor y la PD [97,100,123].

En el tejido nervioso, la COMT está presente en las membranas postsinápticas, y principalmente, en la glía, pero no en las terminales presinápticas [100,123,124].

Las dos isoformas de la enzima se encuentran tanto en neuronas, como en oligodendrocitos, astrocitos y microglía [97,100,124], pero principalmente en las primeras [123].

Se ha sugerido que la isoforma soluble es de origen glial, mientras que la forma membranal se expresa en las neuronas [123].

En algunos estudios, se ha localizado a la isoforma soluble de la COMT en el citosol y a la isoforma membranal en la cara citosólica del retículo endoplásmico, pero no en la membrana celular [97,100,123].

En el tejido cerebral humano, se ha localizado a la enzima en cada región analizada; éstas incluyen Crb, Amg, tálamo, CS, mesencéfalo, médula espinal y la Cx de los lóbulos frontal, temporal y parietal [123].

Su expresión es mayor en las neuronas dopaminérgicas del área tegmental ventral (VTA, que inervan el NAc) que en las de la *substantia nigra* (SN) *pars compacta* (que inervan el CS) [97].

La PROG aumenta la actividad de la COMT en el útero, mientras que el E2 la reduce en el hígado y la aumenta en el riñón [97,100]; el gen que codifica esta enzima contiene varios elementos de respuesta a estrógenos [123].

Su actividad en la médula espinal está disminuida en la enfermedad de Huntington y aumentada en la esclerosis lateral amiotrófica [100].

I.2.3. Transportador vesicular de monoaminas

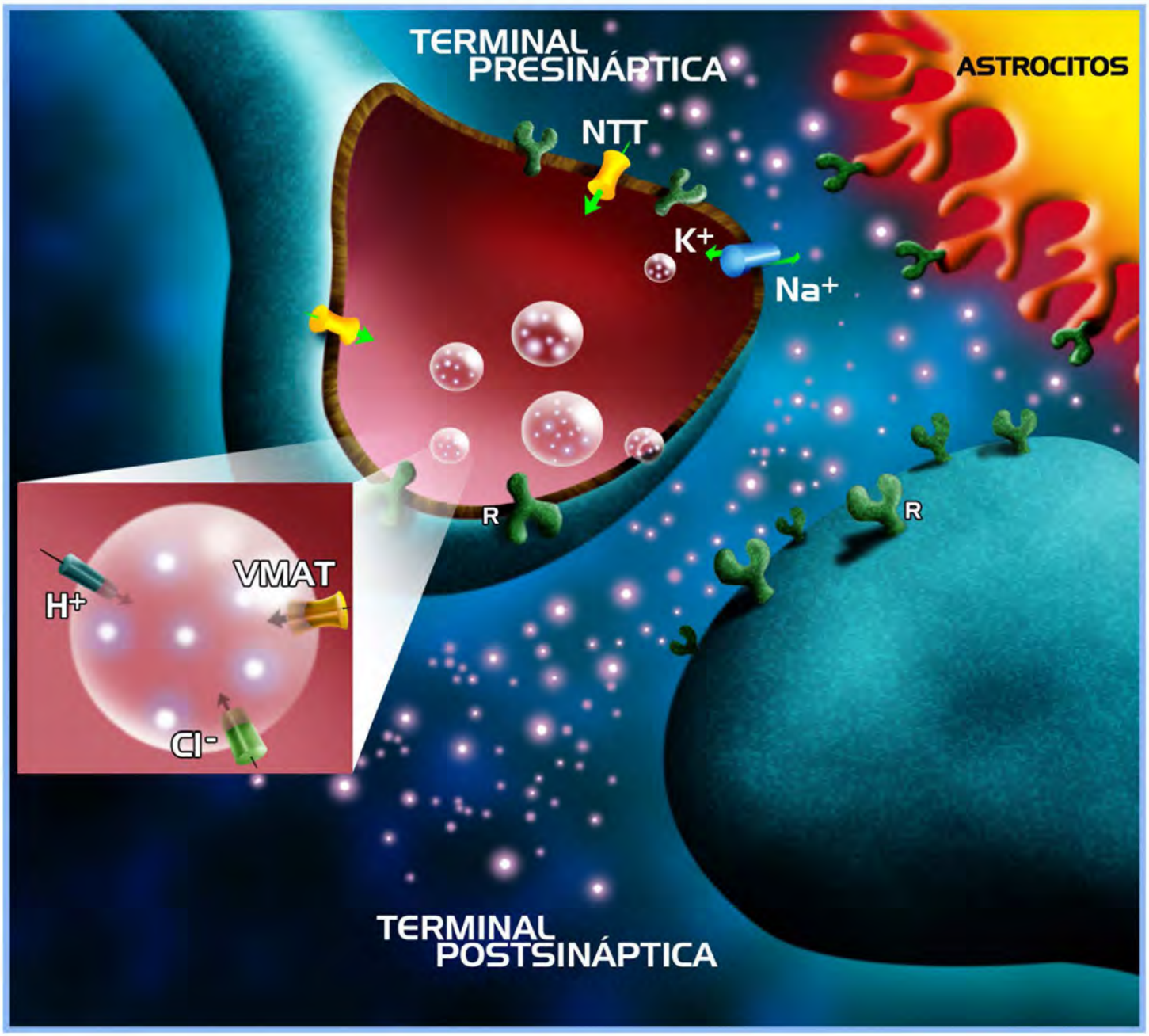
El transportador vesicular de monoaminas (VMAT) reconoce como sustratos a DA, adrenalina, NA, 5-HT e histamina [125,126].

Existen dos genes que codifican para esta proteína; uno de ellos da lugar al VMAT1 que se expresa en el sistema endócrino, y el otro da lugar al VMAT2, el cual se expresa en las neuronas [125-127].

El VMAT utiliza un gradiente de protones para acumular a las monoaminas en el interior de las vesículas sinápticas, hasta alcanzar una concentración alrededor de 10,000 veces mayor respecto a la del citosol [125,126,128].

Una bomba, que gasta ATP para

Figura 11. Esquema general de la transmisión sináptica. NTT, transportador de neurotransmisores; R, receptor; VMAT, transportador vesicular de monoaminas.



transportar iones H^+ al interior de las vesículas sinápticas, mantiene el gradiente que se requiere para la vesiculación de las monoaminas (Fig. 11) [126,128].

El aumento en la expresión del VMAT incrementa la concentración de monoaminas en las vesículas sinápticas y, por tanto, la cantidad de moléculas que se libera de las mismas [129].

A nivel celular, este transportador puede encontrarse a lo largo de la neurona, desde el axón hasta las dendritas, donde se considera que participa en la liberación somatodendrítica de monoaminas, tanto en la SN como en el VTA [89,125,127,130].

La actividad de este transportador aumenta por activación de receptores para DA tipo D2 [128].

Su fosforilación por PKA reduce el transporte vesicular de monoaminas [125].

La actividad eléctrica de las células aumenta la expresión del VMAT2 [125].

Las neuronas dopaminérgicas son más sensibles a la muerte por estrés oxidante cuando se bloquea al VMAT [128,131], por lo que la actividad de esta proteína es relevante para la neurodegeneración.

I.2.4. Transportador de dopamina

El transportador de DA (DAT) utiliza el gradiente de Na^+ para recapturar al neurotransmisor en la terminal sináptica; une dos iones de Na^+ y uno de Cl^- por cada molécula de DA [125,127,132-134].

Este es el principal mecanismo de terminación de la señalización dopaminérgica (Fig. 11) [133,135].

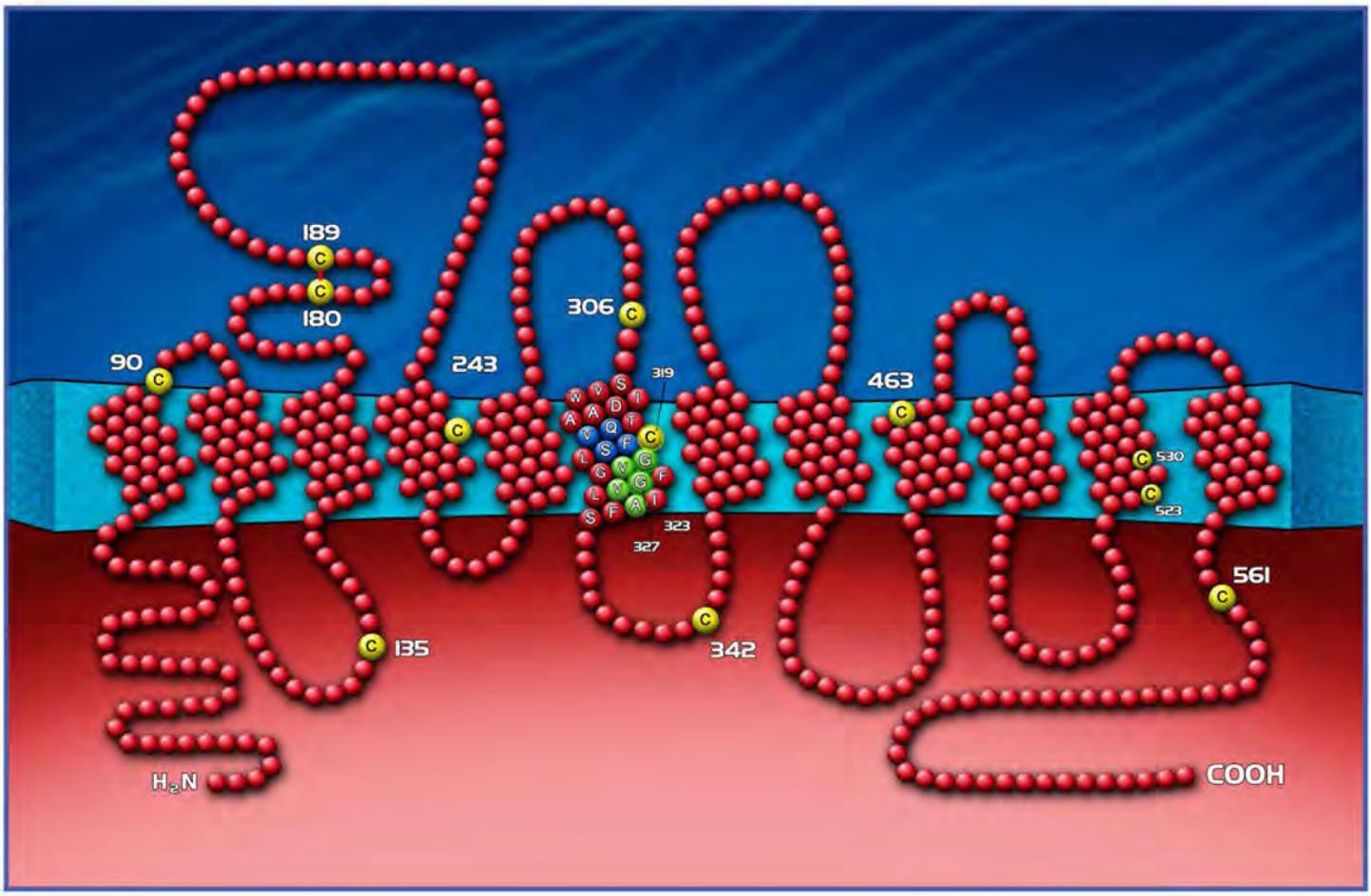
Su dominio C-terminal es importante para su localización hacia la membrana plasmática (Fig. 12) [135].

Algunos cationes, como Zn^{2+}, pueden reducir la recaptura de DA [132].

El DAT se encuentra glicosilado en su porción extracelular, lo cuál es importante para estabilizarlo en la membrana plasmática [134,136,137].

El movimiento de iones a través de la membrana genera corrientes eléctricas dependientes de sodio que pueden aumentar la excitabilidad neuronal [125,134,138-140].

Figura 12. Estructura del DAT.



La α-Sinucleína contribuye a estabilizar al transportador en la membrana, aunque algunos estudios reportan que esta proteína tiene un efecto inhibidor sobre el DAT [134].

El DAT puede formar oligómeros, los cuáles favorecen su desplazamiento a la membrana plasmática [134-137,141].

La oligomerización del DAT con la proteína PICK1 es importante para la localización del transportador en la membrana plasmática, por lo que aumenta la recaptura de DA [142].

La despolarización reduce la recaptura de DA mientras que la hiperpolarización la aumenta [89,134,135].

Las toxinas mitocondriales [143] y el NO [134] reducen la actividad del DAT, mientras que el ácido araquidónico la aumenta [134].

El etanol puede aumentar la expresión del transportador en la membrana plasmática [134] y, posiblemente, la recaptura de DA.

En el cerebro humano, la mayor expresión del DAT se ha localizado en la SN [127].

Algunos estudios han localizado al DAT en neuronas pero no en glía [125].

La exposición repetida a sus sustratos reduce su actividad en el CS (pero no en el NAc) por un mecanismo que depende de PKC, que involucra la disminución en la expresión del transportador en la membrana celular [134,135,138].

El bloqueo crónico del DAT aumenta la recaptura de DA a corto plazo, pero a largo plazo la reduce [135].

A nivel subcelular, el DAT se localiza tanto en el soma y las dendritas como en el axón de las neuronas, pero no en la membrana presináptica ni en la glía [89,125,127,134, 135,144].

Dicha localización sugiere que el DAT podría estar involucrado en la liberación somatodendrítica de DA.

Algunos estudios han reportado que el DAT libera DA en la SN por transporte inverso, como parte de un mecanismo de autoinhibición mediado por receptores D2 somatodendríticos [89,134,145].

El transporte inverso es un mecanismo de liberación de DA mediado por el DAT que puede ser activado por sustancias de abuso como las anfetaminas, y neurotransmisores como glutamato y 5-HT [89,134,135,146].

El transporte inverso es activado por PKC o por los receptores σ_2, es independiente de calcio y puede ocurrir durante la isquemia cerebral [42,89,134,135,146].

Sin embargo, cuando es activado por receptores σ_2, el transporte inverso es dependiente de los almacenes intracelulares de calcio y de la activación de PKC [42].

La activación de canales de sodio dependientes de voltaje puede aumentar la liberación de DA por transporte inverso inducida por anfetaminas [146].

La fosforilación del DAT por PKA aumenta la recaptura de DA en el Hip y el CS [125,134].

PKC puede inhibir la actividad del DAT por fosforilación [89,125], por activación de receptores D2 o por el NO [89].

Algunos autores reportan que la recaptura de DA aumenta por activación de receptores D2 [135], aunque estos resultados no han sido replicados en ovocitos de *Xenopus laevis* que expresan el DAT [147], por lo que podría requerir de algún otro mecanismo de señalización.

PKC fosforila al DAT en su dominio

N-terminal [135,148]; la activación de esta cinasa aumenta la internalización del transportador por un mecanismo indirecto que probablemente involucra a otras proteínas [134,141].

La fosfatasa de proteínas I puede desfosforilar al DAT [148].

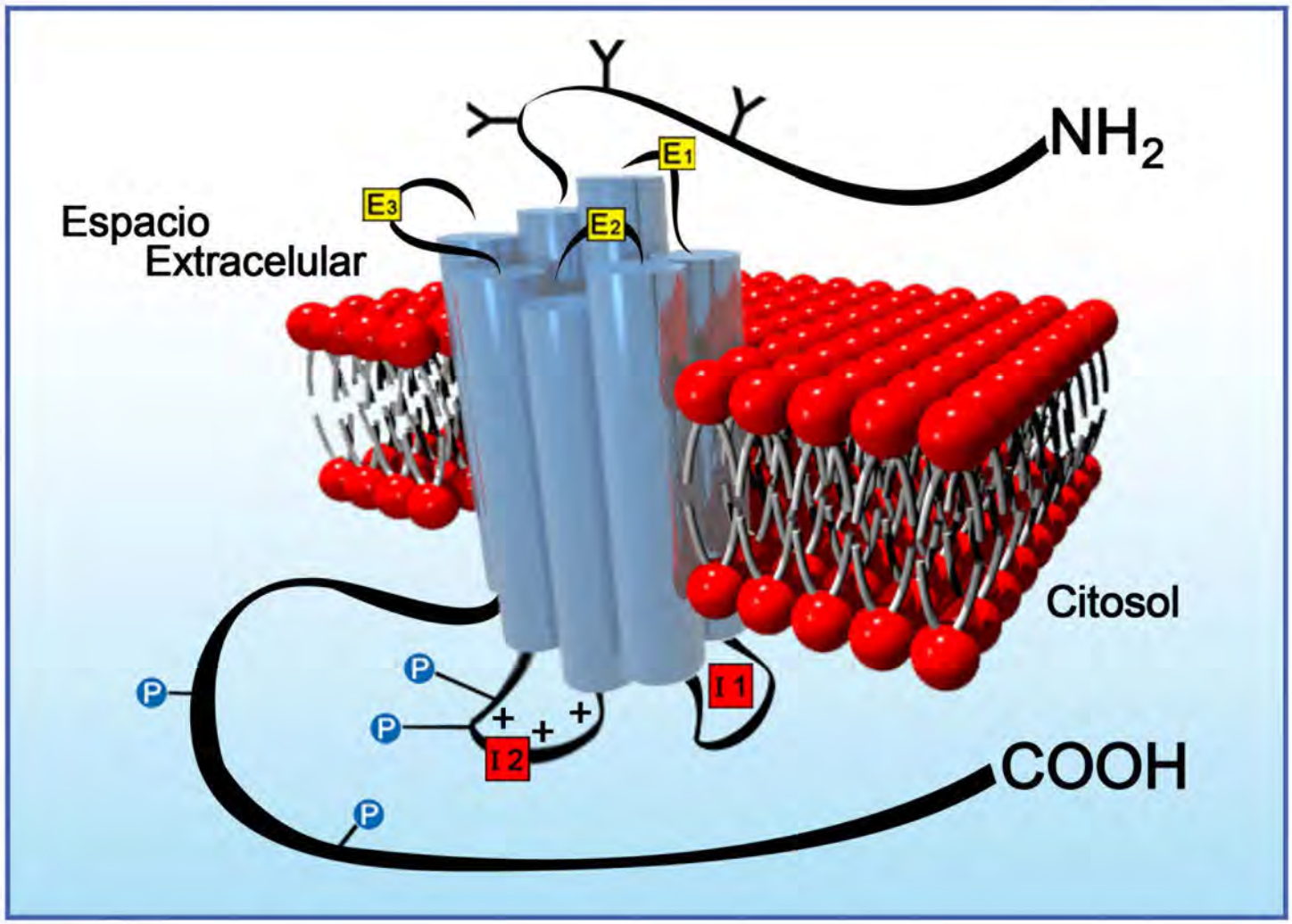
La recaptura de DA también puede estar mediada por el transportador de NA, (NET) el cual no solo tiene más afinidad por DA que el DAT (DAT K_m=2.5 µM, NET K_m= 0.67 µM), sino que tiene más afinidad por dicho neurotransmisor que por la misma NA (K_m=2.6 µM) [125].

La presencia de un grupo m-metoxi en el anillo del catecol aumenta la constante de afinidad por el DAT de 4.3 µM para DA a 272 µM para 3-MT; la ausencia del grupo amino en la cadena alifática, como en el DOPAC, también aumenta su constante de afinidad hasta 4.02 mM [150].

I.2.5. Receptores para dopamina

Existen cinco tipos de receptores para DA, todos pertenecientes a la familia de receptores acoplados a proteínas G que modulan la actividad de adenilato ciclasa (Fig. 13) [149,151-153].

Figura 13. Estructura general de los receptores para DA.



Los cinco subtipos se expresan en el CS [154].

Estos se dividen en dos grupos: los receptores de tipo D1 (D1 y D5) y los de tipo D2 (D2, D3 y D4) [149,151,152].

En el NAc y en cultivos de neuronas estriatales, prácticamente todas las células expresan tanto receptores D1 como D2 [152,155] aunque en el CS se han localizado diferentes poblaciones neuronales que expresan cada subtipo de receptor [149,156] así como poblaciones que expresan ambos receptores [154].

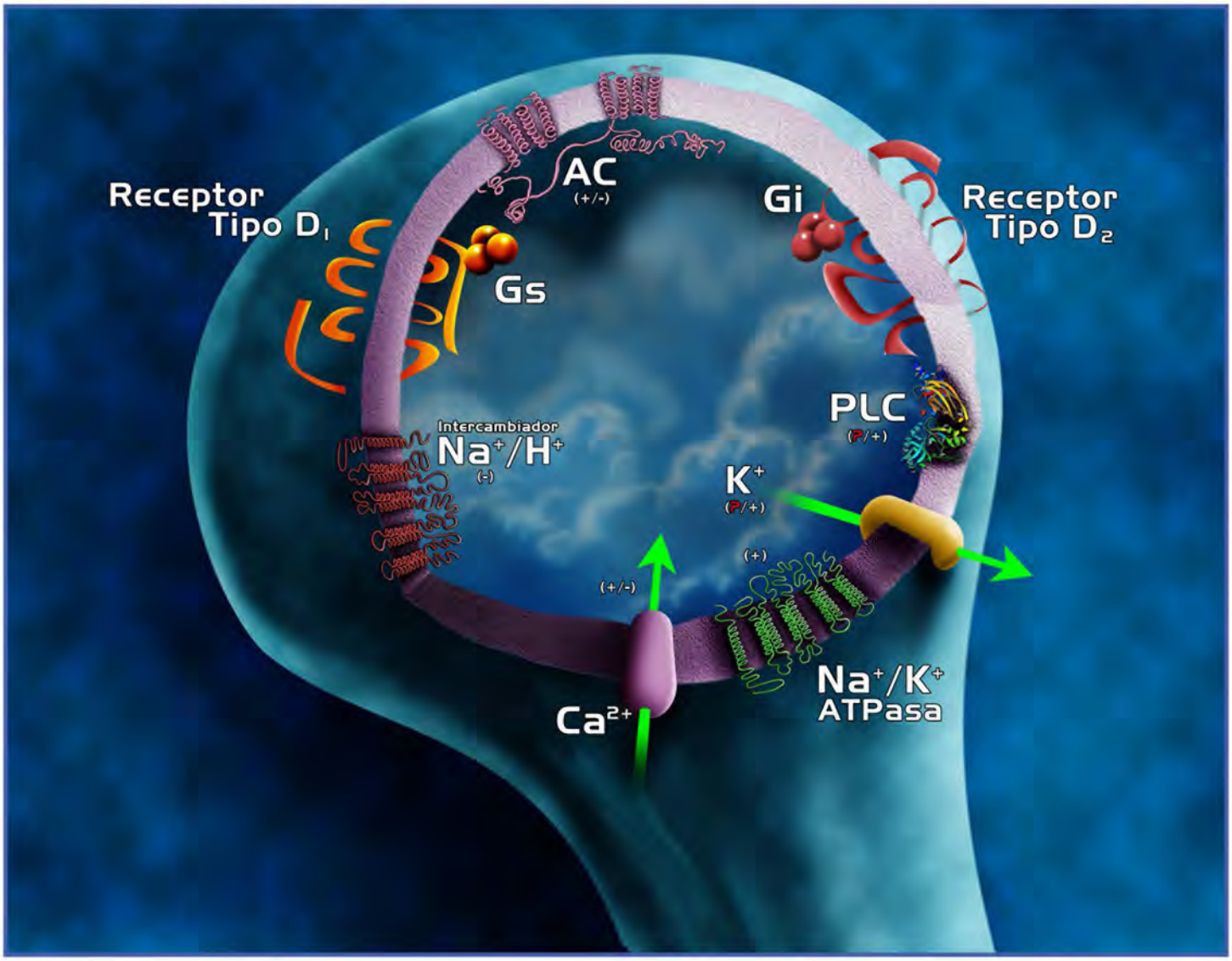
1.2.5.1. Receptor D1

El receptor D1 está codificado en el brazo largo del cromosoma 5 [149]; está acoplado a proteínas G_s que activan a adenilato ciclasa y, en consecuencia, la síntesis de AMPc (Fig. 14) [152,157].

Adicionalmente, se ha sugerido que el receptor D1 puede modular otros mecanismos de señalización.

Se ha reportado que la activación del receptor D1 puede estimular la hidrólisis de

Figura 14. Mecanismos de señalización modulados por los receptores para DA. AC, adenilato cidasa; G_i, proteína G inhibidora; G_s, proteína G estimuladora; PLC, fosfolipasa C.



fosfatidilinositol por activación de fosfolipasa C, provocando la liberación de calcio de reservorios intracelulares y la activación de PKC (Fig. 14) [149].

Este receptor se localiza con muy poca frecuencia a nivel presináptico (Fig. 15) [149,156].

Los receptores D1 también modulan a los canales iónicos.

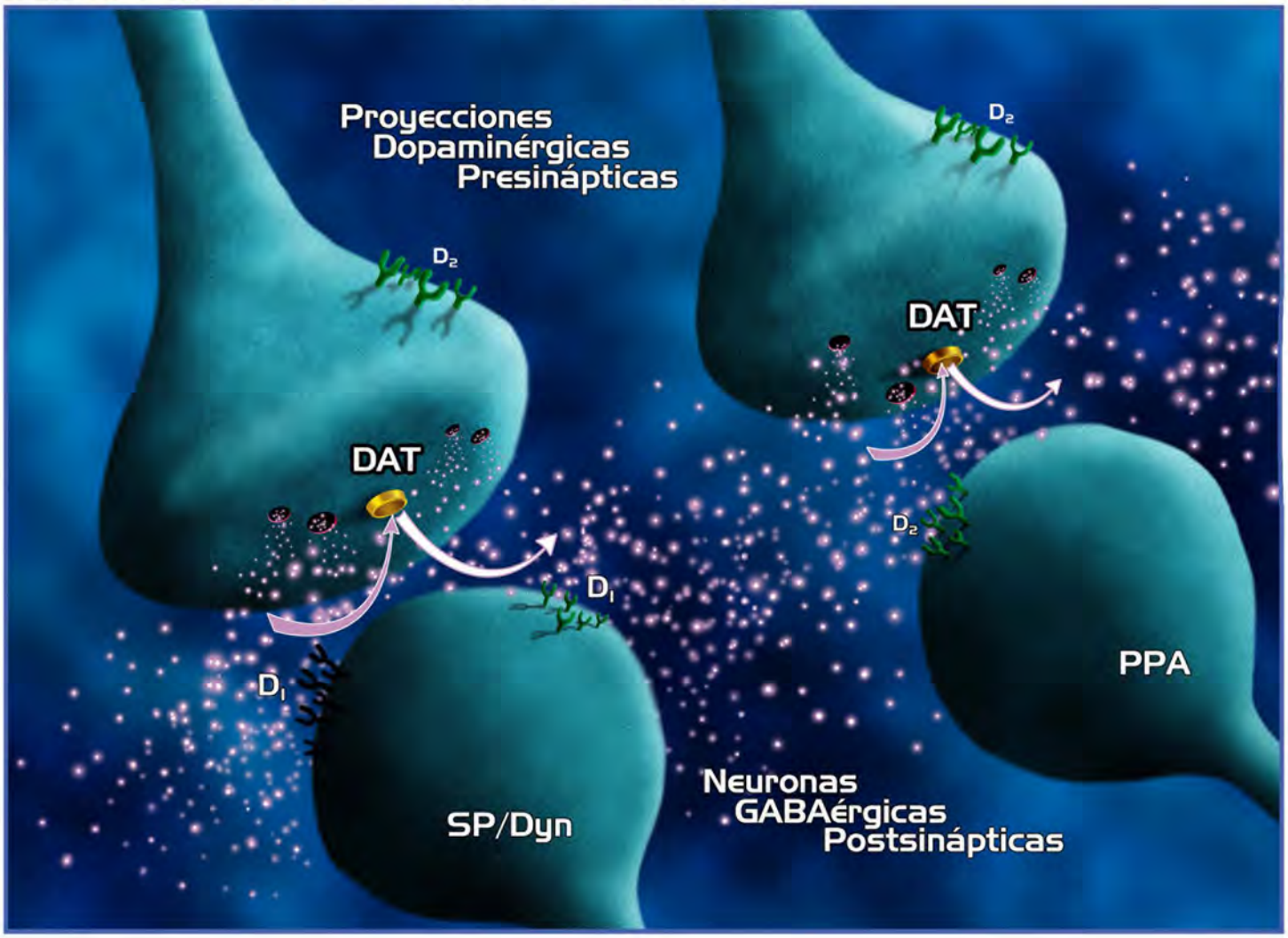
La activación de estos receptores aumenta las corrientes de calcio de los canales tipo L por un mecanismo dependiente de PKA, aunque reduce las corrientes de los canales tipo N y P (Fig. 14) [149].

Pueden aumentar o reducir las corrientes de potasio por un mecanismo dependiente de AMPc, e inhibir a la ATPasa de Na^+/K^+ (Fig. 14) [149].

Este receptor puede localizarse en una gran variedad de regiones cerebrales, como CS, Amg, bulbos olfatorios, Hic, globo pálido, Hip, SN, NAc y a lo largo de la Cx [149,152,157].

Los ratones KO para este receptor no presentan alteraciones neurológicas aparentes, pero presentan retardo en su crecimiento, menor supervivencia, aumento en el contenido mesencefálico de DA, hiperactividad y alteraciones en la

Figura 15. Localización de los receptores D1 y D2 para DA a nivel pre- y post-sináptico. D1, receptor D1; D2, receptor D2; DAT, transportador de dopamina; Dyn, dinorfina; PPA, proencefalina A; SP, sustancia P.



coordinación motora [149,152].

Estos ratones no presentan diferencias en la respuesta al efecto reforzador de la cocaína, pero muestran una menor respuesta ante otros reforzadores, como etanol o sacarosa [152].

Este tipo de receptor es regulado por diferentes mecanismos.

Es internalizado después de ser activado, como desensibilización; el acoplamiento de este receptor con el de glutamato tipo NMDA reduce este efecto [151].

Otro mecanismo de desensibilización del receptor D1 es su fosforilación [158].

Adicionalmente, el receptor puede ser regulado por su interacción con otras proteínas, entre las que se encuentran receptores para otros neurotransmisores.

Los receptores D1 pueden formar complejos oligoméricos con los receptores para glutamato tipo NMDA [151,159].

La activación de receptores D1 aumenta la de los receptores NMDA, por un mecanismo que involucra la fosforilación del receptor para glutamato mediada por PKA [80,160-162], aunque algunos estudios han observado el efecto contrario [162].

La activación del receptor NMDA mediada por DA está involucrada en algunos mecanismos de señalización de este neurotransmisor, como la expresión de genes [163].

De manera recíproca, la activación del receptor NMDA aumenta la síntesis de AMPc inducida por DA [159].

El receptor D1 también puede formar complejos oligoméricos con receptores para adenosina A1 [164].

1.2.5.2. Receptor D5

El receptor D5 está codificado en el brazo corto del cromosoma 4.

Existen dos pseudogenes de este receptor, que codifican formas truncadas y no funcionales de esta proteína.

La DA tiene 10 veces más afinidad por este subtipo de receptor que por el D1.

Los receptores D5, pero no los D1, están presentes en las interneuronas colinérgicas del CS [149].

Los ratones KO para el receptor D5 muestran menos alteraciones conductuales respecto de los KO para el receptor D1 [152], aunque también presentan retardo en su crecimiento y, adicionalmente, hipertensión arterial [152].

Este receptor se localiza en algunas regiones cerebrales, como el Hic, la CxF, los núcleos de la base, el tálamo y el Hip.

En el Hic, la expresión del receptor D5 es mayor a la del D1 [149,152].

El receptor D5 puede formar complejos oligoméricos con receptores para GABA tipo A, ambos se inhiben recíprocamente [162].

1.2.5.3. Receptor D2

Los receptores tipo D2 están acoplados a proteínas $G_{i/o}$ que, contrario a los receptores tipo D1, inhiben la actividad de adenilato ciclasa y la síntesis de AMPc.

Es posible que estos receptores activen también otros mecanismos de señalización.

Algunos estudios han mostrado que el

receptor D2 puede aumentar o reducir el metabolismo del fosfatidilinositol, modulando así la liberación de calcio de reservorios intracelulares.

Adicionalmente, los receptores D2 pueden modular la actividad de canales iónicos.

Se ha reportado que la activación de estos receptores reduce la entrada de calcio y aumenta la salida de potasio, a través de canales dependientes de voltaje (Fig. 14) [149].

Este receptor se localiza tanto a nivel postsináptico como presináptico (Fig. 15), donde actúa como autorreceptor inhibidor [86,152,165]; la activación de este receptor reduce los potenciales excitadores glutamatérgicos en el VTA [166].

Este receptor está codificado en el brazo largo del cromosoma 11 [149] y se encuentra en los grupos neuronales dopaminérgicos, así como en el CS, NAc, tubérculos olfatorios, Cx, áreas septales, Amg, Hic, globo pálido, SN e Hip [149,152,157,167, 168].

Los animales KO para este receptor presentan un menor contenido estriatal de DA, hipertensión arterial, menor liberación de la hormona de crecimiento, tumores hipofisiarios e hipertrofia adrenal [152].

A nivel conductual, estos animales presentan menor actividad y coordinación motoras, además de una menor respuesta al efecto de diferentes sustancias reforzadoras [149,152].

Existen dos variantes del receptor D2, generadas por procesamiento alternativo a partir de un mismo gen [149,152,169]; las dos formas del receptor inhiben la actividad de adenilato ciclasa [169].

La expresión de la forma larga del receptor ($D2_L$) es de 5 a 10 veces mayor a la del receptor corto ($D2_S$) [149,152,154,169,170].

La función de estas isoformas del receptor es diferencial.

La forma $D2_S$ está probablemente involucrada en la regulación de la liberación de hormonas hipofisiarias [152].

El receptor $D2_L$ está relacionado principalmente con la generación de las respuestas postsinápticas de la neurotransmisión dopaminérgica, mientras que el receptor $D2_S$ está involucrado en las funciones presinápticas de este sistema [86,152].

Existen poblaciones de neuronas que coexpresan ambas isoformas del receptor [154].

También se ha descrito la existencia de una tercera variante de procesamiento alternativo para el receptor D2 ($D2_{longer}$), la cual contiene solamente dos aminoácidos adicionales al receptor $D2_L$ [170,171].

Los animales KO para el receptor $D2_L$ probablemente sufren una disminución en la neurotransmisión dopaminérgica, ya que presentan una menor respuesta al efecto reforzador de la morfina y menor actividad motora [152].

La actividad de los receptores D2 tiene una influencia importante sobre la neurotransmisión dopaminérgica.

El bloqueo de los receptores D2 en el VTA aumenta la liberación de DA en ésta región así como en el NAc y la CxF [172].

La liberación de DA también aumenta, tanto en la CxF como en el NAc, cuando se bloquean los receptores D2 en la CxF [172].

El bloqueo de los receptores D2 en el VTA

Ánimo es vida. Idea original: Iván Pérez-Neri, Enrique Chávez Esparza; Fotografía: José Luis Bueno; Edición: Enrique Chávez Esparza.

no modifica la liberación de DA en el NAc cuando se bloquean los receptores D1 en la CxF [172].

Los receptores D2 pueden formar complejos oligoméricos con los receptores D3 [151,173].

I.2.5.4. Receptor D3

El receptor D3 está codificado en el brazo largo del cromosoma 3 [149].

La DA tiene 20 veces más afinidad por este subtipo de receptor que por el D2 [149].

Los ratones KO para el receptor D3 son viables, fértiles y no presentan alteraciones neurológicas evidentes, pero sufren hipertensión arterial [152].

La expresión de este receptor es menor a la del D2 y está restringida principalmente a regiones límbicas y paralímbicas [149,152], también se localiza en la SN, el globo pálido ventral, los tubérculos olfatorios, el CS, el VTA y el Crb [149,167].

Este receptor podría estar involucrado en la regulación de la temperatura corporal [152].

A nivel conductual, los ratones KO para el receptor D3 presentan hiperactividad motora, menor conducta de ansiedad y mayor efecto reforzador de sustancias psicoestimulantes [152].

Existen variantes de procesamiento alternativo para el receptor D3, las cuales codifican proteínas no funcionales [149].

I.2.5.5. Receptor D4

El receptor D4 está codificado en el brazo corto del cromosoma 11 y existen al menos tres variantes polimórficas del mismo [149].

Los animales KO para el receptor D4 son viables, fértiles y no presentan alteraciones neurológicas evidentes [152].

Este subtipo de receptor podría estar involucrado en las respuestas adaptativas de la retina a los cambios en la iluminación [152].

Puede encontrarse en el CS, la CxF, el Hic, la Amg, el mesencéfalo, el Hip y la retina [149,152].

Los ratones KO para este subtipo de receptor muestran una mejor coordinación motora que sus similares de tipo silvestre, y un aumento en la actividad motora inducida por psicoestimulantes [152].

A nivel neuroquímico, estos KOs presentan mayor síntesis y recambio de DA en el CS, pero no así en el NAc o la CxF [152].

La participación del sistema dopaminérgico en la fisiología del SNC ha sido ampliamente estudiada por muchos años.

Su relevancia para la modulación de las emociones y el movimiento voluntario ha sido avalada por muchos estudios, y resulta aún más evidente para la convergencia entre dichas funciones, como ocurre en el movimiento voluntario dirigido por una emoción, hacia un objetivo.

Por estas razones, la disfunción de este sistema se encuentra involucrada en patologías asociadas con el estado de ánimo y las funciones motoras, particularmente en enfermedades neurológicas que cursan con síntomas psiquiátricos, como es el caso de la PD.

De este modo, la modulación del sistema dopaminérgico es un blanco terapéutico para algunos trastornos, por lo que cobra importancia determinar el efecto de moduladores potenciales que puedan ayudar en el control de varios síntomas de una misma enfermedad; entre ellos, la DHEA.

1.3. Efecto de la DHEA sobre el sistema Dopaminérgico

1.3.1. Activación de receptores para dopamina

Algunos estudios sugieren que la DHEA modula a los receptores para DA.

La DHEA y el haloperidol, antagonista de receptores dopaminérgicos D2, tienen un efecto sinérgico sobre la disminución de la temperatura corporal.

Este efecto no depende del metabolismo de la DHEA, ya que un análogo no-metabolizable del esteroide, la 16α-cloroepiandrosterona, también reduce, mientras que algunos de sus metabolitos (androstendiol, androstendiona y E2) no alteran, la temperatura corporal [49].

Además, la DHEA (pero no el androstendiol), antagoniza la inhibición de la liberación de prolactina mediada por DA [52] como lo hacen los antagonistas D2 [174], lo que sugiere que la DHEA reduce la activación de estos receptores.

Entre los diferentes metabolitos de la DHEA, algunos aumentan, mientras que otros reducen, la activación de los receptores D2.

La 7α-OHDHEA, al igual que la misma DA, inhibe la liberación de prolactina [52], mientras que la DHEAS aumenta el antagonismo de receptores D2 inducido por espiperona y sulpiride [51].

Respecto de la activación de receptores D2, tanto la DHEA como la DHEAS tienen un efecto inhibidor similar.

A partir de esos resultados, puede sugerirse que tanto la DHEA como la DHEAS inhiben, mientras que la 7α-OHDHEA estimula, la señalización mediada por el receptor D2.

Sin embargo, si ésta hipótesis es correcta, probablemente el mecanismo involucrado en dicho efecto no es la modulación de la actividad de adenilato ciclasa, ya que la DHEA no modifica la síntesis de AMPc inducida por forskolina in vitro [52].

La modulación de los receptores para DA, ya sea mediada por la DHEA o por sus metabolitos, probablemente depende del subtipo de receptor involucrado.

La DHEAS (20 µM, 4 min) aumenta la actividad de la proteincinasa A en sinaptosomas, tanto del Hic como de la Cx, por un mecanismo que depende tanto del receptor σ_1 como del D1 [50], lo que sugiere que la DHEAS aumenta la activación del receptor D1 a través del receptor σ_1; el efecto de la DHEA sobre la activación del receptor D1 no ha sido reportado.

1.3.2. Liberación de Dopamina

Se ha reportado que tanto la DHEA como la DHEAS aumentan la liberación de DA, pero en diferentes condiciones experimentales.

La DHEAS (10^{-7}-10^{-8} M) aumenta la liberación de DA en cultivos hipotalámicos [43] y células PC12 [41].

La DHEA aumenta la liberación de DA en células PC12, pero a tiempos más cortos que la DHEAS [41].

Es decir, tanto la DHEA como la DHEAS aumentan la liberación de DA, pero probablemente a través de mecanismos diferentes.

El efecto de la DHEA en células PC12 no depende por completo del metabolismo del esteroide, dado que la Test no tiene efecto en este sistema [41], aunque otros metabolitos no han sido evaluados.

El efecto estimulador de la DHEA sobre la liberación de DA en células PC12 es transitorio, se pierde después de un periodo de incubación de 3 horas [41].

En cambio, la DHEAS provoca un aumento en la liberación de DA que alcanza su máximo a las 36 horas y es bloqueado por inhibidores tanto de la TH como de la descarboxilasa de aminoácidos aromáticos [41], lo que sugiere que este efecto es dependiente de la síntesis de DA.

De este modo, es probable que aún cuando tanto la DHEA como la DHEAS aumentan la liberación de DA en células PC12, cada uno de los esteroides modula un mecanismo distinto.

Es posible que la DHEA aumente la concentración extracelular de DA inhibiendo a los receptores D2, como se discutió anteriormente, y no a través del bloqueo del DAT, ya que la DHEA inhibe la recaptura del neurotransmisor sólamente a concentraciones relativamente altas (IC_{50} 52.5 µM) [48].

Respecto de la DHEAS, su efecto sobre el DAT no ha sido reportado, por lo que no puede descartarse si el transporte del neurotransmisor está involucrado en el efecto del esteroide sobre la concentración extracelular de la DA.

De acuerdo con esta hipótesis, si la DHEA y la DHEAS inhiben la activación de receptores D2, ambos esteroides podrían modular la neurotransmisión dopaminérgica a nivel tanto presináptico como postsináptico.

Por ejemplo, la administración de la DHEA (o la DHEAS) podría aumentar la liberación de DA [41,43] por bloqueo de los receptores D2 presinápticos, y reducir la actividad motora [34,38,175] por bloqueo de los receptores D2 postsinápticos.

Además de su posible efecto inhibidor sobre los receptores D2 presinápticos, la DHEA y la DHEAS podrían aumentar la liberación de DA a través del receptor σ_1, ya que ambos esteroides son agonistas del mismo [176].

Los agonistas del receptor σ_1 aumentan la liberación de DA por transporte inverso inducida por anfetaminas [42], la concentración extracelular de DA en el CS y el NAc, y (contrario al efecto de la DHEA) inducen hiperactividad motora [177].

Sin embargo, determinar el papel del receptor σ_1 en la modulación de la neurotransmisión dopaminérgica mediada por la DHEA y la DHEAS requiere estudios adicionales.

Más aún, diferentes mecanismos activados por la DHEA o la DHEAS podrían participar de forma conjunta estimulando la liberación de DA, ya que los agonistas del receptor σ_1 y los antagonistas D2 aumentan de forma sinérgica la concentración extracelular de DA en el NAc [177].

Por otro lado, la DHEA y la DHEAS podrían también inhibir la liberación de DA, indirectamente a través del receptor σ, ya que los agonistas de dicho receptor reducen

Arbolesco, estampa. Mauricio Soltero.

la liberación del neurotransmisor inducida con NMDA en el CS [178].

Esos estudios muestran que los receptores σ pueden tener efectos tanto estimuladores como inhibidores sobre la liberación de DA dependiendo del mecanismo involucrado, aumentando la liberación inducida por bloqueo de los receptores D2 [177], pero reduciendo aquella inducida con NMDA [178].

1.3.3. Metabolismo de la dopamina

La DHEA también modula el metabolismo de la DA, aunque su efecto depende de las condiciones experimentales en las que se pruebe y la región cerebral analizada.

La administración de la DHEA a 25 mg/kg aumenta el contenido de DA en el Hip lateral [47], mientras que la dosis de 75 mg/kg reduce el contenido del neurotransmisor en el núcleo paraventricular del Hip [46], dos horas después de la administración del esteroide en ambos casos.

Las dosis de 25 [175] o 100 mg/kg [179] de la DHEA no alteran el contenido de DA o de sus metabolitos en la corteza occipital, el Crb, el CS o el mesencéfalo, 2 horas post-administración.

Esos resultados sugieren que el aumento en el contenido de DA inducido por la DHEA a la dosis de 25 mg/kg es dependiente de la región cerebral que se analiza.

Además, también es posible que las dosis bajas de la DHEA (25 mg/kg) aumenten, mientras que las dosis altas (75 mg/kg) reduzcan, el contenido de DA; de cualquier modo, no puede descartarse la dependencia regional de estos efectos dado que la dosis de 30 mg/kg de la DHEA no modifica el contenido de DA en el CS ni en el NAc, 2 h post-administración [180].

A nivel de la Cx, se ha reportado que el tratamiento con la DHEA (25 mg/kg/día i.p.) reduce el contenido de DA después de 2 y 8 semanas, en ratas de 8 meses de edad, sin tener efecto en ratas mas jóvenes (2 meses de edad) a ninguno de los dos tiempos [181].

En el Hip, el esteroide reduce el contenido de DA a las 8 semanas en ratas jóvenes (2 meses), mientras que lo aumenta en las ratas adultas (8 meses) desde las 2 semanas de tratamiento [181].

En dicho estudio, la concentración plasmática de la DHEA correlacionó inversamente con el contenido de DA en el Hip [181], lo que sugiere que la disminución en el contenido de DA es, efectivamente, causada por la DHEA.

La DHEA podría reducir la síntesis de DA; aún cuando el esteroide no tiene efecto hasta por 24 horas en células PC12 [41], reduce el número de células inmunopositivas para TH en el CS 4 días después de una inyección intraestriatal [48] y reduce el ARNm de la TH en el núcleo arqueado del Hip de ratas tratadas con el esteroide por 2 días [45].

La DHEAS aumenta el ARNm y la proteína de TH desde las 8 horas de tratamiento en células PC12 [41]; de este modo, respecto de la expresión de la TH, la DHEA y la DHEAS generan efectos opuestos.

De forma similar al efecto agudo (2 horas de tratamiento) de la dosis de 25 mg/kg, la DHEA aumenta el contenido de DA, mientras que reduce el de DOPAC y HVA, así como sus cocientes de recambio, en el Hip de ratón, cuando se administra en la dieta por 1 día [44], lo que sugiere una disminución en la liberación del neurotransmisor o en la actividad de MAO.

La androstendiona genera el efecto contrario, disminuyendo el contenido de DA en el núcleo ventromedial del Hip bajo las mismas condiciones experimentales [181]; sin embargo, otros metabolitos de la DHEA no han sido evaluados.

De acuerdo con un estudio previo, cuatro días después de una microinyección intraestriatal de la DHEA (10 µg/2 µl) en ratas hembra, se observó una disminución en el contenido de DOPAC y una tendencia de disminución del de HVA, sin alterar los niveles de DA [48].

En ese estudio, la administración de algunos metabolitos de la DHEA generó efectos distintos; la Test disminuyó los contenidos de DA y de DOPAC, probablemente por disminución de la síntesis del neurotransmisor, mientras que el E2 no tuvo efecto [48].

De acuerdo con esos resultados, la disminución en el contenido de DOPAC, causada por la DHEA en el CS, no depende de su metabolismo a hormonas sexuales.

El recambio de DA también se reduce en el NAc después de un tratamiento crónico con la DHEA [37].

Dado que la síntesis de los metabolitos de la DA puede ocurrir después de la recaptura del neurotransmisor, el efecto de la DHEA sobre el contenido de DOPAC y HVA sugiere que el esteroide podría reducir la liberación de la DA o la actividad de MAO; algunos estudios han explorado estas hipótesis.

Se ha reportado que el tratamiento crónico con la DHEA reduce el aumento en la actividad total de MAO inducido por el envejecimiento (14 y 24 meses, en ratas), sin alterar dicha actividad enzimática en animales adultos (4 meses) [183].

Esos resultados muestran que la DHEA inhibe la actividad de MAO, aunque no determinan si el efecto involucra a una o ambas isoformas de la enzima.

13.4. Efectos conductuales de la deshidroepiandrosterona

La DHEA aumenta la preferencia de lugar inducida con cocaína por un mecanismo dependiente del receptor σ [184], lo que sugiere que estos receptores estimulan algunos de los efectos conductuales de dicho fármaco.

Estos resultados podrían estar asociados con el efecto estimulador de los receptores σ sobre la liberación de DA, como se discutió previamente.

Los antagonistas del receptor σ reducen el aumento en la actividad motora [184-186] y el reforzamiento [184,187] inducidos con cocaína.

Esos resultados sugieren una modulación positiva de la DHEA sobre la neurotransmisión dopaminérgica a través del receptor σ, contrario al efecto inhibidor del esteroide sobre la actividad motora espontánea [34,38,175], el cuál sugiere más bien una disminución en la neurotransmisión dopaminérgica.

Es posible que la DHEA pueda reducir (actividad motora) así como aumentar (condicionamiento de preferencia de lugar) algunas conductas asociadas a la DA.

A partir de esos estudios bioquímicos y conductuales, puede sugerirse que la DHEA y la DHEAS presentan efectos tanto estimuladores como inhibidores sobre la neurotransmisión dopaminérgica.

Dos hipótesis podrían explicar esta discrepancia: 1) que la DHEA (y también la

DHEAS) inhiben la señalización dopaminérgica en receptores D2 postsinápticos mientras que estimulan a este sistema a través de receptores σ y/o D1 (en el caso de la DHEAS) [50], o 2) que la DHEA inhibe la neurotransmisión dopaminérgica mientras que estimula el reforzamiento y la recompensa, inducidos con cocaína, por mecanismos no dopaminérgicos.

13.4.1. Efecto de la DHEA sobre la actividad motora

Uno de los efectos conductuales que han sido reportados después del tratamiento agudo con la DHEA, es la inhibición de la actividad motora espontánea, aunque el mecanismo de acción para este efecto no es del todo conocido.

Dicho efecto podría involucrar la disminución en la motivación, en la capacidad o en la fuerza para realizar la actividad motora; además, podría ser un efecto central (cerebral) o periférico (muscular).

La DHEA reduce la actividad motora espontánea cuando se administra de forma aguda [38,175].

Algunos estudios detectan este efecto inhibidor de forma más tardía, a las 24 h post-administración [32].

De acuerdo con otros, a las 24 h su efecto inhibidor ha desaparecido [188], pero si se administra repetidamente por 10 días, aún puede observarse [34]. DHEAS puede inhibir [32] o aumentar [189] la actividad motora.

El mecanismo responsable de dicho efecto inhibidor se desconoce.

Es posible que el esteroide modulara, a nivel periférico, la fuerza o la capacidad para realizar actividad física; sin embargo, algunos estudios difieren de esa propuesta.

Respecto de la fuerza muscular, más que sugerir que la DHEA tenga un efecto inhibidor, se sugiere comúnmente que el esteroide puede aumentar la fuerza, al ser precursor de andrógenos; sin embargo, no existe suficiente evidencia que apoye ésta hipótesis [190], aunque algunos estudios reportan un efecto benéfico de la DHEA sobre el desarrollo muscular [191].

Algunos otros estudios muestran que el consumo de la DHEA por varias semanas no modifica la capacidad [192-196] o la fuerza [190,197] para realizar ejercicio.

Si bien parece ser que la DHEA no modifica la capacidad para realizar actividad física, es más bien el ejercicio el que altera la concentración del esteroide.

A nivel periférico, el ejercicio aumenta la liberación de ACTH [198,199], el contenido de DHEA en el músculo esquelético de ratas [200], y la concentración sérica del esteroide en humanos [198,199,201-205].

Sin embargo, no parece que tal aumento en la concentración de la DHEA favorezca la realización del ejercicio; por su parte, la concentración de la DHEAS no correlaciona con la actividad física en mujeres [206] y no se modifica después del ejercicio [198,199,201,204,207,208]; aunque puede reducirse durante la fase de recuperación [208], algunos estudios reportan más bien un aumento [209-212].

Contrario al ejercicio agudo, las concentraciones de DHEA y DHEAS se reducen cuando éste se realiza de forma crónica [196].

Por lo anterior, no parece que la DHEA tenga un efecto inhibidor sobre la actividad

motora al actuar, a nivel periférico, sobre la fuerza o la capacidad para realizarla.

Es posible que el esteroide modulara, a nivel central, al principal sistema de neurotransmisión responsable del movimiento voluntario, involucrado también en la motivación: la DA.

13.4.2. Efecto de la dopamina sobre la actividad motora

El efecto facilitador de la DA sobre la actividad motora espontánea se ha estudiado por muchos años.

Se ha descrito que los fármacos que estimulan este sistema de neurotransmisión (especialmente en el NAc), como cocaína, anfetaminas y agonistas de receptores para DA D1, provocan hiperactividad motora [185,213-222].

Por el contrario, la disminución en la señalización dopaminérgica, tanto en el NAc como en el CS, está asociada con hipoactividad y catalepsia [213,215,217,218, 223-228]; por ejemplo, los ratones KO para el receptor D1 presentan una menor actividad motora espontánea [229].

El bloqueo de los receptores para DA D1 puede incluso inhibir la actividad motora inducida por sustancias que no modulan directamente al sistema dopaminérgico, como la morfina y la cafeína [223].

Lo anterior muestra que la neurotransmisión dopaminérgica está directamente involucrada en el control de la actividad motora, lo que sugiere que la liberación del neurotransmisor debe ocurrir durante dicha conducta; diferentes estudios apoyan esta hipótesis.

El aumento en la actividad motora va acompañado de un aumento en la concentración extracelular de DA [230-232] y de sus metabolitos [233-235] en el NAc y el CS.

Incluso, la concentración extracellular de HVA en el CS correlaciona con la actividad motora de los animales [233,235].

Cuando la actividad motora se reduce, puede observarse un menor contenido de DOPAC en el CS [236].

La liberación de DA coincide con el aumento en la concentración extracelular de sus metabolitos [237-239]; una menor liberación del neurotransmisor da el efecto contrario [237].

El aumento en la concentración de los metabolitos puede ser posterior al de la DA; aunque el aumento del neurotransmisor puede detectarse desde los primeros minutos, la concentración de sus metabolitos puede requerir 60-120 min para alcanzar su máximo. [238,239].

Por estas razones, la concentración de los metabolitos de la DA puede ser mejor indicador de activación dopaminérgica, cuando se mide de forma tardía.

El recambio de DA ha sido utilizado por muchos estudios para estimar la liberación del neurotransmisor [236,240] y su catabolismo por MAO [240].

Se ha reportado que una menor concentración extracelular de DA coincide con un menor recambio medido en el tejido cerebral [241]; cuado la liberación es mayor, se observa el efecto contrario [242-244].

Por todo esto, es posible sugerir que la influencia de la DHEA sobre la neurotransmisión dopaminérgica, puede deducirse analizando su efecto sobre el recambio del neurotransmisor, dado que

éste aporta información sobre la liberación, la recaptura y el metabolismo del neurotransmisor, además de ser relevante para la neuroprotección en la PD. ■

A través de la ciencia. Idea original: José Luis Bueno; Fotografía: José Luis Bueno; Edición: Enrique Chávez Esparza.

2.1. Objetivos

2.1.1. Objetivo general

Determinar el efecto de la DHEA sobre el metabolismo de la DA en el NAc y el CS.

2.1.2. Objetivos particulares

Determinar el efecto de la DHEA sobre el contenido y recambio de monoaminas.

Evaluar el efecto de la DHEA sobre la actividad de MAO in vivo.

Describir el efecto de la DHEA sobre la actividad de MAO in vitro.

2.2. Hipótesis

La DHEA reduce el recambio de DA.

2.3. Métodos

2.3.1. Reactivos

DA, DOPAC, HVA, 5-HT, ácido 5-hidroxi-indolacético (5-HIAA), trans-DHEA, octil sulfato de sodio, propilen glicol (grado USP), quinolinol, dibromhidrato de kinuramina, selegilina [clorhidrato de R-(-)-deprenil], y clorgilina [clorhidrato de N-metil-N-propargil-3-(2,4-diclorofenoxi)-propilamina] fueron obtenidos de Sigma (St. Louis, MO, USA).

Bitartrato de NA fue obtenido de Merck (Darmstadt, Alemania).

El metanol absoluto grado HPLC se obtuvo de Mallinckrodt Baker (México).

Los demás reactivos fueron obtenidos de proveedores diversos y fueron de grado analítico.

2.3.2. Tratamiento

La DHEA se disolvió en propilen glicol y se inyectó a distintas dosis (30, 60 y 120 mg/kg, i.p.) a ratas Wistar macho de 200-250 g de peso (n 6-8).

El grupo control recibió un volumen equivalente del vehículo.

Los animales fueron sacrificados por decapitación dos horas después de la administración del esteroide; se disecaron el CS y el NAc y fueron almacenados a -70 °C hasta su análisis.

Las dosis de la DHEA fueron seleccionadas para cubrir un amplio rango de dosis utilizadas en estudios previos; además, la elección del vehículo, la vía de administración y el tiempo del tratamiento, también se eligieron de acuerdo con esos estudios [46,47,175,179].

2.3.3. Contenido de dopamina y sus metabolitos

El análisis se realizó de acuerdo con estudios previos [245].

Las muestras fueron descongeladas y

Perfil psicomisticoide, estampa. Mauricio Soltero.

homogenizadas en una solución de metabisulfito de sodio al 0.1% en ácido perclórico 0.4 N.

Los homogenados fueron centrifugados a 18 500 *g* por 15 min y los sobrenadantes se mantuvieron en hielo durante el análisis.

Las muestras fueron analizadas por HPLC con detector electroquímico como ha sido reportado [245], con ligeras modificaciones.

Las muestras se inyectaron a una bomba isocrática (LC 250, Perkin Elmer) usando una válvula Rheodyne con un asa de 20 µl.

La fase móvil consistió de un amortiguador de fosfatos (30 mM, pH 3.1) con octil sulfato de sodio (2 mM), EDTA (1.6%) y 20% de metanol absoluto (grado HPLC), a una velocidad de flujo de 0.8 ml/min.

Las señales se registraron con un detector electroquímico Metrohm 656 (ajustado a un potencial de oxidación de 800 mV y 1 nA) y fueron integradas usando el programa Turbochrom 4.10 (Perkin Elmer).

Los límites de detección, determinados como una proporción señal:ruido de 3:1 para 10 inyecciones blanco, se encontraron entre 9 y 36 nM para todos los analitos.

Los límites inferiores y superiores de cuantificación fueron 0.1-0.3 y 2.5-10.0 µM, respectivamente, para todos los analitos.

La respuesta fue lineal entre los dos límites (r=0.999) y no estuvo influenciada por la matriz biológica.

La variación intra-ensayo fue 3.46-14.93% para todos los analitos y no fue dependiente de la concentración.

Los resultados se expresan como ng/g de tejido.

2.3.4 Actividad de monoamino oxidasa

El ensayo de actividad enzimática se realizó de acuerdo con estudios previos [106,246-249].

El día del análisis, las muestras fueron descongeladas y homogenizadas en agua desionizada enfriada en hielo.

Se preincubaron, a 37 °C, alícuotas de cada muestra con PBS (50 mM, para la actividad total de MAO), con selegilina (para la actividad de MAO A) o clorgilina (para la actividad de MAO B), disueltas en PBS a una concentración final de 1 µM, por al menos 15 min.

En los estudios in vitro, homogenados de NAc y CS, obtenidos de animales sin tratamiento previo, fueron preincubados con concentraciones crecientes de la DHEA (concentración final 100 nM-1mM, n=3) preparadas en dimetil sulfóxido (concentración final 2.5% v/v) por 5 min a 37 °C, de acuerdo con estudios previos [48].

La reacción se inició agregando kinuramina (disuelta en PBS) a concentración final de 22 µM, y se detuvo agregando ácido tricloroacético al 10%, 30 min después.

Las mezclas de reacción fueron centrifugadas a 18 500 *g* por 15 min; alícuotas del sobrenadante se mezclaron con un volumen equivalente de hidróxido de sodio 1 M.

Se midió la intensidad de fluorescencia a 315 nm de excitación y 380 nm de emisión, en un espectrofluorómetro Perkin Elmer LS 50B y se interpoló en una curva de calibración generada con concentraciones crecientes de quinolinol.

El ensayo de actividad se basa en la conversión de kinuramina en quinolinol, el cuál es fluorescente.

La actividad enzimática se expresó como nmol/mg proteína/h.

Se determinó la concentración de proteínas por el método de Lowry [250].

2.3.5. Análisis estadístico

Se realizaron pruebas de normalidad (Kolmogorov-Smirnov) y homogeneidad de varianzas (Levene).

Se realizó ANOVA de una vía seguido de Dunnett, así como *t* de Student para muestras pareadas, análisis de varianza de Kruskal-Wallis, y prueba de correlación de Pearson, usando el programa SPSS 17.

Se realizó regresión no-lineal con el programa GraphPad Prism 5.01.

Los resultados se expresan como media±EEM.

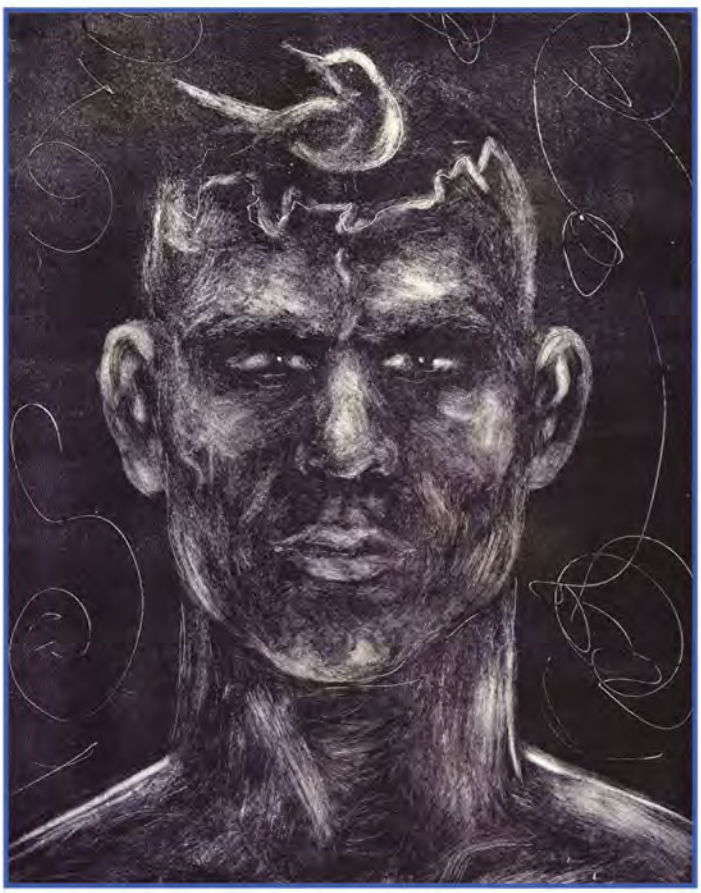
Los resultados del experimento in vitro se expresan como porcentaje de actividad, considerando el efecto de la DHEA 100 nM como 100%. Se consideró como significativo un valor de $p<0.05$.

2.3.6. Consideraciones éticas

Los experimentos se realizaron de acuerdo con las Declaraciones Basel y Helsinki.

Se realizaron todos los esfuerzos por minimizar el número de animales utilizados y su sufrimiento. ■

Tristísimo, estampa. Mauricio Soltero.



Brainy birdy, estampa. Mauricio Soltero.

3.I. Contenido de dopamina y sus metabolitos

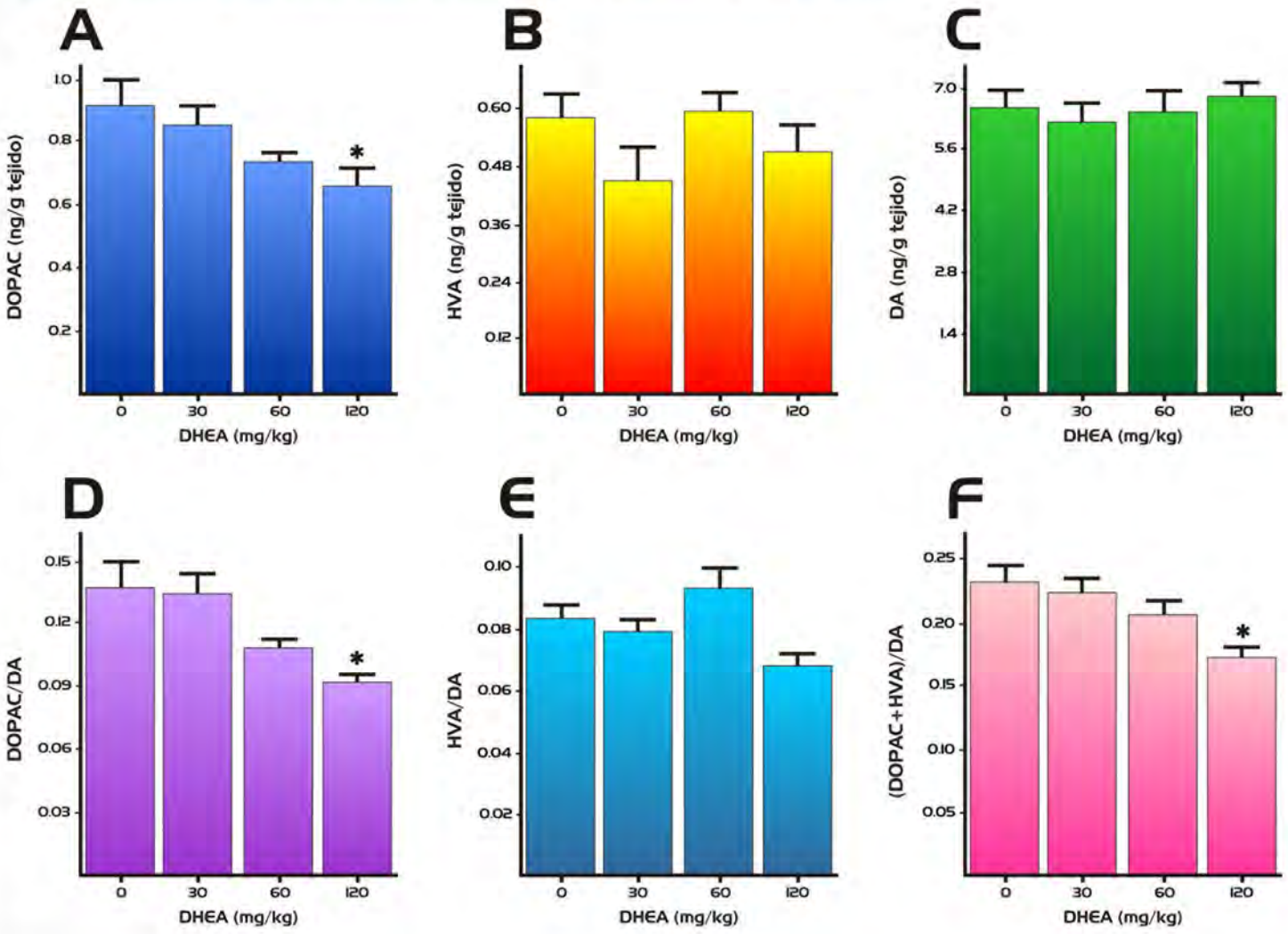
El análisis de varianza mostró que la DHEA modificó tanto el contenido de DOPAC (F=3.3, p=0.034; Fig. 16A) como el cociente DOPAC/DA (Fig. 16D) (F=5.7, p=0.004), en el CS, de forma dependiente de la dosis.

El análisis post hoc indicó que la DHEA redujo el contenido de DOPAC (control 0.91±0.07 ng/g tejido, DHEA 0.65±0.05 ng/g tejido; p=0.022) y el cociente DOPAC/DA (control 0.14±0.01, DHEA 0.09±0.01; p=0.003) a la dosis de 120 mg/kg.

El recambio total de DA en el CS [(DOPAC+HVA)/DA], también fue modificado por el tratamiento con la DHEA (F=3.5, p=0.030; Fig. 16F).

El esteroide redujo el cociente (DOPAC+HVA)/DA a la dosis de 120 mg/kg (0.17±0.01), respecto del grupo control (0.23±0.01, p=0.013). Se observó una tendencia en el cociente HVA/DA (F=3.0,

Figura 16. Efecto de la DHEA sobre el contenido y recambio de DA en el CS



p=0.050; Fig. 16E) pero al análisis post hoc mostró que ninguno de los grupos tratados con la DHEA fue distinto del control (p>0.160). No se observaron efectos significativos sobre los contenidos de DA (F=0.2, p=0.840; Fig. 16C) o HVA (F=1.3, p=0.288; Fig. 16B) en esta región.

En el NAc, no se observaron efectos sobre los contenidos de DA (F=1.3, p=0.285; Fig. 17C) y DOPAC (χ^2=1.9, p=0.574; Fig. 17A), o en los cocientes HVA/DA (F=2.7, p=0.064; Fig. 17E) o (DOPAC+HVA)/DA (F=1.0, p=0.385; Fig. 17F).

El análisis de varianza detectó un efecto en el contenido de HVA (F=4.1, p=0.016; Fig. 17B) pero el análisis post hoc mostró que ninguno de los grupos tratados con la DHEA fue distinto del control (p>0.70).

En esta región cerebral, sólo se observó una tendencia de disminución en el cociente DOPAC/DA (F=0.9, p=0.419; Fig. 17D); sin embargo, el contenido de DOPAC (r^2=0.156, p=0.031; Fig. 18A), HVA (r^2=0.203, p=0.013; Fig. 18B) y el cociente (DOPAC+HVA)/DA (r^2=0.164, p=0.029; Fig. 18C), correlacionaron positivamente entre el NAc y el CS en la muestra total.

No se observaron correlaciones, entre el NAC y el CS, en el contenido de DA (r^2=0.022, p=0.427), el cociente DOPAC/DA (r^2=0.094, p=0.099) y HVA/DA (r^2=0.066, p=0.194).

Figura 17. Efecto de la DHEA sobre el contenido y recambio de DA en el NAc

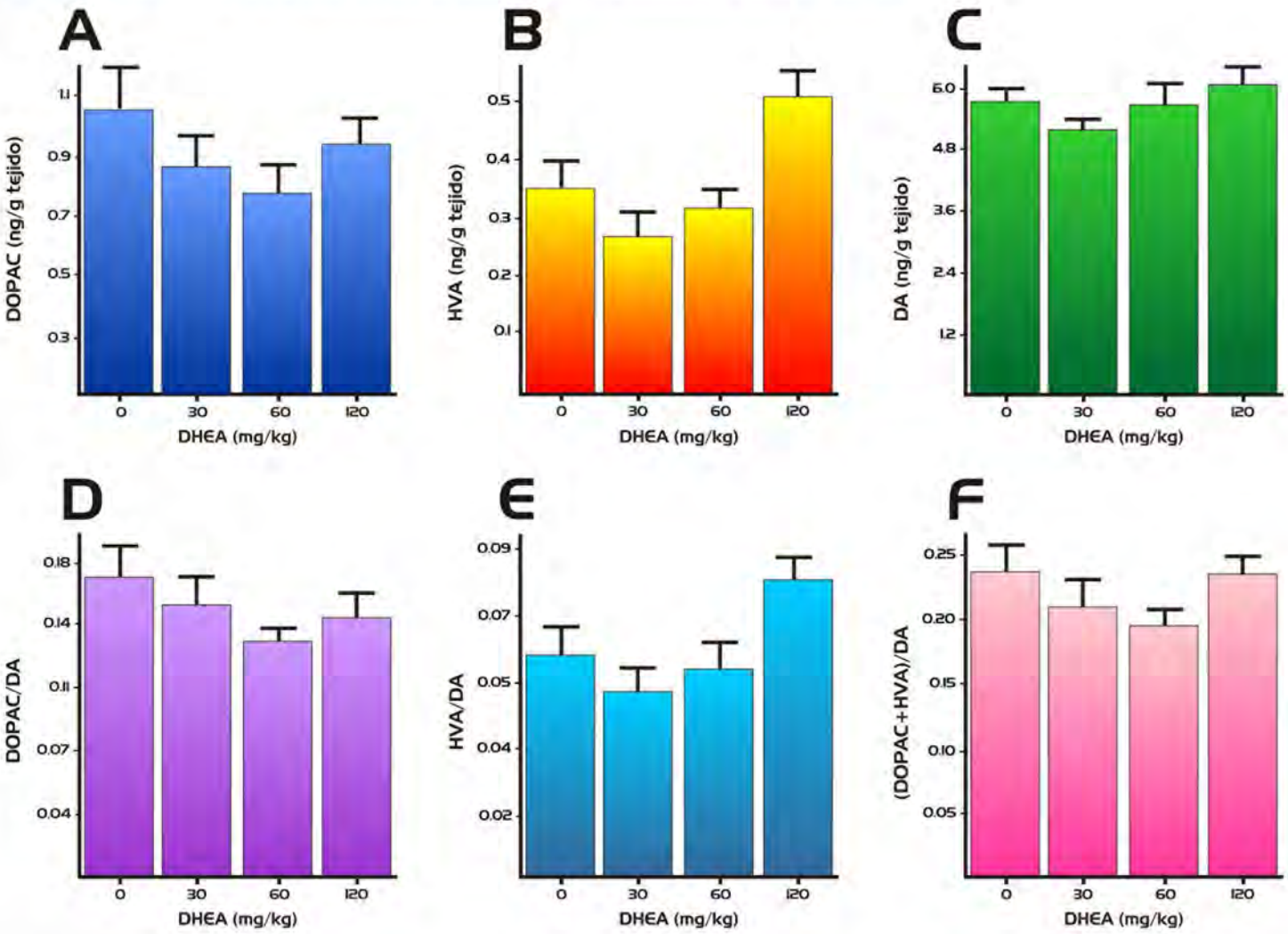
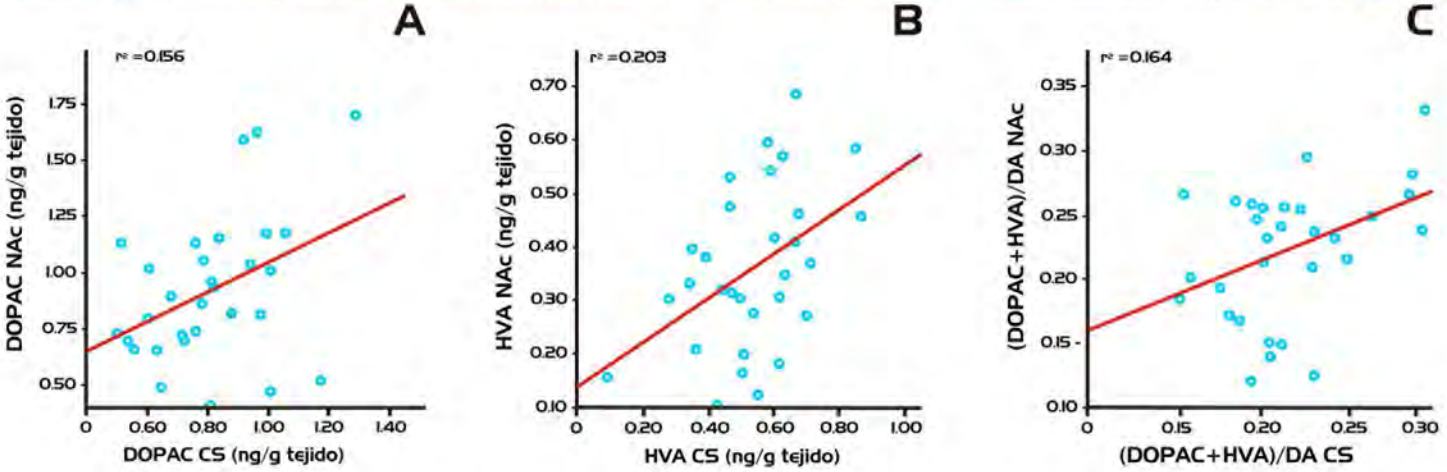


Figura 18. Análisis de regresión. Los contenidos de DOPAC (A; r^2=0.156, p=0.031) y HVA (B, r^2=0.203, p=0.013), así como el cociente DOPAC+HVA)/DA (C; r^2=0.164, p=0.029), correlacionaron entre el NAc y el CS.



En el grupo control, tanto el contenido de HVA (CS, 0.55±0.05 ng/g tejido; NAc, 0.33±0.04 ng/g tejido; p=0.003) como el cociente HVA/DA (CS, 0.08±0.01; NAc, 0.05±0.01; p=0.008), fueron mayores en el CS que en el NAc.

3.2. Actividad de monoamino oxidasa

3.2.1. Estudios in vivo

El tratamiento con la DHEA modificó la actividad total de MAO en el NAc (F=8.5, p<0.001), reduciéndola en 24% a la dosis de 120 mg/kg (p=0.002; Fig. 19A).

La DHEA también modificó las actividades de MAO A y B (MAO A: F=3.4, p=0.031; MAO B: F=7.0, p=0.001; Fig. 19B,C) en 14.2 y 14.9%, respectivamente, pero el análisis post hoc mostró que ninguno de los grupos tratados con el esteroide fue distinto del control (p>0.05).

En el CS, la DHEA también modificó la actividad total de MAO (F=3.1, p=0.046; Fig. 19D) y la de MAO A (F=5.6, p=0.005; Fig. 19E), mientras que se observó una tendencia de efecto en la de MAO B (F=2.4, p=0.090; Fig. 19E).

Sin embargo, el análisis post hoc mostró que ninguno de los grupos tratados con la DHEA fue distinto del control (p>0.05).

3.2.2. Estudios in vitro

La concentración más alta de la DHEA (1 mM) precipitó al agregarla a la mezcla de reacción, por lo que los resultados de dicha concentración representan el efecto de la máxima concentración soluble del esteroide (entre 100 µM y 1 mM) en nuestras condiciones experimentales, pero también podrían estar influenciados por la presencia de material insoluble; no se observó precipitación con las otras concentraciones utilizadas.

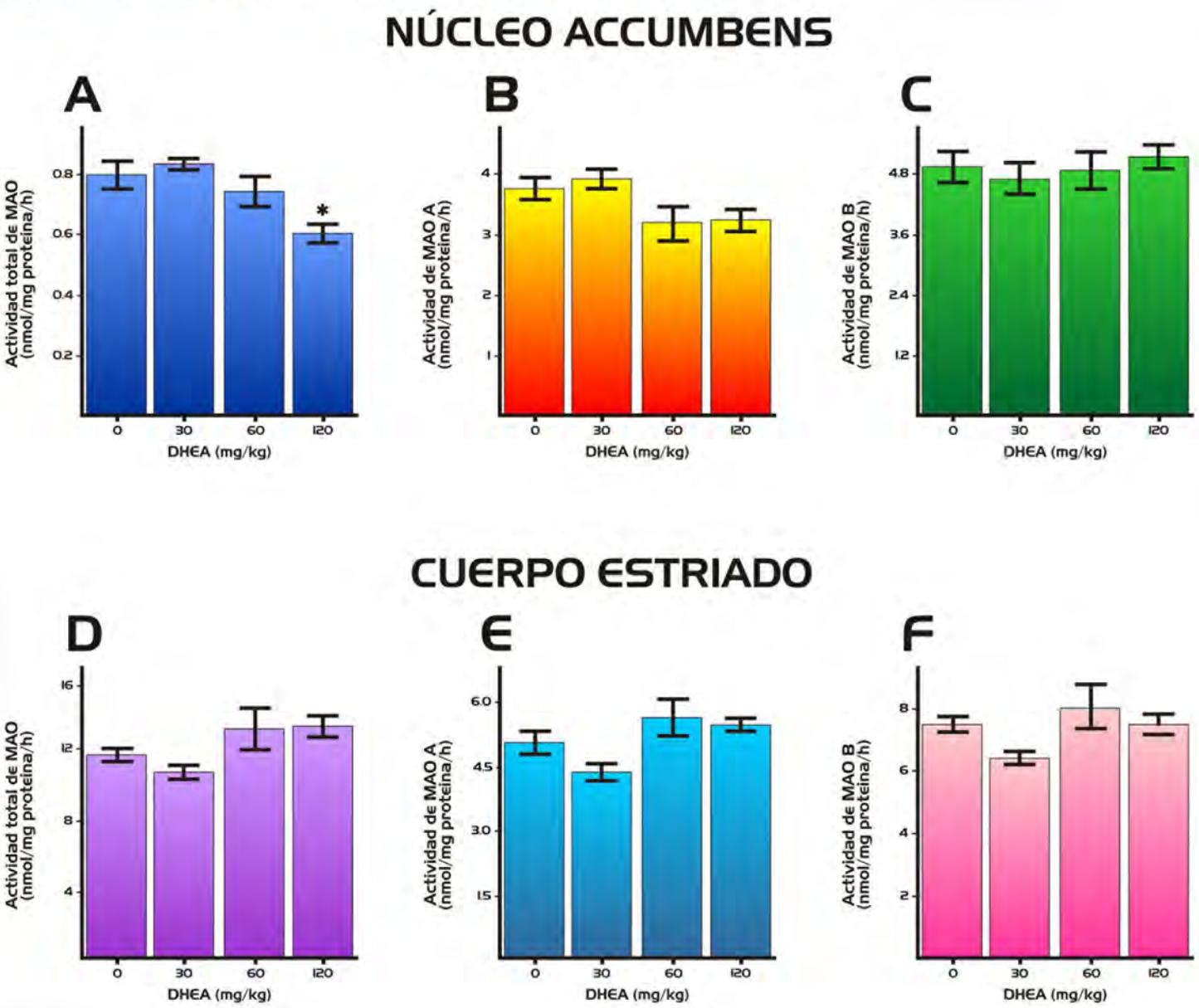
En los homogenados del NAc, la DHEA (100 µM) redujo la actividad total de MAO a 55.7% (Fig. 20A).

Las actividades de MAO A (Fig. 20B) y MAO B (Fig. 20C) fueron inhibidas a la máxima concentración probada, a 28.2 y 54.4%, respectivamente.

Las IC_{50} estimadas para la DHEA sobre MAO total, MAO A y MAO B fueron 11.2, 56.1 y 30.1 µM, respectivamente.

En el CS, la DHEA inhibió la actividad total

Figura 19. Efecto de la DHEA sobre la actividad de MAO in vivo



de MAO a 71.9% a la máxima concentración probada (Fig. 20D).

Las actividades de MAO A (Fig. 20E) y MAO B (Fig. 20F) se redujeron a 44.2 y 61.2%, respectivamente, a esa misma concentración de la DHEA.

Las IC_{50} estimadas fueron 4.7, 14.9 y 11.44 µM para MAO total, MAO A y MAO B, respectivamente.

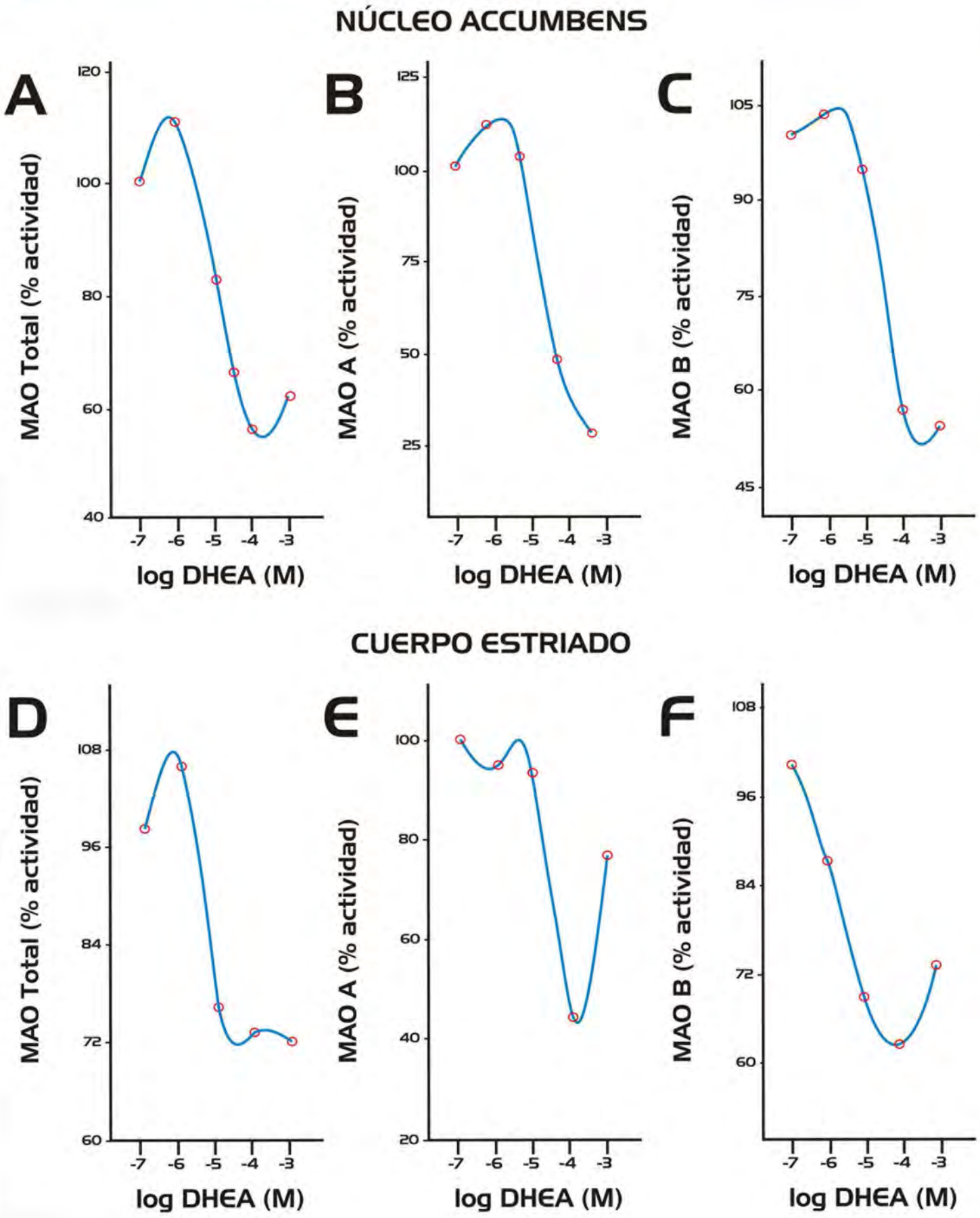
En los homogenados de ambas regiones cerebrales, la actividad de MAO tendió a ser mayor a 1 µM de la DHEA que a 100 nM, y también tendió a ser mayor a 1 mM que a 100 µM (Fig. 20).

3.3. Contenido de serotonina y su metabolito

El tratamiento con la DHEA modificó el cociente 5-HIAA/5-HT tanto en el CS ($F=3.0$, $p=0.045$, Fig. 21C) como en el NAc ($F=7.1$, $p=0.001$, Fig. 22C).

El análisis post-hoc mostró que dicho

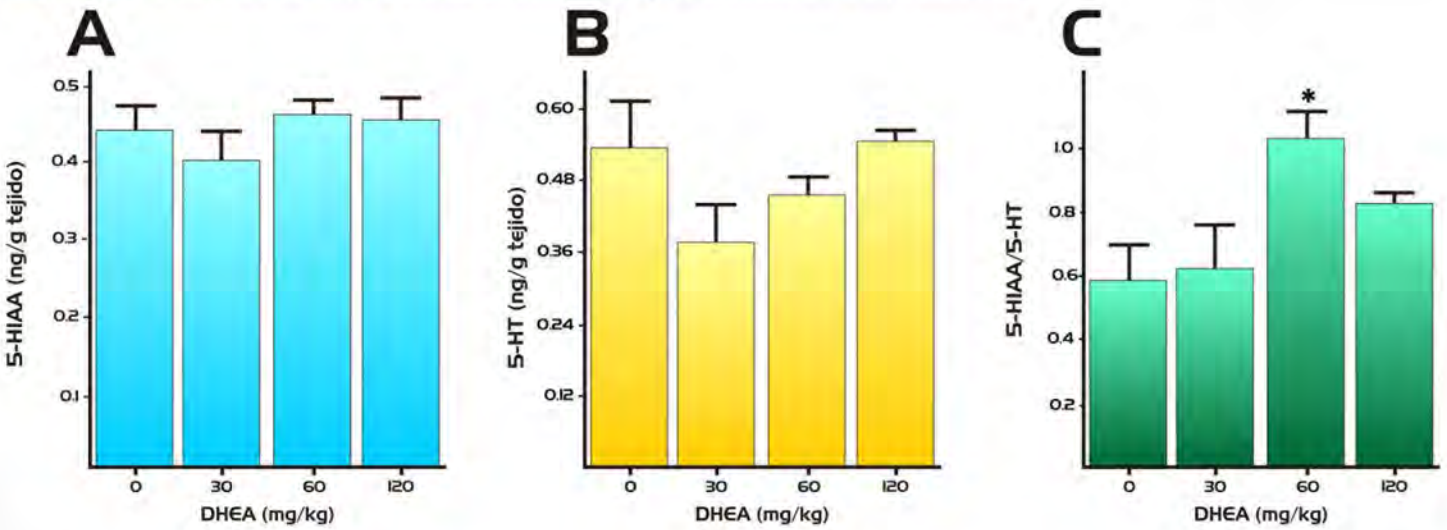
Figura 20. Efecto de la DHEA sobre la actividad de MAO in vitro (n=3).



cociente aumentó a las dosis de 60 mg/kg en el CS (control: 0.58±0.11, DHEA: 1.02±0.08; p=0.029, Fig. 21C) y de 120 mg/kg en el NAc (control: 0.59±0.05, DHEA: 0.92±0.05; p=0.001, Fig. 22C).

No se observaron efectos significativos en los contenidos de 5-HIAA (CS: F=0.5, p=0.627, Fig. 21A; NAc: χ^2=1.7, p=0.617, Fig. 22A) o de 5-HT (CS: χ^2=7.5, p=0.056, Fig. 21B; NAc: F=2.0, p=0.135, Fig. 22B).

Figura 21. Efecto de la DHEA sobre el contenido y recambio de 5-HT en el CS.



3.4. Contenido de noradrenalina

El contenido de NA en el NAc tendió a aumentar con el tratamiento con DHEA (χ^2=5.0, p=0.168, Fig. 23).

Los niveles del neurotransmisor aumentaron, de 0.91±0.16 ng/g en el grupo control, a 1.21±0.18 ng/g a la dosis de 30 mg/kg, 1.43±0.12 a 60 mg/kg y a 1.25±0.05 ng/g a 120 mg/kg de DHEA.

En el CS, se observaron tendencias de aumento y de disminución en el contenido de NA que no parecen estar asociadas a la dosis de la DHEA (F=0.5, p=0.625; Fig. 23).

Figura 22. Efecto de la DHEA sobre el contenido y recambio de 5-HT en el NAc.

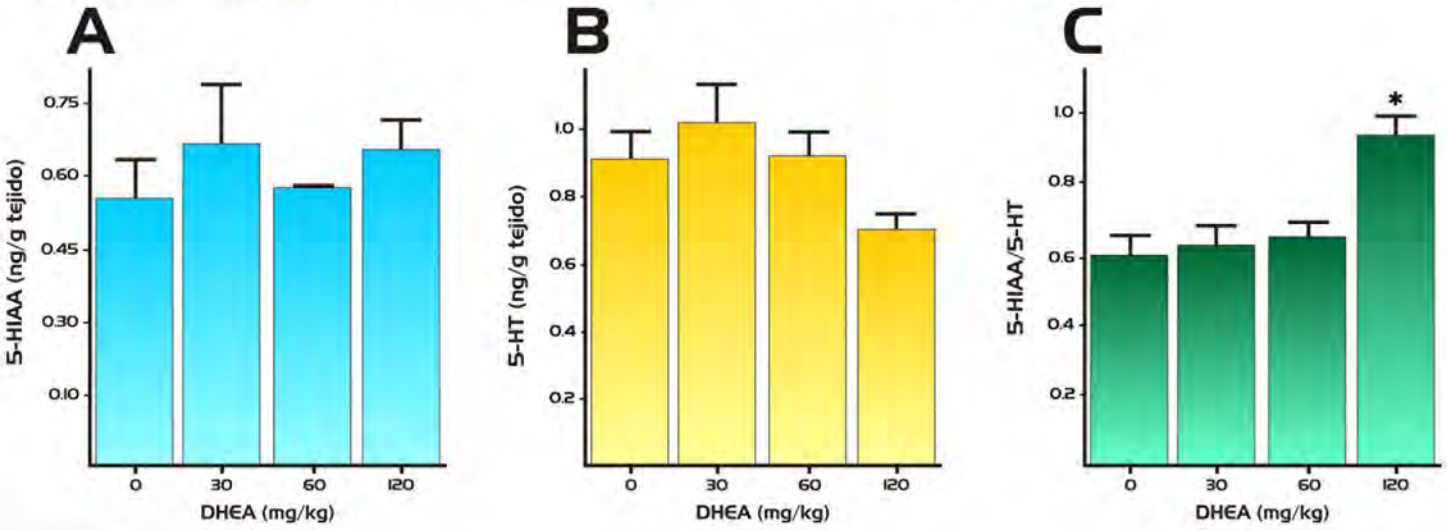
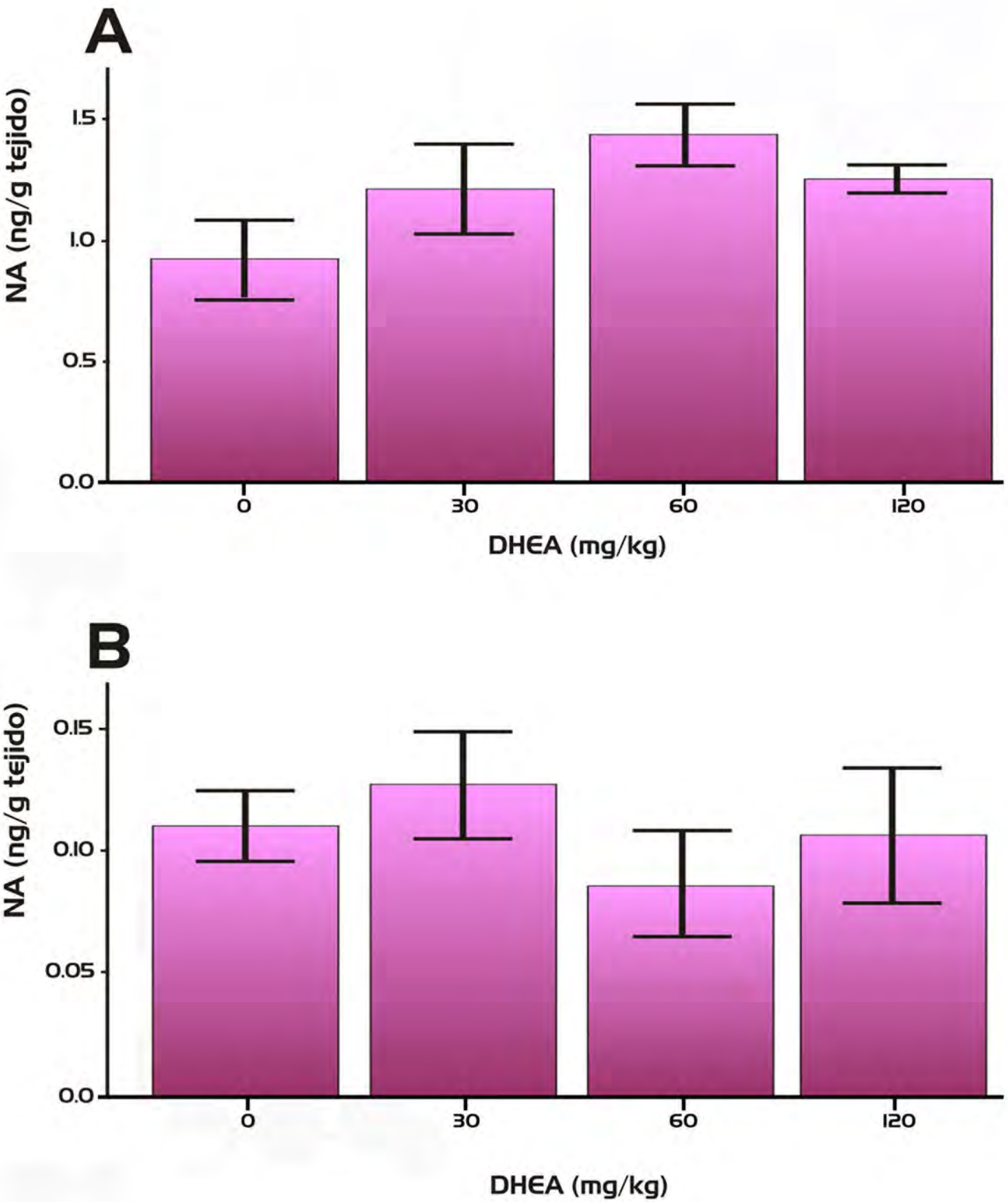
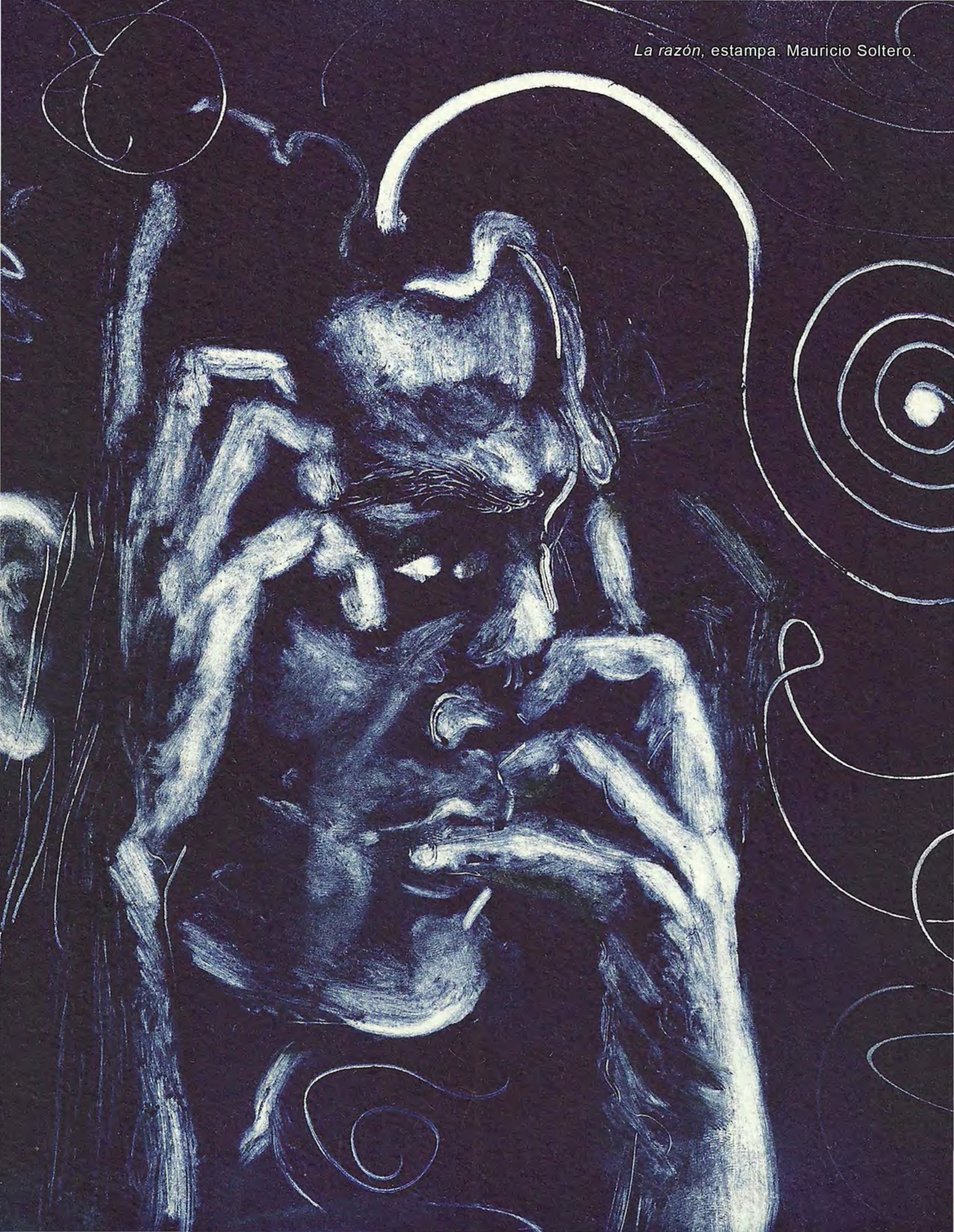


Figura 23. Efecto de la DHEA sobre el contenido de NA en el NAc (A) y el CS (B).





La razón, estampa. Mauricio Soltero.

Discusión

4.1. Contenido de dopamina y sus metabolitos

En el CS, el tratamiento con la DHEA redujo el contenido de DOPAC y los cocientes DOPAC/DA y (DOPAC+HVA)/DA a la dosis de 120 mg/kg sin alterar los contenidos de DA, HVA o el cociente HVA/DA (Fig. 16).

Los tres posibles efectos que explicarían estos resultados son que la DHEA reduzca la recaptura, la liberación, o el catabolismo del neurotransmisor.

La inhibición de la recaptura de DA no es el mecanismo más probable dado que, si bien se ha reportado que la DHEA puede inhibir la actividad del DAT (IC_{50} 52.5 µM) [48], dicho efecto, además de reducir el recambio de DA, aumentaría la actividad motora [219], lo cual contrasta con el efecto inhibidor de la DHEA sobre dicha conducta [34,38,175].

Es posible que la DHEA reduzca la liberación del neurotransmisor o la actividad de MAO; en este último caso, podría esperarse que, además de reducir el cociente DOPAC/DA, también redujera el contenido de HVA y aumentara el de DA, aunque nuestros resultados sólo muestran una disminución en el contenido de DOPAC y los cocientes de recambio del neurotransmisor (Fig. 16).

Sin embargo, es posible que la inhibición de MAO reduzca la disponibilidad del DOPAC sin alterar los niveles de DA y HVA; esto ha sido reportado para algunos fármacos de los que, junto con su efecto inhibidor de MAO, aumentan el contenido de 3-MT (producto de la actividad de la COMT, Figs. 8,24), reduciendo el nivel estriatal de DOPAC, mientras que los de DA y HVA permanecen sin cambio [252].

Dado que el cociente (DOPAC+HVA)/DA también disminuyó por tratamiento con la DHEA (120 mg/kg, Fig. 16), es posible que el esteroide reduzca el catabolismo global de la DA, aunque el posible efecto estimulador del esteroide sobre la actividad de la COMT no puede descartarse.

Respecto del contenido de DA, podría esperarse que la disminución de su recambio aumentara su nivel citosólico, pero esto podría inhibir la actividad de la TH [84], manteniendo su nivel sin cambios.

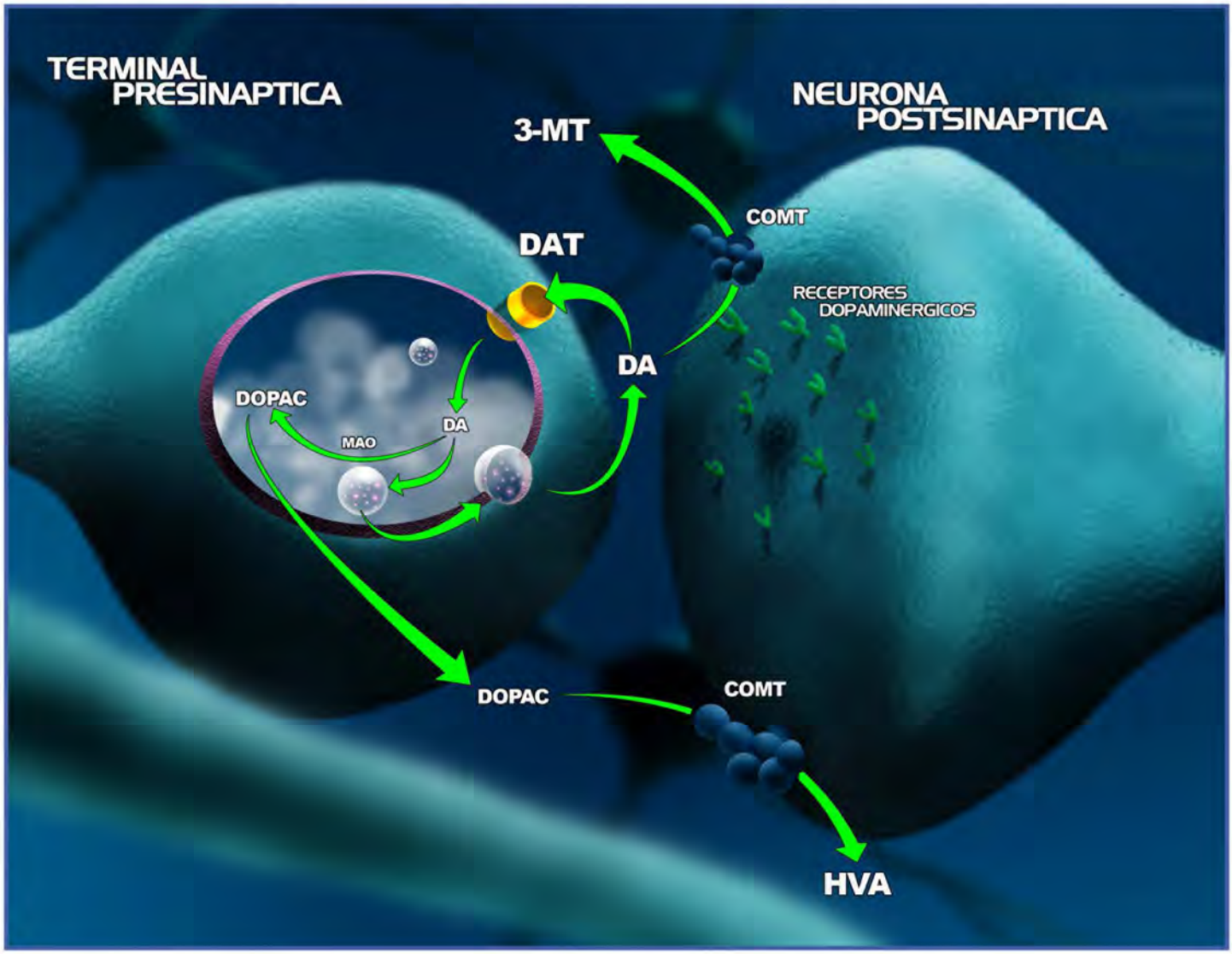
Cabe hacer notar que la dosis de 100 mg/kg de la DHEA no alteró el contenido estriatal de DA en un estudio previo realizado en condiciones experimentales similares a las nuestras [175]; en nuestro caso, no se observó ningún efecto a la dosis de 120 mg/kg (Fig. 16).

No se observaron efectos de la DHEA sobre el contenido de DA o de sus metabolitos en el NAc (Fig. 17); sin embargo, tanto el contenido de DOPAC como el cociente DOPAC/DA tendieron a disminuir a 30 y 60 mg/kg del esteroide.

Aún más, en el NAc y el CS, DOPAC, HVA, y el cociente (DOPAC+HVA)/DA, correlacionaron positivamente (Fig. 18), lo que sugiere que se modificaron de forma similar en ambas regiones.

También cabe considerar que el contenido de HVA y el cociente HVA/DA fueron mayores en el CS respecto del NAc; esto podría reflejar una mayor tasa metabólica de la DA en el CS y podría explicar la ausencia de un efecto de la DHEA en el NAc.

Figura 24. Relación entre el metabolismo de la DA, su liberación y su recaptura.



La microinyección intraestriatal de la DHEA (10 µg/2µl) en ratas hembra, redujo el contenido de DOPAC, y ligeramente el de HVA, sin alterar el de DA [48], cuatro días después de su administración.

En ese estudio, la administración de Test redujo el contenido tanto de DA como de DOPAC, posiblemente por disminución de la síntesis del neurotransmisor, mientras que el E2 no modificó el contenido de DA ni el de sus metabolitos [48].

De acuerdo con esos resultados, la disminución en el contenido de DOPAC inducida con la DHEA no depende de su metabolismo a hormonas sexuales.

En nuestro estudio, se observó que la administración de la DHEA modula el contenido estriatal de DOPAC a las 2 horas post-administración (Fig. 16), aunque la participación de los metabolitos de la DHEA en nuestras condiciones experimentales no puede descartarse por completo.

Es posible que el tratamiento con la DHEA por periodos largos module mecanismos diferentes respecto de sus efectos agudos; de hecho, algunos estudios han abordado este tema. El tratamiento crónico con la DHEA (2 mg/kg) aumenta el contenido de DA

en el NAc, mientras que tiende a disminuir los cocientes DOPAC/DA y HVA/DA respecto del grupo control [37].

A partir de la información reportada sobre este punto, generada de nuestros estudios [180] y los de Maayan et al. [37], puede sugerirse que la administración aguda del esteroide modula el metabolismo de la DA en el CS, mientras que el tratamiento crónico lo hace en el NAc.

Adicionalmente, debe considerarse que el daño selectivo a las neuronas dopaminérgicas con 6-hidroxidopamina, MPTP o su metabolito MPP^+, como modelo experimental de la PD, aumenta la fracción de DA liberada [242-244], el recambio del neurotransmisor [240,242-244] y la actividad de MAO [253,254].

Esto genera peróxido de hidrógeno durante la oxidación de la DA [92-97], el cuál puede provocar estrés oxidante por medio de la reacción de Fenton [92-94,96,97,115].

A través de este mecanismo, MAO puede potenciar el daño y favorecer la muerte de las neuronas dopaminérgicas, por lo que la inhibición del recambio del neurotransmisor por la DHEA podría estar involucrada en su mecanismo neuroprotector en los modelos experimentales de la PD [48,255,256].

4.2. Actividad de monoamino oxidasa

4.2.1. Estudios in vivo

En los experimentos previos, se observó que el tratamiento agudo con la DHEA (120 mg/kg) redujo el recambio de DA en el CS (Fig. 16) [180].

El recambio de la DA depende de su liberación y recaptura, así como de la actividad de MAO (Fig. 24); por esto, entre otras hipótesis, puede sugerirse que el esteroide modula la actividad de la enzima.

En nuestro estudio, se observó un efecto inhibidor de la DHEA (120 mg/kg) sobre la actividad total de MAO en el NAc (Fig. 19).

Se ha reportado un efecto similar después de un tratamiento crónico a una dosis más baja (30 mg/kg) [183], la cual no presentó efecto en nuestras condiciones experimentales (Fig. 19).

El estudio de Kumar et al. [183] mostró que la DHEA inhibe el aumento en la actividad total de MAO asociada al envejecimiento, en homogenados y sinaptosomas de los hemisferios cerebrales, lo cual sugiere que el esteroide da lugar a una disminución generalizada de la actividad enzimática en diferentes regiones.

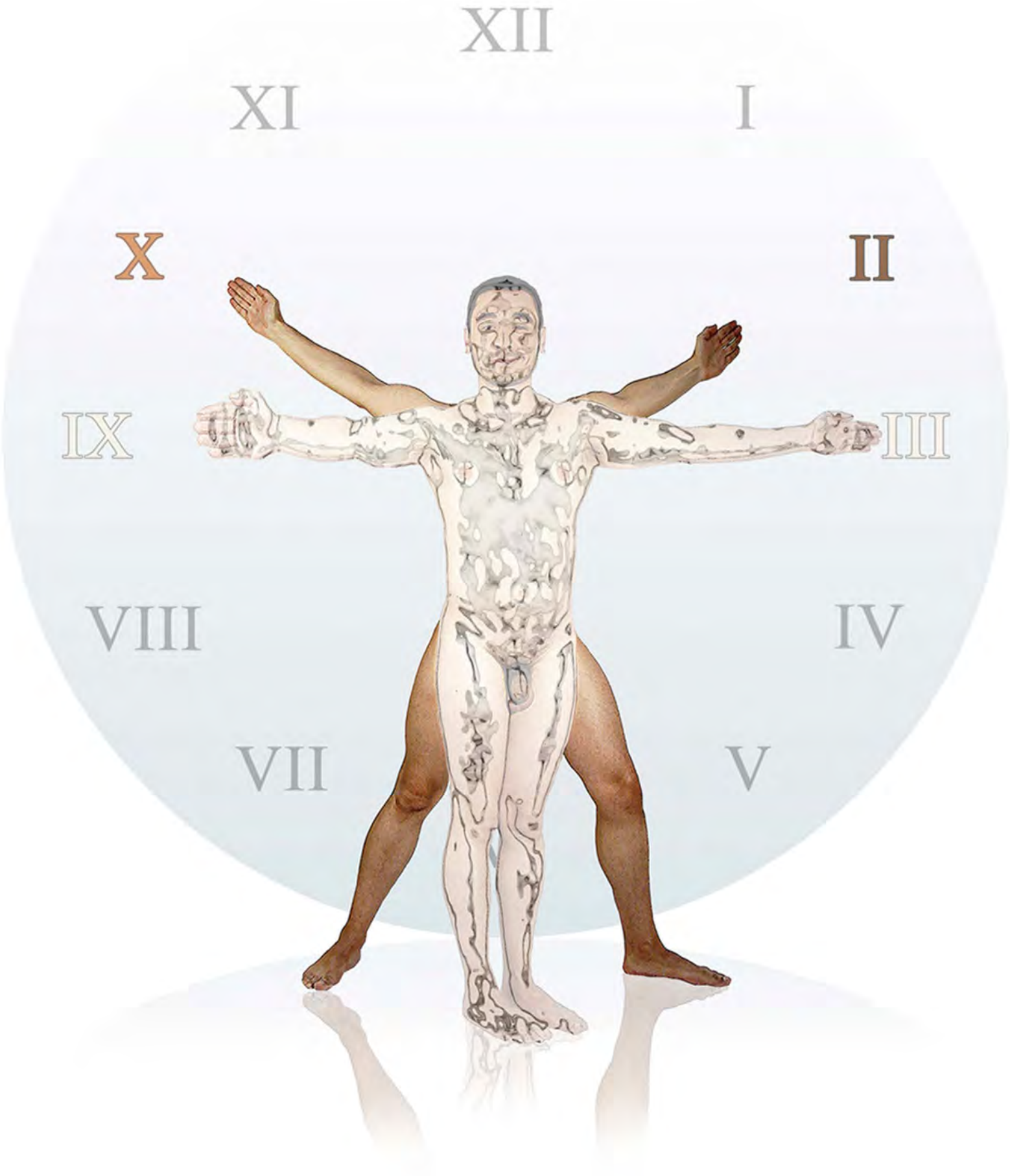
Nuestro estudio complementa dichos resultados mostrando que el efecto agudo de la DHEA sobre la actividad de MAO no es el mismo en todas las regiones cerebrales, ya que disminuye la actividad total de MAO en el NAc pero no en el CS, in vivo (Fig. 19).

Sin embargo, nuestros resultados no descartan que el esteroide también inhiba la actividad de la enzima en otras regiones, provocando así una disminución significativa de la actividad enzimática en los hemisferios cerebrales cuando se analizan completos.

Además, el esquema de tratamiento (agudo [251] o crónico [183]) podría explicar las diferencias entre los estudios.

Determinar el efecto de la DHEA en los sistemas dopaminérgicos de otras regiones cerebrales requiere estudios adicionales.

Es posible que la DHEA inhibiera la actividad de MAO en el CS por algún



Reloj Biológico, inspirado en el *Hombre de Vitruvio* de Leonardo Da Vinci. Idea original: José Luis Bueno, Iván Pérez-Neri; Fotografía: José Luis Bueno; Edición: Enrique Chávez Esparza, José Luis Bueno.

mecanismo reversible, que no tolerara la desintegración del tejido para el ensayo de actividad.

Sin embargo, como el efecto inhibidor de la inyección i.p. de la DHEA sobre MAO en el NAc se observó después de la homogenización del tejido cerebral para el ensayo de actividad (Fig. 19), esto sugiere que el efecto del esteroide se mantiene después de la desintegración del tejido.

Queda pendiente determinar si dicho efecto involucra una modificación permanente de la enzima.

En los estudios in vivo, se observó una tendencia de disminución en las actividades de MAO A y MAO B, dando una disminución en la actividad total de la enzima en el NAc (Fig. 19).

Ambas isoformas de MAO tendieron a disminuir a la dosis de 120 mg/kg de la DHEA, lo que sugiere que podrían ser moduladas por el esteroide a través de un mecanismo común.

Nuestros resultados sugieren que el efecto inhibidor de la DHEA sobre el recambio de la DA en el CS (Fig. 16) no está mediado por la inhibición de MAO (Fig. 19), dado que el esteroide no inhibe la enzima en esta región, por lo que podría reflejar una disminución en la liberación del neurotransmisor.

Por otro lado, los resultados sugieren que la inhibición de la actividad total de MAO en el NAc (Fig. 19) no afecta al metabolismo de la DA (Fig. 17), por lo que podría involucrar a otras monoaminas.

4.2.2. Estudios in vitro

A partir de los resultados de nuestros experimentos in vivo, faltaba determinar si el esteroide inhibe la actividad de MAO en el NAc al interactuar directamente con la enzima.

Para evaluar esta hipótesis, homogenados de tejido cerebral fueron preincubados con la DHEA para determinar su efecto sobre la actividad de la enzima.

La DHEA, en niveles micromolares, inhibió las actividades de MAO A y MAO B, así como la actividad total de la enzima, de forma dependiente de la concentración del esteroide (Fig. 20).

Las IC_{50} estimadas en nuestras condiciones experimentales deben ser consideradas como preliminares, debido al tamaño de muestra para este estudio (n=3); sin embargo, dichos valores son similares a los que se han reportado para el efecto inhibidor de la DHEA sobre la actividad de la glucosa 6-fosfato deshidrogenasa [257-260].

Además, cabe hacer notar que la DHEA inhibió a MAO A en mayor proporción que a MAO B (Fig. 20), lo que concuerda con el efecto antidepresivo del esteroide, el cuál también ocurre con inhibidores selectivos de MAO A [92,96].

La tendencia de aumento de la actividad de MAO a la concentración de 1 µM de la DHEA respecto de la actividad a 100 nM (Fig. 20), sugiere que el esteroide podría aumentar la actividad de la enzima a concentraciones bajas.

Sin embargo, debido al tamaño de muestra en nuestro experimento (n=3), esta hipótesis requiere confirmación experimental.

De forma similar, el aumento aparente en la actividad de MAO a la concentración de 1 mM de la DHEA respecto de la actividad a 100 µM, podría estar afectado por la presencia del precipitado que se formó a esa concentración del esteroide.

Nuestros resultados sugieren que la DHEA modula a las dos isoformas de MAO al interactuar directamente con la enzima; de este modo, el esteroide inhibió la actividad de MAO en el CS in vitro (Fig. 20) aunque no tuvo efecto in vivo (Fig. 19).

Es posible que el esteroide alcance diferentes concentraciones en el NAc y el CS in vivo, generando resultados distintos respecto de la inhibición de MAO.

Más aún, dado que solo se observó una tendencia de disminución en las actividades de MAO A y MAO B en el NAc in vivo (Fig. 19), es posible que la DHEA no se acumule en concentración suficiente, a nivel cerebral, en nuestras condiciones experimentales.

A pesar de la estructura lipofílica del esteroide, su difusión a través de la barrera hematoencefálica podría estar limitada por su unión a proteínas como albúmina y la globulina de unión a hormonas sexuales.

El hecho de que la concentración de la DHEA en el líquido cefalorraquídeo humano represente solo el 5% de su concentración plasmática [261] apoya esta hipótesis.

En nuestros estudios, no se observó en el CS ningún efecto de la DHEA en la actividad de MAO A o la de MAO B in vivo (Figs. 19), lo que sugiere que la inhibición de MAO no es el principal mecanismo involucrado en el efecto del esteroide sobre el recambio de DA, como observamos previamente (Fig. 16) [180].

En cambio, dicho efecto podría involucrar a la liberación del neurotransmisor (Fig. 24); la DHEA puede inhibir la liberación estriatal de DA por activación del receptor σ_1 dado que los agonistas de este receptor inhiben la liberación del neurotransmisor inducida por NMDA y por K^+, en el CS y el NAc [262,263], y la DHEA es un agonista del mismo [264-266].

Como la inhibición de MAO tiene efecto neuroprotector contra la toxicidad de MPTP y el MPP^+ [93,114], nuestros resultados sugieren que este mecanismo podría estar involucrado en el efecto protector de la DHEA en modelos experimentales de la PD [48,255,256].

Otros mecanismos protectores de la DHEA, como antioxidante, antiapoptótico y antiexcitotóxico, también podrían estar involucrados [27,183,267-270].

El efecto de la DHEA en esos modelos de la PD, se ha observado varios días después de una administración única del esteroide [48] o después de su administración repetida [255]; falta determinar si la DHEA inhibe a MAO en el CS en esas condiciones experimentales.

De hecho, el tratamiento crónico con la DHEA redujo la actividad total de MAO en los hemisferios cerebrales de acuerdo con un estudio previo [183], lo que podría contribuir a su efecto neuroprotector.

Con respecto al efecto antidepresivo del esteroide, cabe considerar que los inhibidores de MAO generan dicho efecto [116,117] al igual que la DHEA (Fig. 20) [271-273].

Por esto, la inhibición de MAO por la DHEA en el NAc podría estar involucrada en su efecto antidepresivo.

Los inhibidores selectivos de MAO B son los únicos fármacos que han mostrado un efecto neuroprotector en estudios clínicos para la PD [274], lo que sugiere que la inhibición de MAO B es suficiente para reducir o retrasar la neurodegeneración en esta enfermedad.

Por todo esto, puede considerarse que la inhibición de las dos isoformas de MAO por la DHEA podría, además de su efecto

antidepresivo, ser una alternativa terapéutica en la PD.

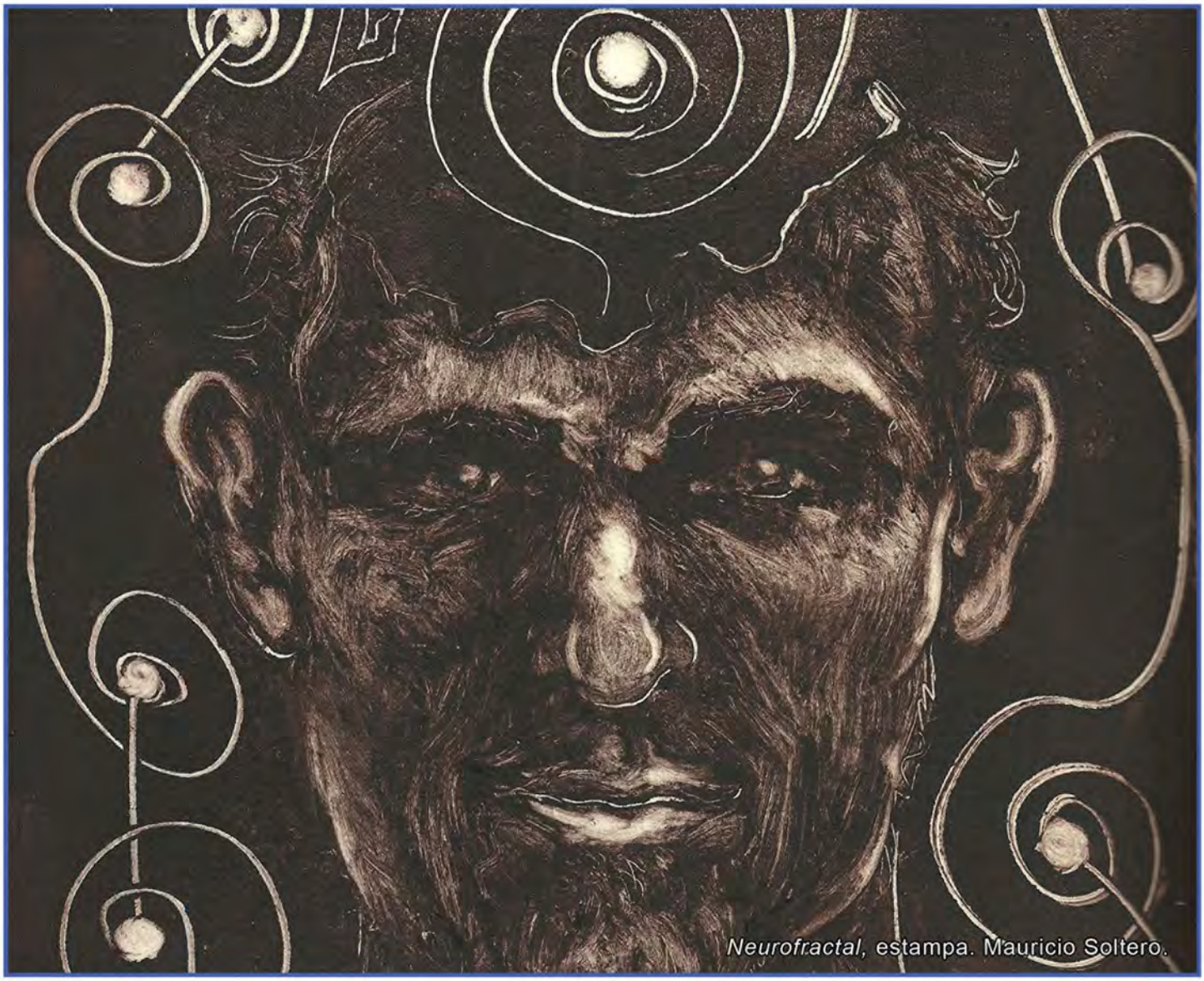
4.4. Contenido de serotonina y noradrenalina

Cabe hacer notar que el efecto inhibidor de la DHEA sobre la actividad de MAO en el NAc (Fig. 19), no coincide con la ausencia de efecto del esteroide sobre el recambio de DA en esta misma región (Fig. 17).

Dado que MAO participa en el metabolismo de otras monoaminas, analizamos también el contenido y recambio de 5-HT y NA, bajo la hipótesis de que la DHEA aumenta el contenido y/o reduce el recambio de alguno de estos neurotransmisores en el NAc.

5-HT tendió a disminuir tanto en el CS (Fig. 21B) como en el NAc (Fig. 22B) mientras que su cociente de recambio aumentó en ambas regiones (Figs. 21C,22C).

En cambio, el contenido de NA tendió a aumentar en el NAc, pero no así en el CS (Fig. 23), lo que sugiere que el efecto inhibidor de la DHEA sobre la actividad de MAO (Fig. 19) está asociado con el metabolismo de este neurotransmisor. ■



Neurofractal, estampa. Mauricio Soltero.

Conclusiones

Capítulo 5

Nuestros resultados sugieren que la DHEA reduce la liberación de DA en el CS, la cuál en exceso es neurotóxica [80] y está asociada con la neurodegeneración en la PD [240,242-244].

Adicionalmente, esta disminución puede reducir también la degradación del neurotransmisor y la generación de ROS por actividad de MAO [92-94,96,97,114].

Esto, junto con la inhibición de MAO B, puede estar involucrado en el efecto neuroprotector de la DHEA en modelos experimentales de la PD [48,255,256].

La DHEA también podría aumentar la liberación de 5-HT en el CS y el NAc.

Además, el esteroide podría estimular la neurotransmisión noradrenérgica al inhibir a MAO A en el NAc.

Estos dos mecanismos podrían estar involucrados en el efecto antidepresivo de la DHEA, dado que tanto los inhibidores selectivos de MAO A [92,96], como los inhibidores de la recaptura de NA y de 5-HT, son antidepresivos [275].

Por lo anterior, es posible sugerir que la DHEA, por su acción sobre los sistemas monoaminérgicos, por sus efectos neuroprotector y antidepresivo, sea una alternativa de tratamiento para reducir tanto la depresión como la neurodegeneración en la PD.

To work, grabado. Mauricio Soltero.

Del otro pulsar, estampa. Mauricio Soltero.

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Review article

Modulation of neurotransmitter systems by dehydroepiandrosterone and dehydroepiandrosterone sulfate: Mechanism of action and relevance to psychiatric disorders

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Abstract

Dehydroepiandrosterone (DHEA) is synthesized in the brain and several studies have shown that this steroid is a modulator of synaptic transmission. The effect of DHEA, and its sulfate ester DHEAS, on glutamate and GABA neurotransmission has been extensively studied but some effects on other neurotransmitter systems, such as dopamine, serotonin and nitric oxide, have also been reported. This review summarizes studies showing the effect of DHEA and DHEAS on neurotransmitter systems at different levels (metabolism, release, reuptake, receptor activation), as well as the activation of voltage-gated ion channels and calcium homeostasis, showing the variety of effects that these steroids exert on those systems, allowing the discussion of its mechanisms of action and its relevance to psychiatric disorders.
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Keywords: Anxiety; Cerebral blood flow; Major depressive disorder; Mood; Schizophrenia

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Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin; CSF, cerebrospinal fluid; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; DOPAC, dihydroxyphenylacetic acid; eNOS, endothelial nitric oxide synthase; ER, estrogen receptor; GABA, γ-aminobutyric acid; HVA, homovanillic acid; LH, lateral hypothalamus; MAO, monoamine oxidase; NAc, nucleus accumbens; NO, nitric oxide; NOS, NO synthase; NOx, nitrite plus nitrate; PREGS, pregnenolone sulfate; PVN, paraventricular nucleus of the hypothalamus; TH, tyrosine hydroxylase; TPH, tryptophan hydroxylase; VMH, ventromedial nucleus of the hypothalamus.

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1. Introduction

Dehydroepiandrosterone (DHEA) has been found in brain tissue independently of its peripheral origin (Robel and Baulieu, 1985) and the enzymes required for DHEA biosynthesis have also been found in the brain (Compagnone et al., 1995a,b; Compagnone and Mellon, 2000; Mellon et al., 2001; Strömstedt and Waterman, 1995), both in astrocytes (King et al., 2002; Zwain and Yen, 1999a,b) and neurons (Hojo et al., 2004; Shibuya et al., 2003; Zwain and Yen, 1999a,b). Although the brain synthesis of DHEA in the adult nervous system awaits further investigation, this steroid might accumulate in the brain coming from peripheral tissues. Thus, it could be suggested that DHEA might exert important functions in the nervous system. Indeed, it has been reported that the steroid, and its sulfate ester (DHEAS) modulate neuronal death and survival (Correa et al., 2003; Kaasik et al., 2003; Kurata et al., 2004; Shin et al., 2001; Xilouri and Papazafiri, 2006), brain development (Compagnone and Mellon, 1998), cognition (Flood et al., 1992; Frye and Lacey, 1999; Migues et al., 2002), behavior (Fedotova and Sapronov, 2004; Haug et al., 1989; Maayan et al., 2006; Melchior and Ritzmann, 1994; Nicolas et al., 2001) and is associated to several psychiatric disorders, in some cases as a pathophysiological mediator and in some others as a therapeutic target. The biosynthesis and metabolism of DHEA is illustrated in Fig. 1.

The effects of DHEA and DHEAS on the nervous system are in part mediated by the modulation of several neurotransmitter systems, such as glutamate and γ-aminobutyric acid (GABA), but some studies regarding dopamine and serotonin (5-HT) neurotransmitter systems, as well as nitric oxide biosynthesis and ion channel function, have also been reported. The effect of these steroids on other neurotransmitter systems is beyond the scope of this review.

It has been reported that DHEA and DHEAS modulate the release (Charalampopoulos et al., 2005; Derbez et al., 2002; Murray and Gillies, 1997) and metabolism (Catalina et al., 2001; Garcia de Yebenes et al., 1995; Pham et al., 2000; Porter et al., 2005; Tomas-Camardiel et al., 2002) of monoamines, as well as the activation of both dopamine (Catalina et al., 2002; Dong et al., 2007; Monnet, 2002; Suárez et al., 2005) and 5-HT (Volontè et al., 1995) receptors. Also, DHEA has been shown to modulate glutamate release (Lhullier et al., 2004) and the activation and expression of both glutamate (Bergeron et al., 1996; Chen et al., 2006a,b; Gonzalez-Alvear and Werling, 1994; Wen et al., 2001) and GABA receptors (Demirgören et al., 1991; Hansen et al., 1999; Huang and Dillon, 2002; Le Foll et al., 1997; Majewska et al., 1990; Park-Chung et al., 1999; Sullivan and Moenter, 2003; Xilouri and Papazafiri, 2006).

DHEA may exert its effects through both genomic and nongenomic mechanisms, activated by the steroid itself or by some of its metabolites. In some cases the effects of its metabolites are similar, but in other cases are different, than those exerted by DHEA. This review summarizes studies showing a modulatory effect of DHEA, and also DHEAS, on neurotransmitter systems, discussing its possible mechanisms of action and its relevance to psychiatric disorders.

2. Dopamine neurotransmission

2.1. Dopamine receptor activation

Some studies suggest that DHEA might modulate dopamine receptor activation (Fig. 2). DHEA-induced decrease in core body temperature is synergized by the dopamine D2 receptor antagonist haloperidol. This effect is independent on DHEA metabolism, since a non-metabolizable analogue (16α-chloroepiandrosterone) also decreases, while some of its metabolites (androstenediol, androstenedione and 17β–estradiol) do not alter, core body temperature (Catalina et al., 2002). Also, DHEA (but not androstenediol), while inactive by itself, antagonizes dopamine inhibition of prolactin release (Suárez et al., 2005) as D2 receptor antagonists do (Cosi et al., 2006), suggesting that DHEA reduces dopamine D2 receptor activation (Fig. 2).

Among the different DHEA metabolites some of them synergize, while others antagonize, D2 receptor activation (Fig. 2). 7α-Hydroxy-DHEA, like dopamine, inhibits prolactin release (Suárez et al., 2005) while DHEAS enhances D2 receptor antagonism by both spiperone and sulpiride (Monnet, 2002). Regarding D2 receptor activation, both DHEA and DHEAS lead to a similar inhibitory effect. From those results, it could be hypothesized that both DHEA and DHEAS inhibit (Fig. 2), while 7α-hydroxy-DHEA enhances, D2 receptor signaling. However, if this assumption holds true, the underlying mechanism for this effect is not likely to be the modulation of adenylate cyclase activity since DHEA does not modify forskolin-induced cAMP synthesis *in vitro* (Suárez et al., 2005).

The modulation of dopamine receptors, mediated by DHEA or its metabolites, may also depend on the receptor subtype involved. DHEAS (20 μM, 4 min) increases protein kinase A activity in synaptosomes, from both the hippocampus and the prelimbic cortex, by a mechanism that is dependent on both sigma1 and D1 receptors (Dong et al., 2007), suggesting that DHEAS increases D1 receptor activation through sigma1 receptors (Fig. 2). To the best of our knowledge, the effect of DHEA on D1 receptor activation remains to be determined.

2.2. Dopamine release

Both DHEA and DHEAS have been shown to increase dopamine release (Fig. 2), but under different experimental conditions. DHEAS (10^{-7}–10^{-8} M) increases dopamine release in

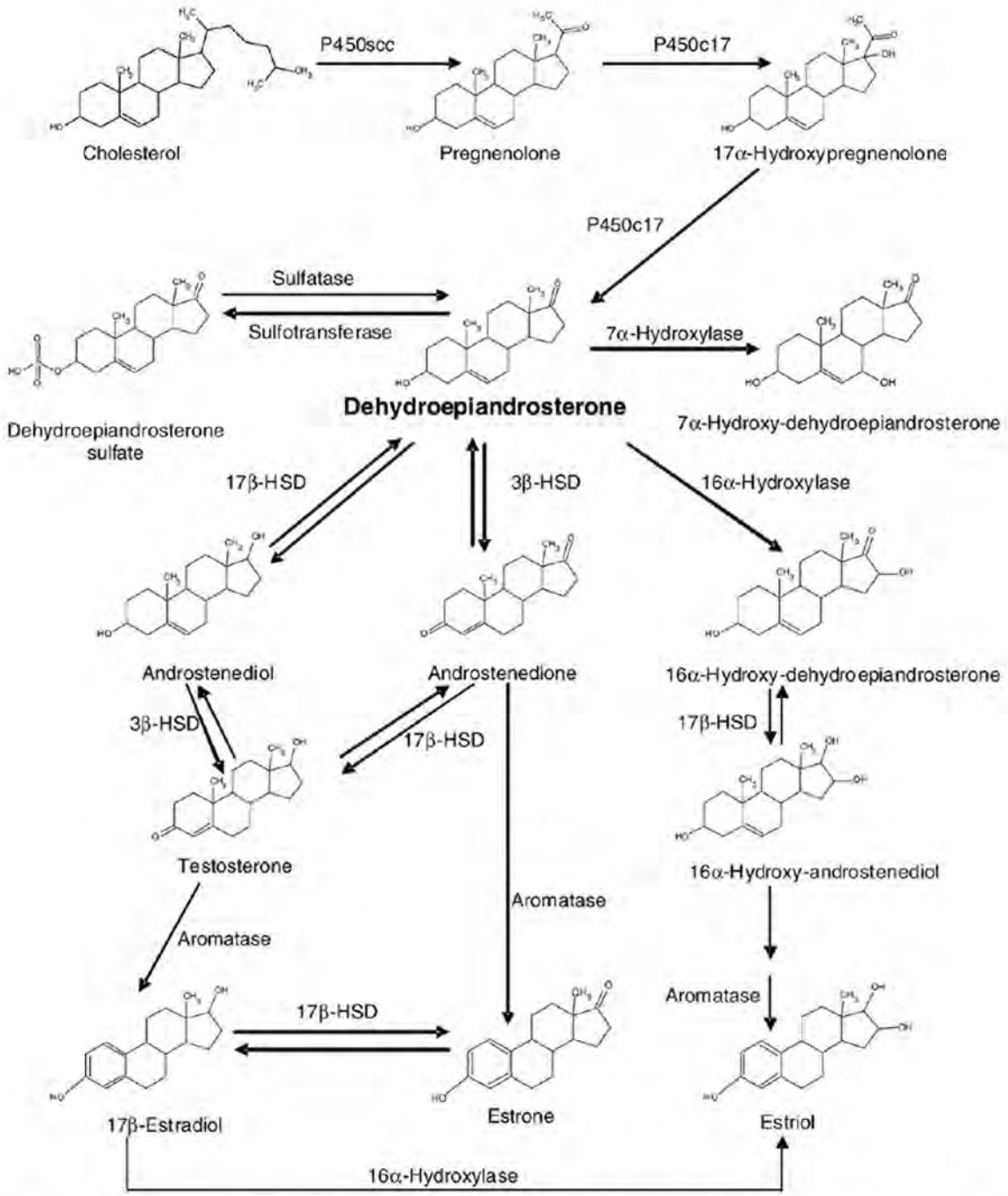

Fig. 1. Biosynthesis and metabolism of DHEA. 3β-HSD, 3β-hydroxysteroid dehydrogenase; 17β-HSD, 17β-hydroxysteroid dehydrogenase; P450scc, P450 side chain cleavage (desmolase).

hypothalamic cell cultures (Murray and Gillies, 1997) and PC12 cells (Charalampopoulos et al., 2005). DHEA also increases dopamine release in PC12 cells, but at earlier times than DHEAS (Charalampopoulos et al., 2005). So, both DHEA and DHEAS increase dopamine release, but probably through different mechanisms. The effect of DHEA on PC12 cells is not completely dependent on its metabolism since testosterone is inactive in this system (Charalampopoulos et al., 2005), although other androgens were not tested. DHEA stimulation of dopamine release in PC12 cells is transient, so it is lost after a 3-hour incubation period (Charalampopoulos et al., 2005); in contrast, DHEAS leads to a long-term increase in dopamine release that peaks at 36 h and is blocked by both tyrosine hydroxylase (TH) and aromatic amino acid decarboxylase inhibitors (Charalampopoulos et al., 2005) suggesting that this effect is dependent on dopamine synthesis. Thus, although both DHEA and DHEAS stimulate dopamine release in PC12 cells, different mechanisms are likely to be involved in each case.

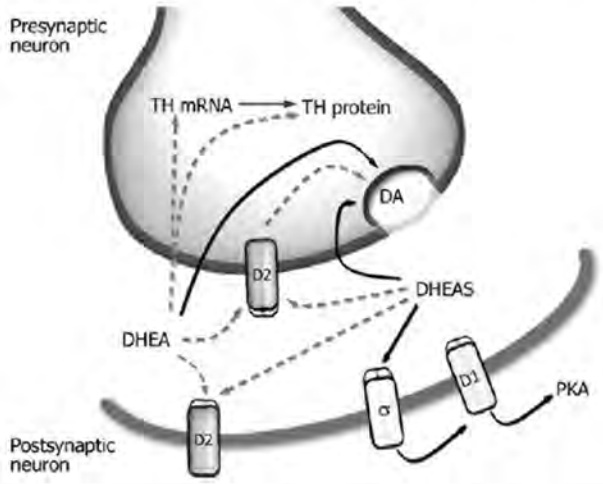

Fig. 2. Stimulatory (solid arrows) and inhibitory (dashed arrows) effects of DHEA and DHEAS on dopamine neurotransmission. DHEA increases dopamine release and might inhibit D2 receptors, while reduces TH expression. DHEAS increases dopamine release and stimulate D1 receptor activation through sigma receptors, but might inhibit D2 receptor activation. σ, Sigma receptor; D1, D1 receptor; D2, D2 receptor; DA, dopamine; PKA, protein kinase A; TH, tyrosyne hydroxylase.

The underlying mechanism for those effects remains to be elucidated, but it is possible that DHEA increases extracellular dopamine concentration through D2 receptor inhibition, as discussed above (Section 2.1, Fig. 2), and not likely through dopamine transporter blockade since DHEA only inhibits dopamine uptake at relatively high concentrations (IC_{50} 52.5 μM) (Tomas-Camardiel et al., 2002); regarding DHEAS, its effect on dopamine transporter has not been reported so far, so it can not be concluded if dopamine transport is involved in the effect of DHEAS on extracellular dopamine concentration.

According to this model, if DHEA and DHEAS inhibit D2 receptor activation (Section 2.1, Fig. 2) both steroids could exert modulatory effects on dopamine neurotransmission at presynaptic and postsynaptic sites; for example, DHEA (or DHEAS) administration could lead to increased dopamine release (Charalampopoulos et al., 2005; Murray and Gillies, 1997) through presynaptic D2 receptor blockade, and to reduced motor activity (Fedotova and Sapronov, 2004; Melchior and Ritzmann, 1994; Nguyen et al., 1999) through postsynaptic D2 receptor blockade (Fig. 2). However, to support this hypothesis, the effect of DHEAS on locomotor activity awaits to be elucidated.

Along with the possible inhibition of presynaptic D2 receptors (Section 2.1, Fig. 2), DHEA and DHEAS might also increase dopamine release through the sigma1 receptor since both steroids have been shown to act as agonists at this site (Maurice et al., 2001). Sigma receptor agonists increase amphetamine-induced dopamine release by reverse transport (Derbez et al., 2002), increase extracellular dopamine concentration in the striatum and nucleus accumbens (NAc), and (in contrast to the effect of DHEA) induce motor hyperactivity (Volontè et al., 1995). However, the role of sigma receptors on DHEA- and DHEAS-induced modulation of dopamine neurotransmission awaits further investigation. Furthermore, different mechanisms activated by DHEA or its sulfate ester might cooperatively stimulate dopamine release since sigma receptor agonists and D2 receptor antagonists show an additive effect to increase extracellular dopamine concentration in the NAc (Volontè et al., 1995). It is possible that DHEA increases dopamine release through presynaptic D2 receptor inhibition and/or sigma receptor activation, while reducing locomotor activity through postsynaptic D2 receptor blockade (Section 2.1, Fig. 2).

On the other hand, DHEA and DHEAS might also inhibit dopamine release indirectly through sigma receptor activation, since sigma receptor agonists reduce NMDA-induced dopamine release in the striatum (Gonzalez-Alvear and Werling, 1994). These studies show that sigma receptors may lead to both stimulatory and inhibitory effects on dopamine release depending on the mechanism involved, enhancing D2 receptor blockade-induced (Volontè et al., 1995), but reducing NMDA-induced (Gonzalez-Alvear and Werling, 1994), dopamine release.

2.3. Dopamine metabolism

DHEA modulates dopamine metabolism, although its effect depends on the experimental conditions tested and the brain region examined. DHEA administration at the dose of 25 mg/kg increases dopamine content in the lateral hypothalamus (LH) (Porter et al., 2005) while 75 mg/kg decreases dopamine content in the paraventricular nucleus of the hypothalamus (PVN) (Pham et al., 2000), 2 h after steroid administration in both studies. Doses of 25 (Nguyen et al., 1999) or 100 (Gillen et al., 1999) mg/kg DHEA do not alter the content of dopamine or its metabolites either in the occipital cortex, cerebellum, striatum or midbrain 2 h post-administration. Those results suggest that DHEA-induced increase in dopamine content at the dose of 25 mg/kg is region-dependent. In addition, it is possible that low doses of DHEA (25 mg/kg) increase, while high doses (75 mg/kg) decrease, dopamine content; however, the regional dependency for those effects can not be ruled out since 20 mg/kg DHEA does not alter dopamine content in neither the striatum nor the NAc 2 h post-administration (Pérez-Neri I, Méndez-Sánchez I, Montes S, Ríos C, unpublished results).

Similar to the early (2 h) effect of 25 mg/kg, DHEA increases dopamine content, while reducing dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) contents and turnover ratios, in the mice hypothalamus when administered in the diet for 1 day (Catalina et al., 2001) suggesting reduced monoamine oxidase (MAO) activity. Androstenedione leads to the opposite effect, reducing dopamine content in the ventromedial nucleus of the hypothalamus (VMH) in the same experimental model (Hargrave et al., 1997); however, other DHEA metabolites were not tested.

Four days after a single intrastriatal injection of DHEA (10 μg/2 μL) to female rats resulted in a significant decrease in DOPAC and a slight decrease in HVA levels, while dopamine content remained unchanged (Tomas-Camardiel et al., 2002). In this study, administration of some DHEA metabolites yielded different results; testosterone treatment led to a decrease in both dopamine and DOPAC contents, possibly due to reduced dopamine synthesis, while 17β–estradiol did not affect the content of neither dopamine nor its metabolites (Tomas-Camardiel et al., 2002). According to

those results, DHEA-induced decreased DOPAC content is not dependent on DHEA conversion to sex hormones.

Long-term DHEA treatment might lead to a decreased dopamine synthesis. DHEA, while it is inactive for up to 24 h in PC12 cells (Charalampopoulos et al., 2005), reduces the number of TH-immunopositive terminals in the striatum 4 days after a single intrastriatal administration (Tomas-Camardiel et al., 2002) and reduces TH mRNA in the arcuate nucleus of the hypothalamus when animals are treated for 2 days (Garcia de Yebenes et al., 1995). In contrast, DHEAS increases TH mRNA and protein levels as early as 8 h in PC12 cells (Charalampopoulos et al., 2005); thus, regarding TH expression, DHEA and DHEAS exert opposite effects.

2.4. Dopamine-related behavior

DHEA increases cocaine-induced place preference by a sigma receptor-dependent mechanism (Romieu et al., 2003), suggesting that sigma receptors stimulate some of the behavioral effects of cocaine. These results might be related to the stimulatory effect of sigma receptors on dopamine release as discussed on Section 2.2.

Also, sigma receptor antagonists reduce the hyperlocomotor (Katz et al., 2003; McCracken et al., 1999a,b) and rewarding (Katz et al., 2003; Romieu et al., 2003) effects of cocaine. Those results suggest a positive modulation of DHEA on dopamine neurotransmission through sigma receptors, in contrast to the inhibitory effect of this steroid on spontaneous locomotor activity (Fedotova and Sapronov, 2004; Melchior and Ritzmann, 1994; Nguyen et al., 1999), in turn suggesting reduced dopamine neurotransmission. It is possible that DHEA may reduce (locomotor activity) as well as increase (conditioned place-preference) some dopamine-related behavior.

From those biochemical and behavioral studies, it seems that DHEA and DHEAS may exert both stimulatory and inhibitory effects on dopamine neurotransmission. Two hypotheses might explain this apparent discrepancy: 1) that DHEA (and also DHEAS) inhibits dopamine signaling through inhibition of postsynaptic D2 receptors (Section 2.1, Fig. 2) while stimulating this system through sigma and/or (in the case of DHEAS) D1 receptors (Dong et al., 2007), or 2) that DHEA inhibits dopamine neurotransmission while stimulating cocaine-induced reinforcement and reward by non-dopaminergic mechanisms.

2.5. DHEA, DHEAS and schizophrenia

Dopamine neurotransmission is associated to the positive symptoms (delusions, hallucinations) of schizophrenia and it has been suggested that DHEA and DHEAS could be involved in the pathophysiology of this disorder. Plasma DHEA concentration was increased in both male and female schizophrenic patients compared to healthy subjects independently of antipsychotic treatment (di Michele et al., 2005). Although another study failed to find a significant difference in serum DHEA levels in male patients (Strous et al., 2004), this study found increased serum concentration of this steroid in female patients. Also, serum DHEAS has been reported to be increased in both male and female schizophrenic patients (Strous et al., 2004) although another study found this steroid to be increased only in males (Oades and Schepker, 1994). It is likely that DHEA accumulates in the nervous system of schizophrenic patients since blood and cerebrospinal fluid (CSF) levels of both DHEA and DHEAS are positively correlated (Guazzo et al., 1996) and the content of DHEA has been reported to be increased in the posterior cingulate cortex from those patients in a *post mortem* study (Marx et al., 2006).

DHEA and DHEAS could increase dopamine neurotransmission and, possibly exacerbate psychotic symptoms, since DHEA consumption has been associated to the development of episodes of mania (Dean, 2000; Kline and Jaggers, 1999; Markowitz et al., 1999; Vacheron-Trystam et al., 2002), which are in turn associated to increased dopamine release in the ventral striatum (Drevets et al., 2001). The psychostimulating-like effect of DHEA has been observed after administration of high doses (up to 300 mg/day) during several weeks or months (over 3 months) (Markowitz et al., 1999).

Thus, since DHEA and DHEAS may both enhance or inhibit dopamine neurotransmission, it is not completely clear if DHEA could be involved in the pathophysiology of schizophrenia, if this steroid could be a potential endogenous antipsychotic or even an unrelated epiphenomenon. In this regard, it should be noted that the serum DHEA/cortisol ratio was inversely correlated to the Brief Psychiatric Rating Scale score in schizophrenic patients (Harris et al., 2001), independently of antipsychotic treatment, suggesting that increased serum DHEA compared to cortisol is associated to reduced psychopathology symptoms. The beneficial effect of DHEA administration against negative and other symptoms (anxiety and depression) in schizophrenic patients is discussed in the following sections; thus, it could be suggested that DHEA could be a potential therapeutic agent for schizophrenia.

3. Glutamate neurotransmission

DHEA (100 nM) increases basal, but not depolarization-induced, glutamate release from forebrain synaptosomes while glutamate uptake remains unaltered (Lhullier et al., 2004). Enhanced glutamate release would be expected to increase receptor activation, and in this regard, different studies show that both DHEA and DHEAS increase NMDA receptor activation through their interaction with the sigma receptor, as discussed below (Fig. 3).

DHEAS administration (20 mg/kg, 7 days) increases NMDA receptor-mediated calcium influx (Chen et al., 2006b) (Fig. 3) and long-term potentiation in the hippocampus by a sigma1 receptor-dependent mechanism (Chen et al., 2006a); an effect that is not likely to be mediated by DHEAS conversion to estrogens since 17β–estradiol (10 μM and above) inhibits NMDA-dependent increase in intracellular calcium concentration in cultured hippocampal neurons (Kurata et al., 2001, 2004) (Fig. 3). In addition to the effect of DHEAS, DHEA (0.1 mg/kg, iv) increases the response of hippocampal CA3 neurons to NMDA; this effect lasts for at least 40 min and is dependent on both $G_{i/o}$ proteins and sigma receptors (Bergeron et al., 1996).

Also, DHEAS administration (30 mg/kg twice a day for 5 days) increases [^{3}H]MK-801 binding sites at the NMDA receptor in the

hippocampus and cortex (Wen et al., 2001); so, this steroid may also modulate NMDA receptor expression.

As a consequence of the modulation of glutamate neurotransmission, DHEA (1 nM) increases neurite growth and intracellular calcium concentration (Compagnone and Mellon, 1998), while DHEAS increases the proconvulsant effect of pentylenetetrazol (Reddy and Kulkarni, 1998b), by NMDA receptor-mediated mechanisms.

Those results consistently show that both DHEA and DHEAS, in contrast to the inhibitory effect of 17β–estradiol, positively modulate glutamate neurotransmission (Fig. 3).

However, in contrast to the stimulatory effect of DHEA on NMDA receptor activation in the hippocampus, this steroid might inhibit glutamate neurotransmission through the sigma receptor in other brain regions. Sigma receptor agonists reduce NMDA-induced dopamine release in the striatum (Gonzalez-Alvear and Werling, 1994). These opposing effects might reflect different coupling mechanisms between sigma and NMDA receptors, or different sigma receptor subtypes, in the striatum compared to the hippocampus.

The enhancing effect of DHEA on glutamate neurotransmission might reduce glutamate hypofunction and improve negative symptoms in schizophrenia; some studies support this hypothesis. DHEA administration to schizophrenic patients (25–100 mg/day, 6 weeks), along with antipsychotic medication, significantly reduced negative symptoms (Strous et al., 2003). In a different study, serum DHEA and DHEAS concentrations were positively correlated to working and semantic memory, respectively, in schizophrenic patients (Harris et al., 2001). Also, both plasma DHEAS concentration and DHEAS/cortisol ratio were positively correlated to performance on several cognitive and memory tasks in patients with schizophrenia (Silver et al., 2005).

Thus, it is possible that DHEA and DHEAS improve negative symptoms by reducing glutamate hypofunction in schizophrenia. The potential role of nitric oxide (NO) in this effect is discussed in the next section.

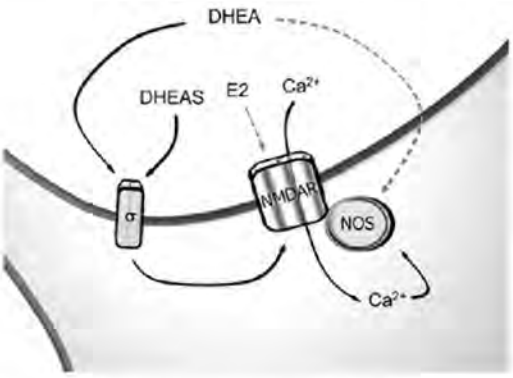

Fig. 3. Stimulatory (solid arrows) and inhibitory (dashed arrows) effects of DHEA and DHEAS on glutamate neurotransmission and NMDA receptor-dependent NO synthesis. Both DHEA and DHEAS stimulate NMDA receptor activation and Ca^{2+} influx through sigma receptors. However, DHEA reduces NMDA receptor-induced NOS activity. 17β–Estradiol is not likely to be responsible for the DHEA-mediated stimulation of NMDA receptors since this metabolite inhibits NMDA receptor-induced Ca^{2+} influx. σ, Sigma receptor; E2, 17β–estradiol; NMDAR, NMDA receptor; NOS, nitric oxide synthase.

Although plasma DHEAS levels are decreased in patients with Alzheimer's disease compared to healthy controls (Hillen et al., 2000), the association of the steroid to cognitive function has failed to be replicated in elderly subjects as measured by the correlation between the levels of the steroid and cognitive scale scores (Carlson and Sherwin, 1999); however, among patients with Alzheimer's disease, those with higher plasma DHEAS levels perform better in some cognitive tasks compared to the patients with lower levels of the steroid (Carlson et al., 1999).

4. Nitric oxide biosynthesis

NO is a modulator of neurotransmitter systems (Centonze et al., 1999; Trabace and Kendrick, 2000; West and Grace, 2000). NO is important for cognitive function (García-Arenas et al., 2004; Prast and Philippu, 2001) and cerebral blood flow regulation (Lavi et al., 2003), which are both impaired in schizophrenia (Bachneff, 1996; Honey and Fletcher, 2006). For those reasons, it should be considered that NO synthesis, in both neurons and endothelial cells, is important for the modulation of brain function; some studies regarding this issue are discussed below.

DHEA binds with high affinity (K_d=48.7 pM) to a membrane-bound G protein-coupled receptor in endothelial cells and activates NO synthase (NOS) activity at 1 nM when incubated for as short as 10 min (Liu and Dillon, 2002, 2004; Simoncini et al., 2003). The mechanism for this effect is independent on transcription, it is not likely to be due neither to DHEA conversion to sex hormones nor to activation of classical hormone receptors, and it is mediated by a G protein-coupled receptor (Simoncini et al., 2003). This binding to endothelial cell membranes is not displaced by some DHEA metabolites (DHEAS, androstenedione, 17β–estradiol and testosterone) or precursor (17α-hydroxypregnenolone) (Liu and Dillon, 2002), indicating a specific interaction with DHEA. As a consequence of NOS activation, DHEA increases nitrite plus nitrate (NOx) release and cGMP synthesis at 0.1 nM (Liu and Dillon, 2004). 17β–Estradiol (10–20 nM) leads to a similar increase on NOS activity by an estrogen receptor (ER)-dependent mechanism but antiestrogens do not alter DHEA-mediated stimulation of NOS activity (Liu and Dillon, 2002, 2004) showing that DHEA leads to a similar stimulating effect on NO synthesis through a different mechanism than 17β–estradiol.

DHEA (100 nM) increases endothelial NOS (eNOS) protein in cultured endothelial cells after 16 h of incubation with the steroid (Williams et al., 2004). This effect is not likely to be dependent on DHEA metabolites and is due to decreased eNOS protein turnover (Simoncini et al., 2003).

In addition, DHEAS administration to humans (200 mg, i.v.) increases plasma NOx concentration (Manabe et al., 1999), possibly through its conversion to DHEA since DHEAS itself, as well as androstenedione, (1 pM–1 μM) does not alter NOS activity in cultured endothelial cells (Liu and Dillon, 2004). Although DHEA is able to increase NOS activity independently of its conversion to estrogens, chronically administered DHEA and 17β–estradiol supplemented diets (0.3% for 10 weeks) increase plasma NOx concentrations by an ER-mediated mechanism

(Hayashi et al., 2000) suggesting that the chronic administration of DHEA might lead to an estrogen-mediated stimulation of NOS activity.

The NOS inhibitor L-NAME reduces DHEAS antiamnesic effect against both dizocilpine-induced and ageing-related learning impairment (Reddy and Kulkarni, 1998a), suggesting that DHEAS-induced increase in NO synthesis improves memory. It should be noted that DHEAS does not increase NOS activity in endothelial cells (Liu and Dillon, 2004) but its effect on other cell types (especially neurons) remains to be determined.

In addition to the DHEA-mediated stimulation of NOS activity, this steroid and its sulfate ester may modulate vascular function by additional mechanisms. Intra-arterial administration of DHEA (3 mg/kg) reverses chronic hypoxia-induced pulmonary artery hypertension by increasing calcium-activated potassium channel activity (Bonnet et al., 2003). DHEAS (1.5 μM) produces vasorelaxation in the rat aorta (Barbagallo et al., 1995) through activation of voltage-gated potassium channels (Gupte et al., 2002a). Finally, DHEAS (10 fmol) induces vasodilation by a histamine-dependent mechanism (Uchida et al., 2003). Those results suggest that DHEA and DHEAS may also modulate vascular function by NO-independent mechanisms.

On the other hand, some studies show that DHEA may also lead to vasoconstriction, possibly through inhibition of NO synthesis. DHEA infusion (1 mg/h) reduces coronary (Molinari et al., 2003), mesenteric, renal and ilial (Molinari et al., 2004) blood flow, and increases vascular resistance (Molinari et al., 2003, 2004) in anaesthetized pigs. Epiandrosterone (30 μM), a DHEA metabolite, reduces myocardial NADPH (NOS cofactor) and nitrite (NO product) contents (Gupte et al., 2002b); thus, the possible DHEA-induced inhibition of NO synthesis could be mediated through its conversion to epiandrosterone.

In contrast to the stimulatory effect of DHEA on NMDA receptor activation, 10 μM DHEA inhibits NMDA-induced NOS activity (Fig. 3) while inhibiting intracellular calcium rise only at high concentrations (60 μM) in hippocampal neurons (Kurata et al., 2004). These results suggest that, although DHEA stimulates NMDA receptor activation, it inhibits NOS activity by a mechanism that is not dependent on inhibition of NMDA-induced increased intracellular calcium concentration. Also, those results show that DHEA differentially modulates neuronal and endothelial NO synthesis.

It could be suggested that the modulatory effect of DHEA on vascular function might impact cerebral blood flow and, thus, influence brain function. It has been reported that regional cerebral blood flow is altered in schizophrenia (Bachneff, 1996), which may be associated to reduced NO biosynthesis. Actually, some studies have reported that NO synthesis is decreased in this disorder (Ramirez et al., 2004; Xing et al., 2002) and some authors have suggested that it could be associated to the negative symptoms of schizophrenia (Suzuki et al., 2003). Thus, it is possible that the stimulating effect of DHEA on NOS activity favors cerebral blood flow and ameliorates negative symptoms in schizophrenic patients. Also, since activation of NMDA glutamate receptors increases NOS activity and DHEA stimulate those receptors as discussed above, glutamate neurotransmission might be involved in the stimulatory effect of DHEA on NO biosynthesis. As discussed in Section 3, the therapeutic effect of DHEA administration against the negative symptoms of schizophrenia has already been reported.

5. 5-HT neurotransmission

Several effects of DHEA on 5-HT metabolism have been reported under different experimental conditions. 5-HT levels tended to decrease, while those of its metabolite 5-hydroxyindoleacetic acid (5-HIAA) are significantly decreased, in the hypothalamus of B6 mice fed with DHEA supplemented diets (0.45% w/w) for 7 days (Catalina et al., 2001) suggesting reduced 5-HT synthesis. DHEA (200 μg, icv) does not alter tryptophan hydroxylase (TPH) activity 90 min after administration (Singh et al., 1994) but a time course for this experiment remains to be evaluated.

In contrast, 5-HIAA levels are unchanged and 5-HT levels are increased in BDF1 mice with the same treatment as above (Catalina et al., 2001), and with a single injection of DHEA (100 mg/kg) to Zucker rats (Gillen et al., 1999), possibly due to reduced MAO activity mediated by DHEA in those strains. 5-HT content is also increased after 75 mg/kg DHEA in the VMH (Pham et al., 2000). Thus, several factors related to both animal strain and brain region seem to influence the effect of DHEA on 5-HT metabolism.

DHEA (200 mg/kg, ip) increases 5-HIAA content in the midbrain and decreases 5-HT levels in the cerebellum (Nguyen et al., 1999). Also, this steroid (25 mg/kg ip) increases 5-HIAA content in the LH, VMH and the raphe, and increase 5-HIAA/5-HT ratio in the PVN and raphe (Porter et al., 2005). DHEA-mediated increased 5-HT turnover may be due to some DHEA metabolites since androstenedione supplemented diets (0.6%, 1 day) increase 5-HIAA content and 5-HIAA/5-HT ratio in the LH, as well as 5-HIAA/5-HT ratio (when administered for 7 days) while reducing 5-HT content in the PVN (Hargrave et al., 1997).

Those studies show that DHEA and/or its metabolite androstenedione may both increase or decrease 5-HT synthesis and turnover at different doses and brain regions.

On the other hand, serum DHEA levels are positively correlated to 5-HT content in the hypothalamus of BDF1 mice (Catalina et al., 2001); this might reflect a stimulatory modulation of DHEA on 5-HT biosynthesis. DHEA (25 and 50 mg/kg) increases the effect of a 5-HT reuptake inhibitor (*d*-fenfluramine) on caloric intake (Gillen et al., 1999). Thus, the possible stimulatory effect of DHEA on 5-HT neurotransmission is not likely to be due to increased 5-HT release since DHEA (50 μg/kg/day, icv) does not alter the firing rate of dorsal raphe serotonergic neurons (Robichaud and Debonnel, 2005), although it could be related to the modulation of 5-HT reuptake.

Also, DHEA may modulate the activation of some 5-HT receptor subtypes. Sigma receptor agonists increase extracellular dopamine concentration in the NAc by a 5-HT_3 receptor-dependent mechanism (Volontè et al., 1995) suggesting that sigma receptor ligands stimulate 5-HT_3 receptor activation.

Some studies have suggested that 5-HT neurotransmission is involved in the pathophysiology of depressive disorders (Elhwuegi,

2004; Sobczak et al., 2002) and the therapeutic effect of some antidepressant drugs (Delgado et al., 1999). According to those studies, stimulation of this neurotransmitter system is expected to improve mood in depressed patients. As reviewed above, some studies suggest that DHEA might enhance 5-HT neurotransmission and this mechanism could be involved in the stimulatory effect of the steroid on mood.

Plasma DHEA concentration has been reported to be increased in depressed patients (Heuser et al., 1998) but its salivary levels were decreased in another study (Michael et al., 2000). In the case of DHEAS, increased salivary concentration has been reported in depressed patients (Assies et al., 2004). Again, changes of both DHEA and DHEAS blood concentrations are relevant to central nervous system function since those levels are positively correlated to the CSF concentrations of the steroids (Guazzo et al., 1996).

It is possible that DHEA (and perhaps DHEAS) acts as an endogenous antidepressant since salivary DHEA concentration is inversely correlated to Hamilton Depression Scale score in depressed patients (Michael et al., 2000). In placebo-controlled double-blind clinical trials, the administration of 50 mg/day of DHEA to men (Hunt et al., 2000) and women (Arlt et al., 1999) with adrenal insufficiency improves mood after 4 months of treatment. Also, DHEA administration to schizophrenic patients (25–100 mg/day, 6 weeks) reduces depressive symptoms (Strous et al., 2003). Administration of 30–90 mg/day of DHEA also led to an antidepressant effect compared to placebo after 6 weeks of treatment (Wolkowitz et al., 1999). High doses (90 mg/day for 3 weeks followed by 450 mg/day for another 3 weeks) also improve the mood of patients with dysthymia and depression (Bloch et al., 1999; Schmidt et al., 2005). DHEA (100–400 mg/day during an 8-week period) also led to a therapeutic effect against non-major depression in HIV patients (Rabkin et al., 2006).

However, some studies have failed to replicate those results (Arlt et al., 2001), but it should be noted that increased blood DHEAS levels are associated to an antidepressant response after DHEA treatment (Bloch et al., 1999; Rabkin et al., 2006); thus, the failure to increase DHEAS (and possibly DHEA) levels in some patients may be responsible for the absence of a clinical response.

6. GABA neurotransmission

Several studies have supported an inhibitory effect of both DHEA and DHEAS on $GABA_A$ receptor function. DHEAS inhibits [^{3}H]GABA binding to cortical and cerebellar membranes (Sousa and Ticku, 1997). Both DHEA and DHEAS, but not androstenedione, concentration-dependently inhibit GABA-stimulated ^{36}Cl uptake in several brain regions (El-Etr et al., 1998; Imamura and Prasad, 1998; Sousa and Ticku, 1997), while reversibly inhibiting currents mediated by $GABA_A$ receptors with an IC_{50} of 35 μM and 2.36–13 μM for DHEA and DHEAS, respectively (Demirgören et al., 1991; Hansen et al., 1999; Huang and Dillon, 2002; Le Foll et al., 1997; Majewska et al., 1990; Park-Chung et al., 1999; Sullivan and Moenter, 2003). Both steroids also reduce inhibitory postsynaptic potentials in hippocampal neurons (Meyer et al., 1999). The negatively charged group at C3 is important for this inhibitory activity (Park-Chung et al., 1999). 3α-Steroid sulfates are positive modulators of $GABA_A$ receptors (El-Etr et al., 1998; Le Foll et al., 1997; Maksay et al., 2003) while 3β–steroid sulfates are negative modulators (El-Etr et al., 1998) or inactive (Le Foll et al., 1997; Maksay et al., 2003). Other steroids such as pregnenolone sulfate (PREGS) also inhibit $GABA_A$ receptors but, in contrast to the effect of DHEAS, PREGS-mediated inhibition is not completely reversible (Le Foll et al., 1997). 17β–Estradiol inhibits $GABA_A$-mediated responses (IC_{50} 75 μM) in cultured hippocampal neurons, although at relatively high concentrations (Kurata et al., 2001); thus, estrogens might contribute to some extent to the inhibitory effect of DHEA and DHEAS in a cell type in which several metabolic reactions occur leading to 17β–estradiol synthesis from DHEA.

As a consequence of those effects, both DHEA and DHEAS inhibit $GABA_A$-mediated increased intracellular calcium concentration in cultured hippocampal neurons (Kurata et al., 2001); also, DHEAS (150 μg/kg) blocks the inhibitory effect of muscimol (a $GABA_A$ receptor agonist) on rapid tolerance to ethanol (Barbosa and Morato, 2001). However, the inhibitory effect of DHEAS on $GABA_A$ receptor may differ between brain regions, possibly depending on the subunit composition of the chloride channel, since DHEAS (0.01–1 μM) does not alter 3α,5α-tetrahydroprogesterone (allopregnanolone)-mediated inhibition of depolarization-induced gonadotropin-releasing hormone release, which is $GABA_A$ receptor-dependent (Calogero et al., 1998).

DHEAS concentration-dependently inhibits [^{3}H]TBPS binding to the picrotoxin site in $GABA_A$ receptors (Sousa and Ticku, 1997) suggesting that DHEA might bind to this site. However, DHEAS also inhibit $GABA_A$ receptors containing non-functional picrotoxin sites [IC_{50} 2.6 μM (Shen et al., 1999)] indicating that this site is not necessary for the inhibitory effect of the steroid on $GABA_A$ receptors. Some studies have suggested the existence of two binding sites for DHEAS at the $GABA_A$ receptor; high and low affinity sites with apparent dissociation constants of 0.21 nM and 15 μM, respectively (Hansen et al., 1999).

However, some studies suggest that DHEA and its sulfate ester might stimulate GABA neurotransmission. $GABA_A$ receptor antagonist flumazenil blocks the anxiolytic effect of DHEA (6 mg/kg) in the staircase paradigm (Weizman et al., 2001), and bicuculline blocks the neuroprotective effect of DHEAS (50 mg/kg, iv) against reversible spinal cord ischemia (Lapchak et al., 2000). The mechanism for the possible stimulating effect of DHEA and DHEAS on $GABA_A$ receptor function remains to be determined.

On the other hand, DHEA (10 μM), but not DHEAS, increase the expression of the α1 and β2 subunits of the $GABA_A$ receptor (Xilouri and Papazafiri, 2006).

The modulation between DHEA and GABA is reciprocal, and thus, activation of $GABA_A$ receptors inhibits the biosynthesis of different steroids (17-hydroxypregnenolone, dihydrotestosterone, DHEA, 17-hydroxyprogesterone, progesterone) in the hypothalamus (Do-Rego et al., 2000).

GABA neurotransmission is involved in the pathophysiology of anxiety disorders (Möhler, 2006). However, plasma DHEAS

concentration is not altered in patients with generalized anxiety disorder (Semeniuk et al., 2001). Also, serum levels of DHEA and DHEAS are not significantly different than control values in patients with social phobia (Laufer et al., 2005). Plasma DHEA concentration has been reported to be increased in male (Brambilla et al., 2005), but not female (Brambilla et al., 2003), patients with panic disorder.

Administration of DHEA (50 mg/day for 12 months), but not estrogens, reduces anxiety in female patients with anorexia nervosa compared to baseline scores (Gordon et al., 2002). Also, DHEA (25–100 mg/day, 6 weeks), along with antipsychotic medication, reduces anxiety in schizophrenic patients (Strous et al., 2003). Thus, although the antagonistic effect of DHEA on $GABA_A$ receptors should lead to an anxiogenic response, administration of this steroid to humans and rodents yields to an anxiolytic effect. As discussed above, it is possible that DHEA stimulates GABAergic neurotransmission under certain conditions and this mechanism might be involved in the anxiolytic effect of DHEA. On this regard, the anxiolytic effect of DHEA may also be exerted through serotonergic mechanisms as selective 5-HT reuptake inhibitors (Izumi et al., 2006) and $5HT_{2B/2C}$ agonists (Nunes-de-Souza et al., 2008) lead to such effect.

7. Ion channels

Since both neural and endothelial functions are dependent on the activity of ion channels, DHEA may modulate brain and vascular systems through an interaction with those channels and some studies have addressed this issue.

Neither DHEA (40 μM) nor DHEAS (1, 10 or 40 μM) alter depolarization-induced increased intracellular calcium concentration (Büküsogolu and Sarlak, 1996; Liu et al., 1996; Suárez et al., 2005). Incubation of endothelial cells with DHEA (1 pM–1 μM) for 5 min does not alter basal intracellular calcium levels (Liu and Dillon, 2004). A similar lack of effect is observed at lower concentrations that are effective to induce vasorelaxation (500 nM) (Barbagallo et al., 1995) indicating that the vasodilator effect of DHEA is not mediated through inhibition of intracellular calcium rise; both DHEA and DHEAS inhibit depolarization-induced increase in intracellular calcium only at concentrations above 10 (for DHEA) or 60 (for DHEAS) μM, in cultured hippocampal neurons (Kurata et al., 2001).

However, DHEA and its sulfate ester may alter calcium homeostasis by alternative mechanisms. DHEAS increases plasma membrane Ca^{2+}–ATPase activity (EC_{50} 40–50 pM) after a short incubation period (1 min) (Zylinska et al., 1999); this effect is lost after a 5-day treatment (1 mg/kg) (Zylinska et al., 1995). On the other hand, high DHEA concentrations (100–233 μM) induce calcium release from mitochondria (Correa et al., 2003).

It has also been reported that DHEAS (10 μM) reduce voltage-gated calcium channel currents in hippocampal neurons (Ffrench-Mullen and Spence, 1991); another DHEA metabolite, epiandrosterone, also inhibits L-type calcium channel currents (IC_{50} 42 μM) in cardiac myocytes (Gupte et al., 2002b).

Regarding other ion channels, high DHEAS concentrations (1 mM) reduce depolarization-induced intracellular Na^+ rise in chromaffin cells (Liu et al., 1996). Also, DHEA (100 μM) increases calcium-activated potassium channel activity in the rat pulmonary artery (Bonnet et al., 2003) leading to vasodilation.

Results summarized above show that both DHEA and DHEAS alter ion channel function in both neurons and endothelial cells only at relatively high concentrations.

8. Discussion

In the last two decades an increasing body of evidence has shown that DHEA and DHEAS modulate several neurotransmitter systems. However, both stimulatory and inhibitory effects have been reported for them, and the use of different experimental conditions makes difficult to completely understand the modulatory effect of the steroids and its mechanism of action. However, it could be considered that DHEA and its sulfate ester modulate neurotransmitter systems by both genomic and nongenomic effects, mediated either by DHEA itself or by some of its metabolites. The behavioral relevance of those neurochemical effects of DHEA and DHEAS deserves discussion.

Regarding dopamine neurotransmission, biochemical studies suggest that DHEA and DHEAS may act as D2 receptor antagonists (Section 2.1, Fig. 2) in a similar fashion as typical antipsychotics, and clinical studies have found that the serum DHEA/cortisol ratio is inversely correlated to psychopathology in schizophrenic patients (Section 2.5), suggesting that increasing serum DHEA concentration might lead to a therapeutic effect on schizophrenia, as some studies have already reported (Section 3).

The effect of DHEA on glutamate neurotransmission is also a potential therapeutic target. The stimulating effect of DHEA and DHEAS on this neurotransmitter system may reduce glutamate hypofunction in schizophrenia, and seems to be associated to the therapeutic effect of DHEA administration against negative symptoms in this disorder (Section 3). This therapeutic effect might also involve an enhanced NO biosynthesis, which in turn might improve glutamate neurotransmission and to restore regional cerebral blood flow in schizophrenia (Section 4).

5-HT neurotransmission is probably involved in the mood-enhancing effect of DHEA (Section 5). Biochemical studies regarding this issue have led to contrasting results, but some of them suggest that DHEA might stimulate 5-HT neurotransmitter system in a similar fashion as some antidepressant drugs; thus, this mechanism might be responsible for the stimulating effect of DHEA on mood and well-being.

However, in spite of the increasing body of evidence regarding the modulatory effect of DHEA on several neurotransmitter systems, some issues await to be clarified. One of those issues is to integrate the antagonistic effect of DHEA at $GABA_A$ receptors, which should be expected to be anxiogenic, with the contrasting anxiolytic effect of the steroid. Although a great body of evidence support the inhibitory effect of DHEA on this GABA receptor subtype, some studies involve the activation of those receptors in the anxiolytic effect of DHEA (Section 6), suggesting that this steroid might stimulate $GABA_A$ receptor activation through a mechanism that remains to be elucidated. It should also be considered that the anxiolytic effect of DHEA may involve serotonergic mechanisms (Section 6).

From the literature reviewed in this paper, it could be suggested that a variety of mechanisms activated by DHEA modulate several neurotransmitter systems involved in some psychiatric disorders, making this steroid a potential therapeutic target for those diseases.

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Acute dehydroepiandrosterone treatment exerts different effects on dopamine and serotonin turnover ratios in the rat corpus striatum and nucleus accumbens

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ABSTRACT

It has been shown that the steroid dehydroepiandrosterone (DHEA) interacts with dopamine (DA) and serotonin (5-HT) neurotransmitter systems, which are involved in the pathophysiology of neurological and psychiatric diseases such as Parkinson's disease as well as mood and psychotic disorders. To explore if DHEA modulates DA and 5-HT metabolism we analyzed the content of both neurotransmitters and their metabolites in the rat corpus striatum (CS) and nucleus accumbens (NAc) 2 h after steroid administration (30, 60 and 120 mg/kg i.p.). DHEA treatment significantly reduced DA turnover (up to 33%) in the CS, but increased 5-HT turnover (up to 76%) in both regions. Those effects could be relevant to mood and neurodegenerative disorders.

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1. Introduction

It has been shown that dehydroepiandrosterone (DHEA) modulates several neurotransmitter systems and this might be involved in its behavioral effects (Pérez-Neri et al., 2008). Regarding monoamines, some studies suggest that DHEA and its sulfated ester (dehydroepiandrosterone sulfate, DHEAS) may reduce dopamine (DA) D2 receptor activation (Catalina et al., 2002; Suárez et al., 2005), while DHEAS increases D1 receptor-dependent PKA activity (Dong et al., 2007). Also, both DHEA and DHEAS increase DA release from cell cultures (Charalampopoulos et al., 2005; Murray and Gillies, 1997).

Some studies show that DHEA administration alters both DA and serotonin (5-HT) metabolism in the hypothalamus (Catalina et al., 2001; Gillen et al., 1999; Pham et al., 2000; Porter et al., 2005) while other studies did not find significant effects on DA metabolism in other brain regions such as the corpus striatum (CS) and midbrain (Nguyen et al., 1999).

A previous study showed that the intrastriatal injection of DHEA reduces 3,4-dihydroxyphenylacetic acid (DOPAC) content in the CS, suggesting reduced monoamine oxidase (MAO) activity, which might be involved in the neuroprotective effect of DHEA in experimental models of Parkinson's disease (PD) (Tomas-Camardiel et al., 2002).

In the present study we explore the acute effect of DHEA administration on the content of DA, 5-HT and their metabolites in the CS and the nucleus accumbens (NAc) to study the modulation of monoamine metabolism in the main dopaminoceptive nuclei in the rat brain.

2. Materials and methods

2.1. Chemicals

DA, DOPAC, 3-methoxy-4-hydroxyphenylacetic acid (homovanillic acid, HVA), 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), *trans*-DHEA and sodium octyl sulfate were obtained from Sigma (St. Louis, MO, USA). HPLC-grade absolute methanol was obtained from Mallinckrodt Baker (Mexico). All other reagents were analytical grade.

2.2. Animals, treatments and sample processing

DHEA was dissolved in propylene glycol and injected [30 (n=8), 60 (n=6) and 120 (n=6) mg/kg, i.p.)] to male Wistar rats weighing 200–250 g. Control animals (n=10) received an equivalent volume of the vehicle. DHEA doses were selected to cover a wide range used in previous studies; also, the selection of the vehicle, the administration route and the time for sacrifice after treatment were selected according to those studies (Gillen et al., 1999; Nguyen et al., 1999; Pham et al., 2000; Porter et al., 2005).

Two hours after steroid administration animals were sacrificed by decapitation; the whole CS and NAc were dissected out and stored at −70 °C. The day of analysis, samples were thawed and homogenized in 0.4 N perchloric acid containing 0.1% sodium metabisulfite as previously reported (Montes et al., 2001). Homogenates were centrifuged at 18,500×g at 4°C for 15 min and supernatants were kept on ice during analysis. Experiments were carried out according to the

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin; CS, corpus striatum; DA, dopamine; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; DOPAC, 3,4-dihydroxyphenylacetic acid; HPLC, high-performance liquid chromatography; HVA, homovanillic acid; MAO, monoamine oxidase; MAOI, MAO inhibitor; NAc, nucleus accumbens; PD, Parkinson's disease.

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Guidelines for the Care and Use of Laboratory Animals (Ethic Standards for Biomedical Research, Institute of Biomedical Research, National Autonomous University of Mexico) and were approved by our Institutional Scientific Committee. All efforts were made to minimize the number and suffering of the animals used in these experiments.

2.3. Chromatographic analysis of monoamines and their metabolites

Samples were analyzed by high-performance liquid chromatography (HPLC) coupled to electrochemical detection as previously described (Montes et al., 2001) with minor modifications. Samples were injected into an isocratic pump (LC 250, Perkin Elmer) using a Rheodyne valve with a 20-μl loop. The mobile phase consisted of a potassium phosphate buffer (30 mM, pH 3.1) containing 2 mM sodium octyl sulfate and 1.6% EDTA with 20% HPLC-grade absolute methanol pumped at a flow rate of 0.8 ml/min. Signals were recorded with a 656 Metrohm Electrochemical detector (set at an oxidation potential of 800 mV and 1 nA) and integrated using a Turbochrom software version 4.10 (Perkin Elmer). Limits of detection determined as a signal:noise ratio of 3:1 of 10 blank injections were found between 9 and 36 nM for all analytes (DOPAC 9 nM, 5-HIAA 10 nM, DA 33 nM, 5-HT 34 nM, HVA 36 nM). Lower and upper limits of quantification were 0.1–0.3 and 2.5–10.0 μM, respectively, for all analytes. Response was linear between both limits ($r=0.999$) and it was not influenced by the biological matrix. Intra-assay variation was 3.46–14.93% for all analytes, and it was not concentration-dependent. Results are expressed as mean±SEM pg/mg wet tissue.

2.4. Statistical analyses

One-way Analysis of Variance followed by Dunnett's test was used to assess treatment effects on each brain region; Kruskal–Wallis analysis of variance was used when appropriate according to Levene's test for homogeneity of variance. Pearson's correlations were used to determine significant associations between biochemical markers on a single brain region and for a single biochemical marker between both regions. Paired t tests were used to detect significant differences for each biochemical marker between both brain regions. All statistical analyses were performed using the SPSS 15.0 software.

3. Results

Analysis of variance showed that DHEA significantly altered both DOPAC content ($F=3.349$, $p=0.034$) and DOPAC/DA ratio ($F=5.717$, $p=0.004$) in the CS and this effect seems to be dose-dependent. Post hoc analyses showed that DHEA reduces DOPAC content (control: 0.917 ± 0.073 pg/mg tissue, DHEA: 0.655 ± 0.056 pg/mg tissue; $p=0.022$, Fig. 1A) and DOPAC/DA ratio (control: 0.142 ± 0.011, DHEA: 0.096 ± 0.004; $p=0.003$, Fig. 1D) at 120 mg/kg. Total DA turnover in the CS [(DOPAC+HVA)/DA] was also altered by DHEA treatment ($F=3.512$, $p=0.030$). DHEA reduced (DOPAC+HVA)/DA at 120 mg/kg (0.172 ± 0.009) compared to vehicle-

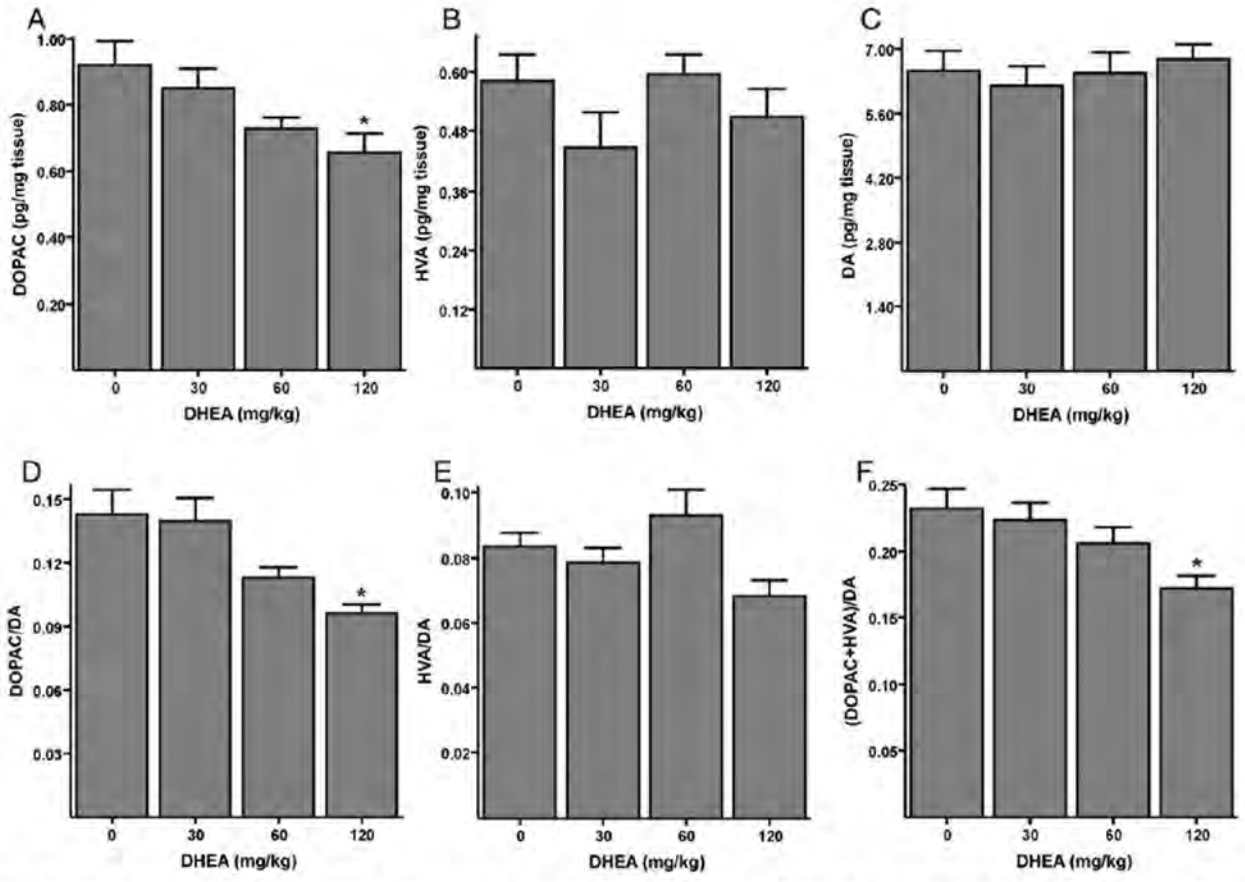

Fig. 1. Effect of DHEA on DOPAC (A), HVA (B) and DA (C) contents, as well as DOPAC/DA (D), HVA/DA (E) and (DOPAC+HVA)/DA (F) ratios, in the CS. Adult Wistar rats were sacrificed 2 h after DHEA administration (i.p.) and monoamine levels were determined by high-performance liquid chromatography. Bars represent mean ± SEM of 6–10 animals per group. *$p<0.05$.

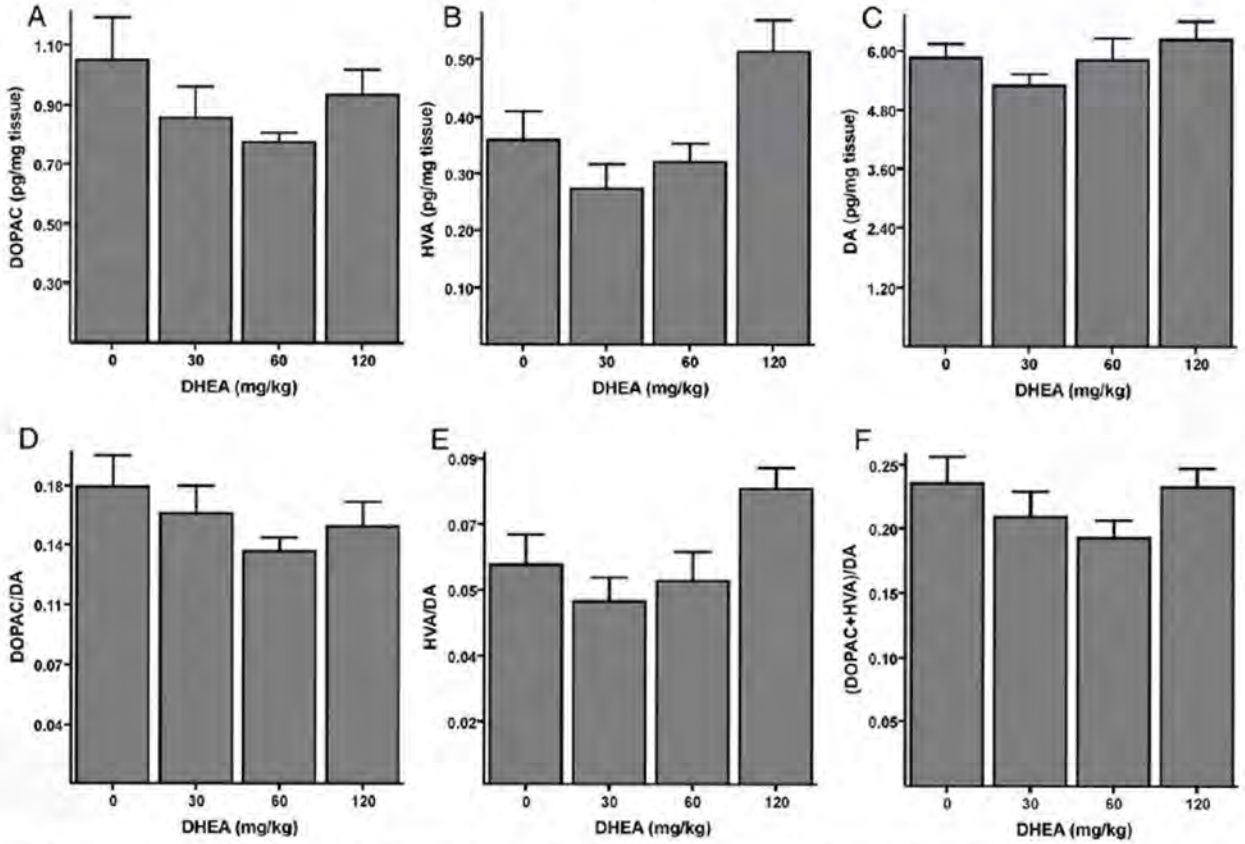

Fig. 2. Effect of DHEA on DOPAC (A), HVA (B) and DA (C) contents, as well as DOPAC/DA (D), and (DOPAC+HVA)/DA (F) ratios, in the NAc. Animals were sacrificed 2 h after DHEA administration (i.p.) and monoamine levels were determined by high-performance liquid chromatography. Bars represent mean ± SEM of 6–10 animals per group. *$p < 0.05$.

treated animals (0.231 ± 0.015, $p = 0.013$, Fig. 1F). A trend towards an effect on HVA/DA ratio was found ($F = 3.030$, $p = 0.050$) but post-hoc tests showed that none of the DHEA-treated groups was different from control values ($p > 0.160$; Fig. 1E). No significant effects were found for DA ($F = 0.279$, $p = 0.840$; Fig. 1C) nor HVA ($F = 1.325$, $p = 0.288$; Fig. 1B) contents in this region.

In the NAc, no significant effects were found for DA ($F = 1.333$, $p = 0.285$; Fig. 2C) and DOPAC ($\chi^2 = 1.993$, $p = 0.574$; Fig. 2A) contents, HVA/DA ($F = 2.728$, $p = 0.064$; Fig. 2E) or (DOPAC+HVA)/DA ratios ($F = 1.054$, $p = 0.385$, Fig. 2F). Analysis of variance showed a significant effect on HVA content ($F = 4.104$, $p = 0.016$) but post-hoc tests revealed that none of the groups was different from vehicle-treated animals ($p > 0.70$; Fig. 2B). We also found a trend towards reduced DOPAC/DA ratio that did not reach statistical significance ($F = 0.976$, $p = 0.419$; Fig. 2D); however, when a sub-analysis including only DHEA-treated animals was performed, DOPAC/DA ratio in the NAc was positively

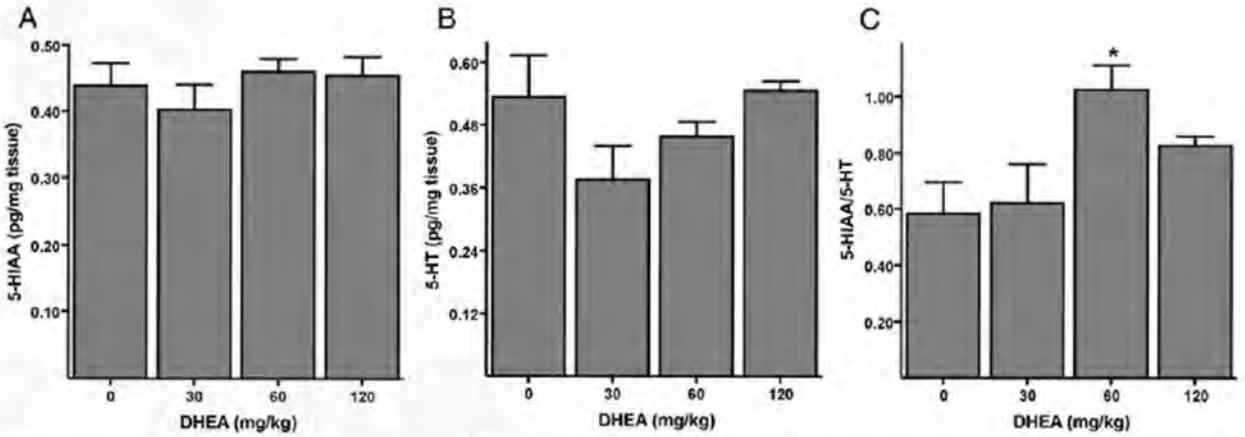

Fig. 3. Effect of DHEA on 5-HIAA (A) and 5-HT (B) contents, as well as 5-HIAA/5-HT (C) turnover ratio, in the CS. Animals were sacrificed 2 h after DHEA administration (i.p.) and monoamine levels were determined by high-performance liquid chromatography. Bars represent mean ± SEM of 6–10 animals per group. *$p < 0.05$.

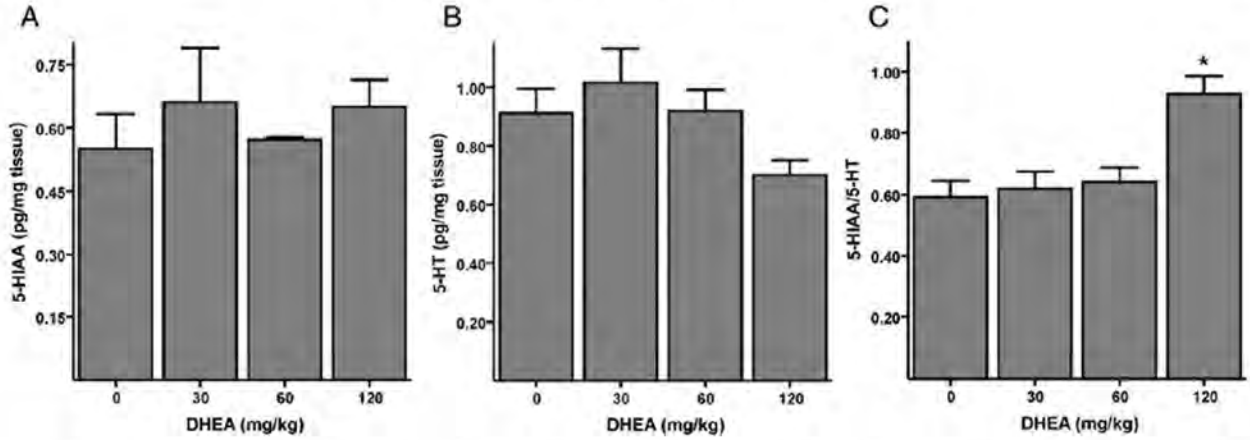

Fig. 4. Effect of DHEA on 5-HIAA (A) and 5-HT (B) contents, as well as 5-HIAA/5-HT (C) turnover ratio, in the NAc. Animals were sacrificed 2 h after DHEA administration (i.p.) and monoamine levels were determined by high-performance liquid chromatography. Bars represent mean ±SEM of 6–10 animals per group. *$p<0.05$.

correlated to that in the CS ($r=0.499$, $p=0.025$), but this correlation was lost when control animals were included ($r=0.307$, $p=0.099$) or analyzed as a subgroup ($r=0.285$, $p=0.425$). In contrast, (DOPAC+HVA)/DA ratio was correlated between the NAc and the CS in the whole sample ($r=0.405$, $p=0.029$).

In the control group, both HVA content (CS, 0.550±0.052 pg/mg tissue; NAc, 0.333±0.049 pg/mg tissue; $p=0.003$) and HVA/DA ratio (CS, 0.083±0.004; NAc, 0.056±0.007; $p=0.008$) were significantly higher in the CS compared to the NAc.

DHEA treatment significantly altered 5-HIAA/5-HT ratio in both the CS ($F=3.076$, $p=0.045$) and the NAc ($F=7.116$, $p=0.001$). Post-hoc analyses showed that this ratio was significantly increased at 60 mg/kg in the CS (control: 0.581±0.114, DHEA: 1.025±0.087; $p=0.029$, Fig. 3C) and at 120 mg/kg in the NAc (control: 0.592±0.051, DHEA: 0.927±0.056; $p=0.001$, Fig. 4C). No significant effects were found for neither 5-HIAA (CS: $F=0.591$, $p=0.627$; NAc: $\chi^2=1.791$, $p=0.617$) nor 5-HT (CS: $\chi^2=7.579$, $p=0.056$; NAc: $F=2.022$, $p=0.135$) contents.

Neither DOPAC/DA nor (DOPAC+HVA)/DA ratio were correlated to 5-HIAA/5-HT ratio in the CS nor in the NAc even when DHEA-treated animals were analyzed as a subgroup ($p>0.3$ in all cases).

4. Discussion

In the CS, DHEA treatment reduced DOPAC content (Fig. 1A) as well as DOPAC/DA (Fig. 1D) and (DOPAC+HVA)/DA (Fig. 1F) ratios at 120 mg/kg without changing DA (Fig. 1C) or HVA (Fig. 1B) contents as well as HVA/DA ratio (Fig. 1E). This result suggests that DHEA reduced MAO activity and could also be expected to reduce HVA and increase DA contents. However, it is possible that MAO inhibition reduces DOPAC availability without affecting DA and HVA levels; this has been reported for some drugs that along their possible MAO inhibition increase 3-methoxytyramine content (the product of COMT activity), decreasing striatal DOPAC levels while those of DA and HVA remain unchanged (Antkiewicz-Michaluk et al., 2001). Since (DOPAC+HVA)/DA ratio was also decreased following DHEA treatment (120 mg/kg), it is possible that the steroid decreases the global turnover of DA, although the possible stimulatory effect of DHEA on COMT activity can not be ruled out.

Regarding DA, reduced turnover for this neurotransmitter could be expected to increase cytosolic DA which, in turn, might be capable to inhibit tyrosine hydroxylase activity (Kumer and Vrana, 1996), possibly maintaining its basal level unchanged. It should be noted that 100 mg/kg DHEA did not alter DA content in the striatum under similar experimental conditions in a previous study (Nguyen et al., 1999); we did not found a significant effect even at the 120 mg/kg dose of DHEA (Fig. 1C).

No significant effects of DHEA on DA or its metabolites were found in the NAc (Fig. 2); however, both DOPAC content (Fig. 2A) and DOPAC/DA ratio (Fig. 2D) tended to be decreased. Furthermore, DOPAC/DA and (DOPAC+HVA)/DA ratios in the NAc were positively correlated to those in the CS, suggesting that DHEA treatment alters DA turnover in both regions in a similar fashion, although the CS seems to be more sensitive than the NAc. Moreover, DOPAC/DA ratio was correlated between both regions only when DHEA-treated animals were independently analyzed, suggesting that this correlation is a treatment effect. It should also be considered that HVA content and HVA/DA turnover ratio were significantly higher in the CS compared to the NAc; this may reflect a higher catabolic rate for DA in the CS and might explain the absence of a significant effect of DHEA in the NAc. Thus, our results suggest that DHEA inhibits MAO activity but it remains to be determined if the steroid selectively modulates MAO A or MAO B activities since DA is a substrate for both enzyme isoforms (Shih and Thompson, 1999).

A single intrastriatal injection of DHEA (10 μg/2 μL) to female rats resulted in a significant decrease in DOPAC and a slight decrease in HVA levels, while DA content remained unchanged (Tomas-Camardiel et al., 2002), four days after treatment. In that study, administration of testosterone led to a decrease in both DA and DOPAC content, possibly due to reduced DA synthesis, while 17β-estradiol did not affect the content of neither DA nor its metabolites (Tomas-Camardiel et al., 2002). According to those results, DHEA-induced decreased DOPAC content is not dependent on steroid metabolism to sex hormones. In our study, we found that the administration of DHEA modulated striatal DOPAC content as soon as 2 h post-treatment while the potential role of DHEA's metabolites under our experimental conditions remains to be determined.

We did not find a significant effect of DHEA on neither 5-HT nor 5-HIAA contents, but 5-HIAA/5-HT ratio was increased in both the CS (at 60 mg/kg; Fig. 3C) and the NAc (120 mg/kg; Fig. 4C). This is consistent with previous studies showing that the 100 mg/kg dose of DHEA does not significantly alter 5-HT or 5-HIAA contents in the CS (Nguyen et al., 1999). Intrastriatal injection of DHEA (10 μg/2 μL) resulted in a trend towards a decreased 5-HT and an increased 5-HIAA content without reaching statistical significance (Tomas-Camardiel et al., 2002). However, 5-HIAA/5-HT ratio was not reported in that study.

Our results indicate that DHEA treatment might stimulate 5-HT neurotransmission. Some studies suggest that DHEA might alter 5-HT transporter function (Gillen et al., 1999), but that effect should be expected to reduce 5-HIAA/5-HT ratio. Also, some studies show that DHEA does not alter the firing rate of raphe nucleus serotonergic neurons (Robichaud and Debonnel, 2005). Thus, the underlying mechanism for the effect of the steroid on 5-HT turnover remains to be determined.

The possible inhibitory effect of DHEA on MAO activity, as suggested by the decreased DOPAC/DA ratio, is not consistent with an increased 5-HT turnover. Also, neither DOPAC/DA nor (DOPAC+HVA)/DA ratio was correlated to 5-HIAA/5-HT ratio in the CS or the NAc, suggesting that both effects involve different mechanisms. It remains to be determined if DHEA exerts a different modulatory effect on both MAO isoforms leading to decreased DA turnover while 5-HT turnover is increased or if 5-HT turnover is altered through a MAO-independent mechanism.

It is possible that MAO inhibition is involved in the neuroprotective effect of DHEA. It has been reported that selective MAO inhibitors (MAOI's, such as selegiline and rasagiline) are neuprotective in experimental models of PD (Chen et al., 2007; Sagi et al., 2007; Youdim and Bakhle, 2006) as well as in other paradigms of cell damage (Mandel et al., 2005; Stefanova et al., 2008). Furthermore, administration of MAOI's to patients with PD led to slower disease progression in controlled trials (Chen et al., 2007; Parkinson Study Group, 2005; Youdim and Bakhle, 2006).

MAO inhibition is also relevant to mood disorders. MAO A radiolabeling is increased in several brain regions of unmedicated depressed patients compared to control subjects, suggesting increased enzyme activity in depression (Meyer et al., 2006). Also MAOI's have been used as antidepressant therapy (Culpepper and Kovalick, 2008; Youdim and Bakhle, 2006).

Major depressive disorder is also present in some cases of PD (McDonald et al., 2003) and MAOI's yield therapeutic effects against both motor deficits and depressive symptoms in those patients (Youdim and Bakhle, 2006). Furthermore, neuronal death has been implicated in major depressive disorder according to some studies (Myint et al., 2007; Rothermundt et al., 2001) and several antidepressant drugs exert neuroprotective effects (Jarosik et al., 2007; Wang et al., 2007), supporting the possible link between neuronal death and depressive disorders. According to this hypothesis, targeting both neuronal death and neurotransmitter systems involved in major depression (like DA and 5-HT) might be relevant for the treatment of depressive symptoms in neurodegenerative disorders such as PD.

In this regard, DHEA has shown neuroprotective properties in models of PD (Bélanger et al., 2006; Tomas-Camardiel et al., 2002) and in other neurodegeneration models (Charalampopoulos et al., in press; Dubrovsky, 2005; Maurice et al., 2006). Also, DHEA administration induce an antidepressant effect both in experimental models and controlled clinical trials (Dubrovsky, 2005; Eser et al., 2006). Thus, the possible modulation of MAO activity by DHEA might be involved in those effects.

Regarding the serotonergic system, our results suggest that acute DHEA administration stimulates 5-HT neurotransmission. This hypothesis deserves further investigation but it is consistent to the effect of the steroid on behavior associated to this neurotransmitter system such as mood, aggression and anxiety.

Serotonin neurotransmission is a therapeutic target for mood disorders (Thase and Sachs, 2000). Increased 5-HIAA/5-HT ratio, as we found in this study, has been associated to the antidepressant effect of some drugs (Suemaru et al., 2006); thus, along MAO inhibition, the beneficial effect of DHEA administration on mood (Pérez-Neri et al., 2008) could be also associated to serotonergic stimulation.

The inhibitory effect of DHEA on aggression (Haug et al., 1989) might also be associated to the serotonergic system since reduced 5-HT neurotransmission has been implicated in this behavior (Nelson et al., 2006; Summers and Winberg, 2006). Administration of 5HT1A receptor agonist reduces androgen-induced aggressive behavior (Ricci et al., 2006). Serotonin turnover in the mice frontal cortex is also reduced following repetitive aggressive behavior (Caramaschi et al., 2008) while DHEA treatment (60 and 120 mg/kg) increases 5-HT turnover in this brain region (Pérez-Neri et al., in press).

Finally, serotonergic drugs (such as a 5-HT reuptake inhibitors and $5\text{-HT}_{2B/2C}$ agonists) are anxiolytic (Izumi et al., 2006; Nunes-de-Souza et al., 2008); thus, it is possible that serotonergic stimulation by DHEA is involved in the anxiolytic effect of the steroid reported on humans (Gordon et al., 2002; Strous et al., 2003) and animal models (Fedotova and Sapronov, 2004; Maayan et al., 2006a).

In this study, we used an acute model to explore the effect of DHEA on monoamine turnover in the rat brain avoiding the influence of several mechanisms that may occur during chronic treatments and could lead to different conclusions. The relevance of the effects described here to chronic disorders awaits further investigation. It is possible that DHEA treatment for long time periods modulate different mechanisms compared to the acute effects of the steroid; in fact, some studies have dealed with this issue. Chronic DHEA administration (2 mg/kg) increases DA and 5-HT content in the rat NAc, while DOPAC/DA, HVA/DA and 5-HIAA/5-HT ratios tended to decrease but were not significantly different to control levels (Maayan et al., 2006b). From the available data on this regard generated from Maayan's study and ours, it might be suggested that acute steroid administration modulates DA metabolism in the CS while chronic treatment does so in the NAc. Serotonin metabolism is modulated by DHEA, acutely and chronically in both regions possibly through different mechanisms. Thus, both acute and chronic studies yield complementary information about the modulatory effect of DHEA on monoaminergic systems.

5. Conclusion

DHEA administration differentially modulates DA and 5-HT turnover in the CS and NAc. On the one hand, reduced DA turnover in the corpus striatum following DHEA treatment might involve MAO inhibition and, in turn, may be associated to the neuroprotective effect of the steroid as well as its beneficial effect on mood disorders. On the other hand, increased 5-HT turnover in both the corpus striatum and the nucleus accumbens suggests the stimulation of the serotonergic system and might be involved in the effect of DHEA on mood, its inhibitory effect on aggressive behavior and its anxiolytic effect.

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Inhibitory effect of dehydroepiandrosterone on brain monoamine oxidase activity: In vivo and in vitro studies

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ABSTRACT

Aims: To evaluate the acute effect of dehydroepiandrosterone (DHEA) on monoamine oxidase (MAO) activity in the corpus striatum (CS) and the nucleus accumbens (NAc) in vivo and in vitro.
Main methods: Male Wistar rats received an i.p. injection of DHEA (30, 60 and 120 mg/kg) and MAO activity was assayed by formation of 4-hydroxyquinoline 2 h later. For in vitro studies, DHEA (100 nM–1 mM) was added to brain tissue homogenates to assay MAO activity.
Key findings: DHEA significantly reduced (−24%) total MAO activity in the NAc ($F=8.5$, $p<0.001$), but not in the CS, at 120 mg/kg dose. No significant difference was observed when MAO A and MAO B activities were independently analyzed. When assayed in vitro, total MAO, MAO A and MAO B activities were reduced by DHEA to 55.7, 28.2 and 54.4% in the NAc and to 71.9, 44.2 and 61.2% in the CS, respectively (IC_{50} 4.7–56.1 μM).
Significance: An inhibitory effect of DHEA on MAO activity may be involved in the antidepressant and neuroprotective effects of the steroid. Since MAO inhibition reduces neurodegeneration in clinical trials for Parkinson's disease, our results suggest that DHEA may be useful to treat depression and to prevent neuronal death in this disorder.

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Introduction

Dehydroepiandrosterone (DHEA) modulates several neurotransmitter systems (Pérez-Neri et al. 2008a). Some studies have focused on the effect of DHEA on monoamine neurotransmission; however, different results have been reported depending on the experimental conditions tested (Catalina et al. 2001; Charalampopoulos et al. 2005; Maayan et al. 2006).

In several brain regions, the effect of DHEA on monoamine content and that of their metabolites has been often studied acutely (2 h after an i.p. injection). Under those experimental conditions, it has been reported that the steroid either increased or decreased the hypothalamic dopamine content (Pham et al. 2000; Porter et al. 2005), reduced that of norepinephrine (Pham et al. 2000) while either increased or decreased serotonin content or that of its main metabolite (5-hydroxyindoleacetic acid) (Gillen et al. 1999; Nguyen et al. 1999; Pham et al. 2000; Porter et al. 2005).

Our group has previously reported that acute DHEA treatment (30–120 mg/kg) reduced dopamine turnover in the corpus striatum (CS), while increased that of serotonin in both the CS and the nucleus accumbens (NAc) (Pérez-Neri et al. 2008b). Similar results have also been reported following a chronic DHEA treatment (Maayan et al. 2006). Those studies suggest a modulatory effect of the steroid on monoamine oxidase (MAO), the main enzyme involved in monoamine catabolism.

It has been reported that a chronic DHEA treatment reduced the aging-induced (14 and 24 months) increase in total MAO activity in the whole brain hemispheres, without altering enzyme activity in adult (4 month old) rats (Kumar et al. 2008). Those results show that DHEA inhibited MAO activity, but it remains to be determined if that effect involves one or both MAO isoforms as well as if it occurs acutely in young animals.

Two isoforms of this enzyme exist. MAO A is present in catecholaminergic neurons and shows high affinity for norepinephrine and serotonin, while MAO B is present in astrocytes, interneurons, and serotonergic neurons and shows high affinity for benzylamine. Dopamine is a substrate for both MAO isoforms (Bortolato et al. 2008; Youdim and Bakhle 2006).

MAO inhibition is relevant to neuroprotection and mood since selective MAO B inhibitors are neuroprotective for Parkinson's disease (PD) in experimental animals and humans (Chen et al. 2007; Mandel et al. 2005; Olanow 2009) while both MAO A and MAO B inhibitors have shown antidepressant action (Bortolato et al. 2008; Pae et al. 2007; Robinson and Amsterdam 2008; Youdim and Bakhle 2006). DHEA leads to both effects (Bélanger et al. 2006; Tomas-Camardiel et al. 2002; Morissette et al. 2008; Rabkin et al. 2006; Schmidt et al. 2005; Strous et al. 2003).

In this study, we tested if DHEA acutely modulates MAO activity (either one or both enzyme isoforms) in young animals as well as in

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brain tissue homogenates, that may shed some light to the mechanism of action for the steroid antidepressant and neuroprotective effects.

Materials and methods

Chemicals

trans-DHEA, USP-grade propylene glycol, 4-hydroxyquinoline (4HQ), kynuramine dihydrobromide, selegiline [R-(−)-deprenyl hydrochloride] and clorgyline [N-methyl-N-propargyl-3-(2,4-dichlorophenoxy)propylamine hydrochloride] were obtained from Sigma (St. Louis, MO, USA). All other reagents were analytical grade.

Animals and treatment

Experimental procedures were performed according to our previous study (Pérez-Neri et al. 2008b). DHEA was dissolved in propylene glycol and injected (30, 60 and 120 mg/kg, i.p.) to male Wistar rats weighing 200–250 g (n 6–8). Control animals received an equivalent volume of the vehicle. Two hours after steroid administration, animals were sacrificed by decapitation, the CS and NAc were dissected out and stored at −70 °C until analyzed. This study was carried out according to the EC Directive 86/609/EEC for animal experiments, all efforts were made to minimize animal number and suffering.

MAO activity

The enzyme activity assay was performed according to previous studies (Krajl 1965; Mazzio et al. 2003; Ro et al. 2001; Samantaray et al. 2003; Xu et al. 2005). The day of analysis, samples were thawed and homogenized in ice-cold deionized water. Sample aliquots were pre-incubated (37 °C, 15 min) with phosphate buffer saline (PBS 50 mM, to assay total MAO activity), selegiline (to assay MAO A activity) or clorgyline (to assay MAO B activity) dissolved in PBS, to 1 μM final concentration.

For in vitro studies, DHEA (100 nM–1 mM final concentration) prepared in DMSO (2.5% v/v final concentration) was added to NAc or CS homogenates without any previous treatment ($n=3$ independent samples for each steroid concentration) and incubated for 5 min at 37 °C according to previous studies (Tomas-Camardiel et al. 2002). To evaluate the effect of DMSO on MAO, another set of animals (n 5–6) was sacrificed without treatment to dissect out the NAc and CS as described above. Enzyme activity in the presence of DMSO was compared to that of the same samples incubated with PBS.

The assay was started by addition of kynuramine (dissolved in PBS) to a final concentration of 22 μM and was stopped by addition of 10% trichloroacetic acid 30 min later. Blank samples were prepared in the same way with the only difference that trichloroacetic acid was added before the substrate. Reaction mixtures were centrifuged at 18,500×g for 15 min, supernatants were mixed with an equivalent volume of 1 M NaOH. Fluorescence was measured at 315 nm excitation and 380 nm emission in a LS 50B spectrofluorometer (Perkin Elmer, Mexico) and interpolated in a 4HQ calibration curve. Protein concentration was determined according to Lowry et al. (1951). Enzyme activity was expressed as nmol/mg protein/h. In vitro results are reported as percent MAO activity considering the mean at 100 nM DHEA as 100%.

Statistical analyses

Tests for normality (Kolmogorov–Smirnov test) and homogeneity of variance (Levene's test) were performed before other analyses. One-way ANOVA followed by the Dunnett's test and paired Student's t test were performed using SPSS 17.0. Non-linear regression of the inhibition curves was performed with GraphPad Prism 5.01. Results are expressed as mean ± SEM. Significant differences were defined at $p<0.05$.

Results

In vivo studies

DHEA treatment significantly altered total MAO activity in the NAc ($F=8.5$, $p<0.001$), reducing this activity by 24% at the 120 mg/kg dose (6.0 ± 0.3) compared to the control group (7.9 ± 0.4, $p=0.002$; Fig. 1A). DHEA also altered both MAO A (Fig. 1B) and B (Fig. 1C) activities (MAO A: $F=3.4$, $p=0.031$; MAO B: $F=7.0$, $p=0.001$), but post hoc analyses showed that no steroid-treated group was different from vehicle-treated animals ($p>0.05$).

In the CS, DHEA also altered total MAO (Fig. 1D) ($F=3.1$, $p=0.046$) and MAO A ($F=5.6$, $p=0.005$) (Fig. 1E) activities while a trend was found for MAO B (Fig. 1F) ($F=2.4$, $p=0.090$). However, post hoc analyses revealed that no DHEA-treated group was significantly different from control levels ($p>0.05$).

In vitro studies

The highest DHEA concentration tested (1 mM) precipitated when added to the reaction mixture; thus, results from this concentration represent the effect of the maximal soluble DHEA concentration (between 100 μM and 1 mM) under our experimental conditions but may be affected by the presence of insoluble material; no precipitation was evident at the other concentration levels.

In NAc homogenates, DHEA (100 μM) reduced total MAO activity to 55.7% (Fig. 2A). MAO A (Fig. 2B) and B activities (Fig. 2C) were maximally inhibited, at the highest concentration tested, to 28.2 and 54.4%, respectively. The estimated IC_{50} for DHEA on total MAO, MAO A and MAO B activities was 11.2, 56.1 and 30.1 μM, respectively.

In the CS, DHEA inhibited total MAO activity to 71.9% at the highest concentration tested (Fig. 2D). MAO A (Fig. 2E) and MAO B activities (Fig. 2F) were reduced to 44.2 and 61.2%, respectively, at 100 μM DHEA. The estimated IC_{50} was 4.7, 14.9 and 11.44 μM for total MAO, MAO A and MAO B activities, respectively.

In the homogenates from both brain regions, MAO activity was apparently higher at 1 μM DHEA than that at 100 nM, and also was apparently higher at 1 mM DHEA than that at 100 μM (Fig. 2).

Discussion

In a previous study, we have reported that acute DHEA treatment (120 mg/kg) reduced dopamine turnover in the CS while increased that of serotonin (at 60 and 120 mg/kg DHEA) in the CS and the NAc (Pérez-Neri et al. 2008b). Monoamine turnover is dependent on neurotransmitter release, reuptake and catabolism by MAO; thus, among other hypotheses, a modulatory effect of the steroid on this enzyme may be suggested. We found an acute inhibitory effect of DHEA (120 mg/kg) on total MAO activity in the NAc (Fig. 1A). A similar effect has been reported in the whole brain hemispheres following a chronic treatment at a lower dose (30 mg/kg) (Kumar et al. 2008), which showed no effect under our experimental conditions (Fig. 1). The study by Kumar et al. (2008) showed that DHEA inhibited the aging-induced increase in MAO activity assayed in homogenates and synaptosomal fractions from the whole brain hemispheres, which may suggest that the steroid led to a general reduction in enzyme activity across brain regions. Our study extended those results showing that the acute effect of DHEA on MAO activity is region-dependent, leading to a significant decrease in total MAO activity in the NAc but not in the CS, in vivo (Fig. 1).

However, our results do not rule out that the steroid inhibits enzyme activity in other brain regions as well, leading to a significant decrease in the brain hemispheres when analyzed as a whole. Also,

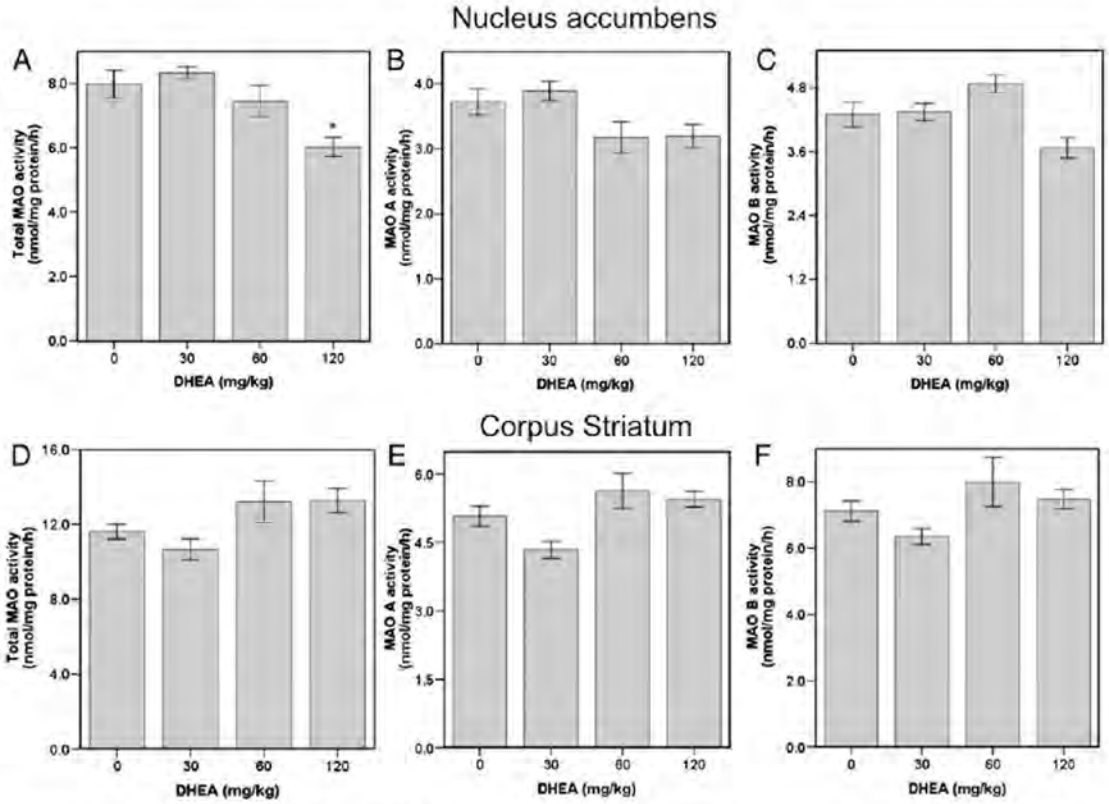

Fig. 1. Effect of DHEA on MAO activity in the NAc and CS in vivo. DHEA significantly reduced total MAO activity (A) and tended to reduce MAO A (B) and B (C) activities in the NAc. No significant effect was found in the CS (D–F). Male Wistar rats received an i.p. injection of DHEA (30, 60 or 120 mg/kg) or an equivalent vehicle volume (n 6–8) and were sacrificed 2 h later. MAO activity was assayed by formation of 4HQ from kynuramine. *Significantly different from control group (one-way ANOVA followed by Dunnett test).

the treatment schedule [acute (present study) versus chronic (Kumar et al. 2008)] might explain the differences between the studies. The possible effect of DHEA on monoamine systems in other brain regions awaits further studies.

In our in vivo studies, we found a trend towards decreased MAO A and B activities leading to a significantly reduced total MAO activity in the NAc (Fig. 1A–C). Since those enzyme isoforms metabolize norepinephrine, serotonin (MAO A) and dopamine (both isoforms) (Bortolato et al. 2008; Youdim and Bakhle 2006), our results suggest that the steroid may modulate the metabolism of all those monoamines in the NAc. Both MAO isoforms were slightly inhibited by 120 mg/kg DHEA to a similar extent (Fig. 1B,C), suggesting that the steroid may modulate them through a common mechanism.

In light of our in vivo experiments, it remained to be determined if the steroid inhibited MAO activity through a direct interaction with the enzyme. To address this issue, we added DHEA to brain tissue homogenates to measure enzyme activity in vitro.

DHEA concentration-dependently inhibited both MAO A and MAO B as well as total MAO activity in vitro at micromolar concentrations (Fig. 2), the estimated IC_{50} values under our experimental conditions should be considered as preliminary due to the small sample size included ($n=3$); however, they are similar to those reported for the inhibitory effect of DHEA on glucose 6-phosphate dehydrogenase (García-Nogales et al. 1999; Gordon et al. 1995; Won et al. 2003; Wu 1996). Also, DHEA inhibited MAO A (Fig. 2B,E) to a greater extent than MAO B (Fig. 2C,F), which is consistent with the antidepressant effect of the steroid, as it occurs with selective MAO A inhibitors (Bortolato et al. 2008; Youdim and Bakhle 2006).

The apparent increase in MAO activity at 1 μM DHEA compared to that at 100 nM (Fig. 2) suggests that the steroid could increase enzyme activity at a lower concentration; however, due to the small sample size in our experiment, this effect awaits confirmation. Also, the apparent increase in MAO activity at 1 mM compared to that at 100 μM may be confounded since the steroid precipitated at such high concentration.

Our results suggest that DHEA modulates both enzyme isoforms through a direct interaction; thus, MAO activity in the CS was inhibited in vitro (Fig. 2D–F) although there was no effect of DHEA in vivo (Fig. 1D–F). It is possible that the steroid reaches a different concentration in the NAc than in the CS leading to a different result on MAO inhibition.

Furthermore, since only a trend towards decreased MAO A and MAO B activities was found in the NAc in vivo (Fig. 1B,C), it is possible that DHEA does not accumulate to a high extent in the rat brain under our experimental conditions. In spite of the lipophilic steroid structure, its diffusion across the blood-brain barrier may be limited due to its binding to plasma proteins such as albumin and sex hormone-binding globulin. The fact that the DHEA concentration in human cerebrospinal fluid represents only 5% of that in plasma (Guazzo et al. 1996) supports this hypothesis.

Since the inhibitory effect of an i.p. injection of DHEA in the NAc was observed after brain tissue homogenization for the enzyme assay, our results suggest that the steroid–enzyme interaction remains after cell disruption. It is still to be determined if this effect involves a permanent modification of the enzyme.

In the present study, no significant effect of DHEA on either MAO A or B activities was observed in vivo (Fig. 1B,C) suggesting that MAO inhibition is not the main underlying mechanism for the effect of the steroid on monoamine turnover as we have reported (Pérez-Neri et al. 2008b); thus, it may be due to an altered neurotransmitter reuptake or release, although these hypotheses await further studies.

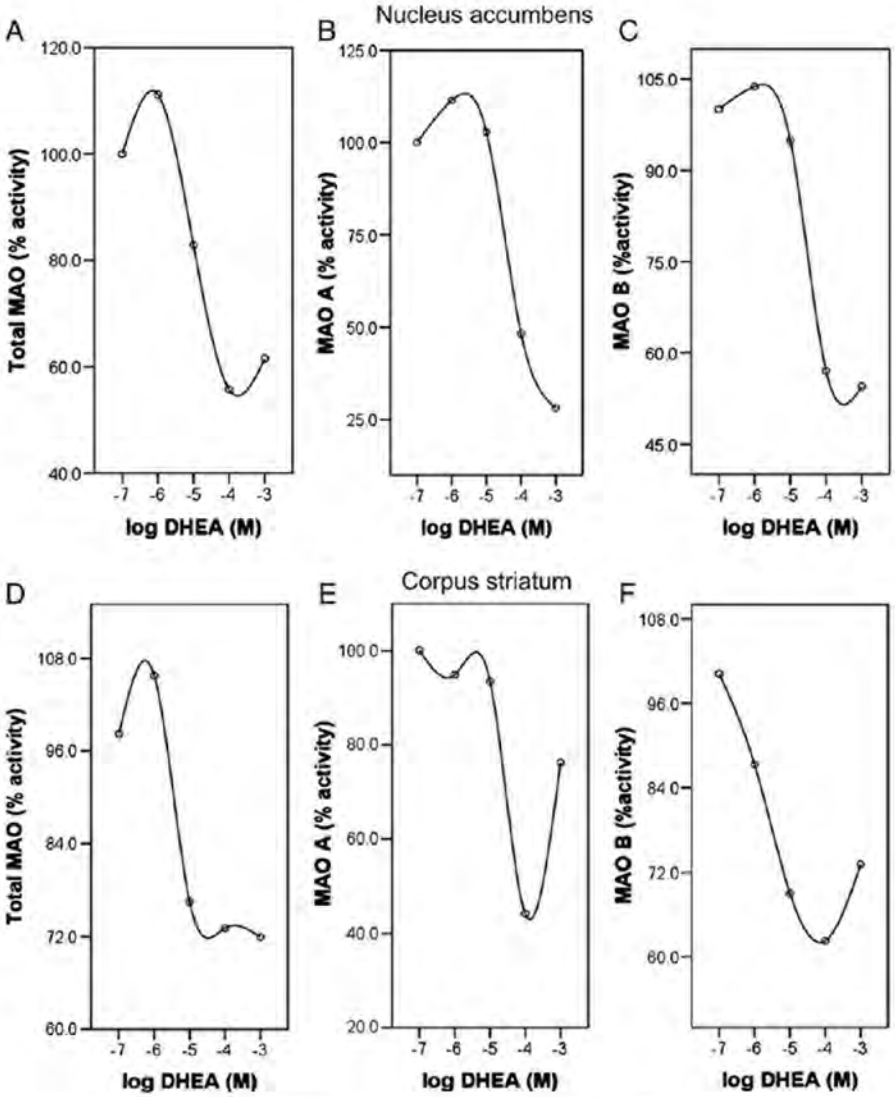

Fig. 2. Effect of DHEA on MAO activity in NAc and CS homogenates in vitro. DHEA inhibited total MAO activity (A,D) as well as MAO A (B,E) and MAO B (C,F) activities. NAc and CS homogenates obtained from Male Wistar rats ($n=3$) without previous treatment were pre-incubated with DHEA (100 nM–1 mM) for 5 min; then MAO activity was assayed by formation of 4HQ from kynuramine.

It has been reported that DHEA inhibits dopamine uptake in vitro (IC_{50} 52.5 μM) (Tomas-Camardiel et al. 2002); it remains to be determined if the steroid reaches those concentrations under our experimental conditions. Also, DHEA may inhibit striatal dopamine release through σ_1 receptor activation since selective agonists of this receptor inhibit NMDA- and K^+-stimulated dopamine release in the CS and NAc (Ault and Werling 2000; Moison et al. 2003), and DHEA is a sigma receptor agonist (Dubrovsky 2006; Monnet and Maurice 2006; Ueda et al. 2001).

Since MAO inhibition is neuroprotective against MPTP/MPP^+ neurotoxicity (Chen et al. 2007; Mandel et al. 2005), our results suggest that this effect may be involved in the protective effect of DHEA in experimental models of PD (Bélanger et al. 2006; Tomas-Camardiel et al. 2002; Morissette et al. 2008). Other protective effects of DHEA, such as antioxidant, antiapoptotic and antiexcitotoxic may also be involved (Charalampopoulos et al. 2006; Kumar et al. 2008; Kurata et al. 2004; Liu et al. 2007; Maninger et al. 2009; Maurice et al. 2006). The beneficial effect of DHEA in those models has been reported following several days after a single administration of the steroid (Tomas-Camardiel et al. 2002) or after repeated treatment (Bélanger et al. 2006), so it remains to be determined if DHEA inhibits MAO in the CS under those experimental conditions. Actually, chronic DHEA treatment reduced total MAO activity in the whole brain hemispheres (Kumar et al. 2008), which may contribute to its neuroprotective effect.

Regarding the antidepressant effect of DHEA, it should also be considered that MAO inhibitors are antidepressant drugs (Pae et al. 2007; Robinson and Amsterdam 2008) and DHEA also leads to this effect (Rabkin et al. 2006; Schmidt et al. 2005; Strous et al. 2003). Thus, MAO inhibition in the NAc by DHEA may be involved in its antidepressant action.

Finally, selective MAO inhibitors are the only drugs that have proven to be neuroprotective in clinical trials for PD (Olanow 2009), suggesting that MAO inhibition is sufficient to reduce or delay neurodegeneration in this disorder. Thus, inhibition of both MAO isoforms by DHEA suggests that, along its antidepressant effect, this steroid may be a neuroprotective approach for PD.

Conclusion

Our results suggest that the acute effect of DHEA on MAO activity may be involved in its antidepressant and neuroprotective effects. This supports the hypothesis that DHEA may be a therapeutic tool to treat depression and prevent neurodegeneration in patients with PD.

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19 The Role of DHEA in Mental Disorders

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INTRODUCTION

Dehydroepiandrosterone (DHEA) and its sulfate ester, dehydroepiandrosterone sulfate (DHEAS), modulate several neurotransmitter systems (Maninger et al. 2009; Pérez-Neri et al. 2008) involved in the pathophysiology of psychiatric disorders such as depression, dementia, schizophrenia, anxiety, and mania. Some studies have found an association between endogenous DHEA levels and the incidence and course of those mental disorders. Also, several controlled clinical trials have reported beneficial effects of DHEA administration.

In spite of an increasing body of evidence in this regard, the actual role of DHEA in mental disease is yet to be completely elucidated. This review summarizes published evidence regarding the possible role of DHEA and DHEAS in psychiatric disorders.

DEPRESSIVE DISORDER

Major depressive disorder is one of the most devastating mental diseases (Alexopoulos and Kelly Jr. 2009). Depressive symptoms include negative affect, sleep disturbance, feelings of guilt, and suicidal ideation, among others (Gotlib and Joormann 2010). Prevalence of depression throughout life has been estimated around 20% in some populations, and the rate of relapse may be as high as 75% (Gotlib and Joormann 2010). The mechanism for antidepressant action is partially understood and a therapeutic response is not achieved in every case (Katz, Bowden, and Frazer 2010).

Several studies have described abnormal DHEA or DHEAS levels in depressive disorders. Plasma DHEA concentration was increased in depressed (Heuser et al. 1998) and psychotic depressed (Maayan et al. 2000) patients, but salivary (Eser et al. 2006b; Goodyer et al. 2001b; Michael et al. 2000) and urinary (Poór et al. 2004) levels were decreased in other studies. Decreased (Jozuka et al. 2003; Maninger et al. 2009; Morgan et al. 2010) and unchanged (Kahl et al. 2006; Maninger et al. 2009; Young, Gallagher, and Porter 2002) blood DHEA levels have also been reported.

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Changes in DHEA and DHEAS salivary and blood concentrations are relevant to central nervous system function as those levels are positively correlated to their cerebrospinal fluid (CSF) counterparts (Goodyer et al. 2001b; Guazzo et al. 1996); however, it is possible that the brain content of the steroids is differently altered or even unchanged in spite of a different level in the extracellular environment. In fact, DHEA content in cingulate and parietal cortices from depressed patients was not significantly different from controls (Marx et al. 2006a), although other brain regions were not studied.

DHEA may be associated not only to the incidence of the disease, but also to the severity of depressive symptoms. Morning salivary DHEA levels were inversely correlated to the severity of depression in some studies (Eser et al. 2006b; Michael et al. 2000), although there was no correlation in patients with burning mouth disorder (Fernandes et al. 2009), healthy elderly (Fukai et al. 2009), or psychotic depressed patients (Maayan et al. 2000).

Moreover, it is possible that salivary DHEA concentration is not altered by the chronicity of the disease because it was not different in boys with chronic major depression compared with those who recovered from a depressive episode (Goodyer, Park, and Herbert 2001a). Thus, DHEA may be altered from the first depressive episode and remain altered throughout the course of the disease independently of remission. This hypothesis is supported by the lack of association between steroid levels and the effect of antidepressants. The therapeutic effect of repetitive transcranial magnetic stimulation was not accompanied by changes in plasma DHEA concentration in depressed patients (Padberg et al. 2002). However, low DHEA levels were associated with the antidepressant effect of sleep deprivation (Schüle et al. 2003).

The role of DHEA as the cause or the consequence of depression remains a matter of debate. Changes in steroid levels should be found before the disease onset if it is involved in the development of the disorder. However, changes in DHEA concentration were absent before the onset of major depression. Also, steroid levels were not significantly correlated to mood scores in adolescents at high risk of developing depressive disorders (Goodyer et al. 2000a). Furthermore, there was no significant difference in DHEA concentration between adolescents at high and low risk for depression (Goodyer et al. 2000a). However, those results may be influenced by the fact that not every high-risk case will finally develop depressive illness (Goodyer et al. 2000a). Actually, an increased DHEA concentration at baseline was significantly associated to the onset of major depression in adolescents at follow-up (Goodyer et al. 2000a,b, 2001b), although this result was not replicated in adults (Harris et al. 2000).

Even if an altered DHEA concentration is the cause or the consequence of depressive disorders, an increasing body of evidence supports a therapeutic effect of the steroid. Several studies have found beneficial effects of DHEA administration for depressive symptoms (Binello and Gordon 2003; Bovenberg, van Uum, and Hermus 2005; Brooke et al. 2006; Dubrovsky 2005; Eser et al. 2006a; Maninger et al. 2009; Ravindran et al. 2009; Schmidt et al. 2005) or psychological well-being (Brooke et al. 2006; Dubrovsky 2005; Maninger et al. 2009; Nawata et al. 2002; Schumacher et al. 2003). In placebo-controlled, double-blind clinical trials, DHEA administration to healthy subjects improves mood (Arlt et al. 1999). The steroid reduces symptom severity in depressed patients (Bloch et al. 1999; Eser et al. 2006b; Schmidt et al. 2005; Wolkowitz et al. 1999), and this effect also occurs in other diseases such as adrenal insufficiency (Binder et al. 2009; Hunt et al. 2000; Maninger et al. 2009), schizophrenia (Strous et al. 2003), and human immunodeficiency virus infection (Rabkin et al. 2006).

However, some studies have failed to replicate those results (Arlt et al. 2001; Kritz-Silverstein et al. 2008), but it should be noted that increased blood DHEAS levels were associated to an antidepressant response after DHEA treatment (Bloch et al. 1999; Rabkin et al. 2006); thus, the failure to increase DHEAS (and possibly DHEA) levels in some patients may be responsible for the absence of a clinical response to DHEA supplementation.

Regarding DHEAS, it is possible that reduced levels of this steroid favor the development of a depressive episode. Low DHEAS concentration is associated to an enhanced negative emotional

reaction following social rejection (Akinola and Mendes 2008). However, increased salivary (Assies et al. 2004; Maninger et al. 2009) and urinary (Eser et al. 2006b) concentrations were reported in depressed patients. Some authors have reported reduced DHEAS concentration in patients with depression (Eser et al. 2006b; Maninger et al. 2009) or dysthymia (Markianos et al. 2007). No difference in DHEAS plasma levels was found in other studies (Jozuka et al. 2003; Paslakis et al. 2010).

Supporting the role of DHEAS deficiency in depression, the steroid was inversely correlated to the severity of depressive symptoms according to some studies (Brzoza et al. 2008; Haren et al. 2007; Maninger et al. 2009; Nagata et al. 2000), although no significant correlations have been reported (Adali et al. 2008; Hsiao 2006; Maayan et al. 2000; Schüle et al. 2009). Also, DHEAS levels were positively correlated to mood scores, showing a better sense of well-being at increased steroid concentration (Valtysdottir, Wide, and Hallgren 2003). Depressive symptomatology in elderly women was associated to low DHEAS levels (Berr et al. 1996).

Even though an increased DHEAS concentration following DHEA administration is associated with an antidepressant response (Bloch et al. 1999; Rabkin et al. 2006), an increased baseline level may interfere with that effect. Depressed patients with high DHEAS levels do not respond to electroconvulsive therapy (Eser et al. 2006a,b) or pharmacological treatment (Schüle et al. 2009).

Thus, some studies suggest that an increased DHEAS baseline level may be detrimental for an antidepressant response; however, changes in DHEAS concentration from baseline are likely associated to the clinical efficacy of antidepressants. Reduction in symptom severity was positively correlated to the decrease in DHEAS levels according to some studies (Fabian et al. 2001; Schüle et al. 2009). Also, DHEA and DHEAS levels decrease following remission from depression (Fabian et al. 2001).

In summary, it may be suggested that DHEA levels are increased before the onset of depression and that those levels decrease when the disease is established. Both DHEA and DHEAS deficiency correlate to an increased symptom severity, and the restoration of DHEAS levels is associated to an antidepressant response; however, an increased baseline DHEA or DHEAS concentration may reduce the antidepressant effect of drugs and electroconvulsive therapy. In spite of the contrasting results regarding endogenous steroid levels, an increasing body of evidence supports the hypothesis that DHEA is reduced in major depression and steroid supplementation reduces symptom severity in this disorder (Table 19.1).

TABLE 19.1
Summary of Studies Reporting Altered DHEA or DHEAS Levels in Patients with Depressive Disorders

Reference	Patients	Diagnosis	Biological Sample	Results
		DHEA		
Heuser et al. (1998)	15 male, 47.7 ± 14.8 years; 11 female, 48.2 ± 18.1 years	Major depressive disorder	Plasma	Increased DHEA levels
Maayan et al. (2000)	7 men, 10 female; 40.4 ± 3.1 years	Major depression with psychotic features ($n = 2$), schizophrenia with comorbid depression ($n = 10$), schizoaffective disorder with depressive symptoms ($n = 5$)	Plasma	Increased DHEA levels

(Continues)

TABLE 19.1 (*Continued*)
Summary of Studies Reporting Altered DHEA or DHEAS Levels in Patients with Depressive Disorders

Reference	Patients	Diagnosis	Biological Sample	Results
		DHEA		
Morgan et al. (2010)	16 female; 54.5 ± 4.9 years	Major depressive disorder	Serum	Decreased DHEA levels
Jozuka et al. (2003)	8 male, 9 female; 40.3 ± 15.1 years	Major depressive disorder	Blood	Decreased DHEA levels
Michael et al. (2000)	12 male, 32 female; 20–64 years	Major depressive disorder	Saliva	Decreased DHEA levels
Poór et al. (2004)	9 male, 46.6 ± 9.9 years; 11 female, 35.3 ± 12.9 years	Major depressive disorder	Urine	Decreased DHEA levels
Kahl et al. (2006)	12 female; 26.3 ± 5.1 years	Major depressive disorder comorbid with borderline personality disorder	Serum	Unchanged DHEA levels
Young, Gallagher, and Porter (2002)	15 male, 29 female; 33 ± 11 years	Major depressive disorder	Saliva	Unchanged DHEA levels
		DHEAS		
Maayan et al. (2000)	7 men, 10 female; 40.4 ± 3.1 years	Major depression with psychotic features ($n = 2$), schizophrenia with comorbid depression ($n = 10$), schizoaffective disorder with depressive symptoms ($n = 5$)	Plasma	Increased DHEAS levels
Assies et al. (2004)	3 male, 10 female; 39.8 ± 11.3 years	Major depressive disorder	Saliva	Increased DHEAS levels
Markianos et al. (2007)	18 male, 47.1 ± 13.3 years; 43 female, 45.2 ± 13.9 years	Dysthymic disorder	Plasma	Decreased DHEAS levels
Jozuka et al. (2003)	8 male, 9 female; 40.3 ± 15.1 years	Major depressive disorder	Blood	Unchanged DHEAS levels
Paslakis et al. (2010)	22 male, 48 female; 51.0 ± 14.8 years	Major depressive disorder	Blood	Unchanged DHEAS levels

DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulfate.

DEMENTIA

Dementia is a cognitive disorder characterized by amnesia that also includes altered abstract thinking, judgment, and behavior among other disturbances. Dementia is an increasing health problem worldwide (Schumacher et al. 2003) that is most frequently present as Alzheimer's disease (AD; Galimberti and Scarpini 2010; Henderson 2010), but it may also be associated with stroke (Pendlebury 2009) or frontal lobar degeneration (Galimberti and Scarpini 2010). The prevalence

of AD has been estimated to be 5% after 65 years of age (Galimberti and Scarpini 2010) and its treatment remains challenging.

It has been reported that DHEAS levels are reduced in the striatum, cerebellum, and hypothalamus from AD patients (Kim et al. 2003; Maninger et al. 2009; Weill-Engerer et al. 2002; Wojtal, Trojnar, and Czuczwar 2006). Those levels were also reduced in cognitively impaired elderly (Ulubaev et al. 2009) and multi-infarct dementia patients (Azuma et al. 1999; Kim et al. 2003; Maninger et al. 2009), suggesting that this alteration may be associated to cognitive dysfunction rather than to a specific disease. That decrease may be related to the degenerative process in AD because serum DHEAS levels were correlated to hippocampal volume (Maninger et al. 2009) and were also associated to the development of AD in women with Down syndrome (trisomy 21; Schupf et al. 2006).

The steroid may accumulate in the brain due, at least in part, to a reduced metabolism because expression of CYP7B, the gene encoding 7α-hydroxylase that converts DHEA to its 7α-hydroxylated metabolite, was reduced in the hippocampus (Hampl and Bicíková 2010; Maninger et al. 2009; Yau et al. 2003); also, plasma 7α-hydroxydehydroepiandrosterone concentration was reduced in AD patients (Maninger et al. 2009).

Additionally, decreased DHEAS content may result from a reduced sulfotransferase activity because DHEA content is increased in the CSF, hypothalamus, hippocampus, and frontal cortex of AD patients (Brown et al. 2003; Kim et al. 2003; Maninger et al. 2009; Marx et al. 2006b; Naylor et al. 2008). Interestingly, CSF DHEA concentration positively correlates with the content of the steroid in the temporal cortex (Naylor et al. 2008).

Some studies have reported that plasma DHEA and DHEAS levels were decreased in AD patients compared with healthy controls (Bernardi et al. 2000; Ferrari et al. 2001a; Hillen et al. 2000; Nawata et al. 2002). Those results may be associated to a reduced adrenocorticotropic hormone release (Näisman et al. 1996). Similar findings have been reported in vascular dementia (Bernardi et al. 2000; Ferrari et al. 2001a; Nawata et al. 2002).

Although some studies have reported that serum DHEA and DHEAS concentrations are positively correlated to cognitive performance in healthy subjects (Maninger et al. 2009; Ulubaev et al. 2009), some other studies have failed to replicate in AD those previous results (Brown et al. 2003; Carlson, Sherwin, and Chertkow 1999; Ferrari et al. 2001a; Fuller, Tan, and Martins 2007; Hoskin et al. 2004; Rasmuson et al. 1998; Schneider, Hinsey, and Lyness 1992). Also, the association of the steroid to cognitive function was not replicated in elderly subjects, as measured by the correlation between steroid levels and cognitive scale scores (Carlson and Sherwin 1999; Ferrari et al. 2001b; Fuller, Tan, and Martins 2007; Maninger et al. 2009; Schumacher et al. 2003; Ulubaev et al. 2009). DHEAS levels were not associated with minimental state examination (MMSE) scores or the incidence of dementia in either the elderly (Berr et al. 1996; de Bruin et al. 2002) or AD patients (Rasmuson et al. 1998). Even inverse correlations between DHEAS levels and cognitive performance in the elderly have been reported (Fuller, Tan, and Martins 2007; Maninger et al. 2009).

However, among AD patients, those with high plasma DHEAS levels performed better in some cognitive tasks compared with those with low steroid levels (Carlson, Sherwin, and Chertkow 1999; Fuller, Tan, and Martins 2007). Plasma 7αOH-DHEA was positively correlated to MMSE scores (Maninger et al. 2009).

Regarding steroid supplementation, cognitive scale scores improve in some studies following DHEAS administration (Azuma et al. 1999; Maninger et al. 2009). Thus, both endogenous and administered DHEA and DHEAS have been associated to cognitive performance in AD and other dementias. Those results suggest that, although DHEA is increased in AD, DHEAS deficiency is related to cognitive dysfunction, and thus, steroid supplementation is beneficial in this disorder (Table 19.2).

TABLE 19.2
Summary of Studies Reporting Altered DHEA or DHEAS Levels in Patients with Dementia

Reference	Patients	Diagnosis	Biological Sample	Results
		DHEA		
Brown et al. (2003)	4 male, 5 female; 74.6 ± 7.2 years	AD	CSF	Increased DHEA levels
Naylor et al. (2008)	25 patients; 81 years	AD	CSF	Increased DHEA levels
Kim et al. (2003)	7 male, 7 female; 75.1 ± 9.8 years	Probable AD	CSF	Increased DHEA levels
Kim et al. (2003)	4 male, 4 female; 78.5 ± 4.8 years	Vascular dementia	CSF	Increased DHEA levels
Brown et al. (2003)	6 male, 6 female; 74.6 ± 7.2 years	AD	Brain tissue	Increased DHEA levels
Marx et al. (2006b)	14 male; 83 years	AD	Brain tissue	Increased DHEA levels
Bernardi et al. (2000)	5 male, 7 female; 64–84 years	AD	Serum	Decreased DHEA levels
Bernardi et al. (2000)	6 male, 6 female; 65–82 years	Vascular dementia	Serum	Decreased DHEA levels
Brown et al. (2003)	5 male; 80.0 ± 6.9 years	AD	Serum	Unchanged DHEA levels
		DHEAS		
Kim et al. (2003)	7 male, 7 female; 75.1 ± 9.8 years	Probable AD	CSF	Decreased DHEAS levels
Azuma et al. (1999)	4 male, 3 female; 69.4 ± 6. years	Multi-infarct dementia	CSF	Decreased DHEAS levels
Kim et al. (2003)	4 male, 4 female; 78.5 ± 4.8 years	Vascular dementia	CSF	Decreased DHEAS levels
Weill-Engerer et al. (2002)	1 male, 4 female; 86.2 ± 3.7 years	AD	Brain tissue	Decreased DHEAS levels
Hillen et al. (2000)	7 male, 7 female; 87.2 ± 1.9 years	AD	Plasma	Decreased DHEAS levels
Azuma et al. (1999)	4 male, 3 female; 69.4 ± 6. years	Multi-infarct dementia	Serum	Unchanged DHEAS levels

DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulfate; AD = Alzheimer's disease; CSF = cerebrospinal fluid.

SCHIZOPHRENIA

Schizophrenia is a mental disorder characterized by psychotic, cognitive, and affective symptoms (Simpson, Kellendonk, and Kandel 2010). Its prevalence has been estimated around 1% worldwide (Stevens 2002). In spite of the scientific efforts to elucidate the disease, its etiology remains unclear and its therapeutics limited (Ritsner 2010; Simpson, Kellendonk, and Kandel 2010). Several factors are involved in the pathophysiology of this disorder: these include genes, environment, and hormones. In this regard, some studies suggest that DHEA has a role in this disorder (Ritsner 2010) although its relevance to the onset, course, and treatment of the disease remains to be completely elucidated.

Some abnormalities in DHEA and DHEAS levels have been reported in schizophrenia. Plasma DHEA concentration was increased in schizophrenic patients compared with healthy patients independently of antipsychotic treatment (di Michele et al. 2005; Maninger et al. 2009; Ritsner 2010; Strous et al. 2004). Also, the content of DHEA was increased in the posterior cingulate cortex from those patients (Maninger et al. 2009; Marx et al. 2006a).

Similar to those of DHEA, DHEAS levels were increased in schizophrenic patients (Oades and Schepker 1994; Strous et al. 2004), and they were associated to symptom severity. DHEAS concentration was positively associated to cognitive performance in schizophrenic patients while DHEA was inversely correlated (Harris, Wolkowitz, and Reus 2001; Ritsner 2010; Ritsner and Strous 2010; Silver et al. 2005). In another study, serum DHEA concentration was positively correlated with working memory performance (Harris, Wolkowitz, and Reus 2001).

In spite of the studies showing an increased DHEA concentration in schizophrenia, steroid supplementation exerted a therapeutic effect. DHEA administration to schizophrenic patients, along with antipsychotic medication, significantly reduced the severity of negative symptoms (Strous et al. 2003). Thus, DHEA may influence the response to antipsychotics; but antipsychotics, in turn, influence DHEAS levels; it has been reported that antipsychotic medication reduces DHEAS concentration in schizophrenic patients (Baptista, Reyes, and Hernández 1999).

Medication-induced side effects are also an important issue during the course of an antipsychotic treatment because those effects may severely compromise patients' health. In this regard, it has been reported that DHEA administration reduced antipsychotic-induced extrapyramidal symptoms in schizophrenic patients (Ritsner 2010), which is the most frequent side effect of first-generation antipsychotics.

In summary, DHEA levels are increased in blood and brain tissue from schizophrenic patients. In spite of those increased levels, high DHEA concentration is associated to a reduced severity of psychiatric symptoms and steroid supplementation leads to a beneficial effect, especially regarding cognitive symptoms and extrapyramidal side effects. It remains to be determined if increased DHEA concentration in schizophrenia is associated to the positive symptoms in this disorder because a further increase is beneficial to the negative symptoms only.

ANXIETY

The term "anxiety" involves a group of mental disorders characterized by feelings of fearfulness that may include panic, psychological complaints, and autonomic symptoms (Tyrer and Baldwin 2006). Its prevalence has been estimated around 30% (Nandi, Beard, and Galea 2009), but it is higher in women than in men (McLean and Anderson 2009). Several anxiolytic drugs are currently in use, but clinical response is achieved in less than half of cases (Tyrer and Baldwin 2006).

Some studies support an association of endogenous or administered DHEA to the incidence or treatment of anxiety disorders. Plasma DHEA concentration was increased in patients with panic (Brambilla et al. 2005; Maninger et al. 2009) and posttraumatic stress disorders (Maninger et al. 2009). Steroid levels were not different between patients and controls in other studies (Brambilla et al. 2003; Eser et al. 2006b; Laufer et al. 2005; Maninger et al. 2009; Semeniuk, Jhangri, and Le Mellédo 2001). Moreover, DHEA levels increase following experimentally induced panic attacks in humans (Eser et al. 2006b).

Interestingly, DHEA concentration was positively correlated to the severity of panic and phobia symptoms and negatively correlated to anxiety symptoms, according to some studies (Brambilla etal. 2003; Luz et al. 2003). DHEAS, in turn, was negatively correlated to the severity of anxiety in patients with chronic urticaria (Brzoza et al. 2008) but was positively correlated to anxiety scores in depressed patients (Hsiao 2006). However, DHEA levels were not correlated to anxiety scores in patients with panic disorder (Brambilla et al. 2005), social phobia (Laufer et al. 2005), or victims of intimate-partner violence (Pico-Alfonso et al. 2004).

Several studies have found beneficial effects of DHEA supplementation for anxiety or psychological distress (Binder et al. 2009). Administration of DHEA, but not estrogens, reduced anxiety in female patients with anorexia nervosa compared with baseline scores (Gordon et al. 2002). Also, DHEA, along with antipsychotic medication, reduced anxiety in schizophrenic patients (Eser et al. 2006b; Strous et al. 2003).

In summary, some studies have found that DHEA concentration is increased in anxiety disorders, that it further increases following panic attacks, and that it is positively correlated to phobia symptoms. In contrast, both DHEA and DHEAS levels were inversely correlated to anxiety symptoms in other studies. It is possible that DHEA is differently involved in phobia and anxiety; the steroid may increase with increasing severity of phobia and panic symptoms, but, by reducing anxiety, the steroid may contribute to control the behavioral response to those symptoms. This issue remains speculative and awaits further investigation; however, some studies support the therapeutic role of DHEA supplementation for anxiety.

AGGRESSIVE BEHAVIOR

Aggression is a complex behavior, displayed by several animal species, that is intended to establish dominance for survival (Soma et al. 2008), but it may also involve a pathological background.

Several studies have associated aggressive behavior to estradiol, testosterone, and other anabolic-androgenic substances, but adrenal steroids also seem to be involved (Soma et al. 2008; Talih, Fattal, and Malone 2007). Some studies have found associations between aggression, but not testosterone, and DHEAS in children (Soma et al. 2008; van Goozen et al. 1998). It is possible that the lower testosterone levels in children compared with adults accounts for that apparent discrepancy. Also, adolescent females with congenital adrenal hyperplasia, leading to increased DHEAS levels, show aggressive behavior (Soma et al. 2008); pharmacologic reduction of DHEAS levels in those patients reduces aggression (Soma et al. 2008). DHEAS levels increase according to the intensity of aggression in 7- to 11-year-old boys (Butovskaya et al. 2005).

However, some studies have failed to replicate the associations between aggression scores and either testosterone or DHEA in 5-year-old boys (Azurmendi et al. 2006; Sánchez-Martín et al. 2009); rather androstenedione is associated in that population (Azurmendi et al. 2006). The relationship between DHEA or DHEAS and aggression in adults is likely to be different. DHEAS levels are lower in highly aggressive patients, compared with controls, following alcohol withdrawal (Ozsoy and Esel 2008).

Several animal models show that DHEA administration reduces aggressive behavior (Soma et al. 2008). Taken together, those results suggest that DHEAS increases, while DHEA decreases, aggressive behavior and, thus, the sulfated and unsulfated steroid lead to opposite effects.

MANIA

Mania is characterized by irritability and euphoria that may be accompanied by high self-esteem, racing thoughts and speech, and increased goal-directed activity; psychotic features are present in some cases. Mania is the main component of bipolar disorder (Mansell and Pedley 2008).

It has been reported that DHEA levels are increased in the posterior cingulate and parietal cortices from patients with bipolar disorder (Marx et al. 2006a). Also, DHEA consumption has been associated to the development of episodes of mania (Dean 2000; Kline and Jaggers 1999; Markowitz, Carson, and Jackson 1999; Vacheron-Trystam et al. 2002). The psychostimulating-like effect of DHEA has been observed after administration of high doses (up to 300 mg/day) during several weeks or months (more than 3 months; Markowitz, Carson, and Jackson 1999), and it remains to be determined if this effect involves DHEA conversion to androgens since anabolic steroid consumption has been associated with mania (Talih, Fattal, and Malone 2007).

Also, it is yet to be elucidated whether DHEA consumption could induce mania in women. In fact, mood-stabilizers (valproic acid) increase the expression of P450scc and P450c17, as well as the

synthesis of DHEA and androstenedione, in ovarian theca cells (Nelson-DeGrave et al. 2004); thus, it is possible that DHEA is involved in the therapeutic effect of those drugs.

In summary, case reports of DHEA-induced mania are anecdotic and may involve androgen formation. However, some studies suggest that DHEA may be involved in the mechanism of action of mood-stabilizers.

SUMMARY

Endogenous DHEA levels are altered in psychiatric disorders as shown by several studies. Some studies suggest that DHEA deficiency may be involved in the pathophysiology of mental disease, but increased steroid levels have been reported before the onset of depression and after that of dementia, schizophrenia, and anxiety. Also, although an increase in DHEA concentration is involved in the effect of some neuroleptics, high steroid levels at baseline may interfere with their therapeutic effect.

DHEA levels were inversely correlated to disease severity according to several studies, suggesting that, in spite of a possible baseline increase, a further increase is beneficial. However, DHEA concentration was positively correlated to the severity of phobia and panic symptoms; thus, the role of the steroid in anxiety remains to be elucidated.

Controlled clinical trials consistently show beneficial effects of DHEA supplementation for several psychiatric disorders. Thus, even though the involvement of DHEA in the pathophysiology of psychiatric disorders remains controversial, the therapeutic effect of steroid administration is supported by an increasing body of evidence.

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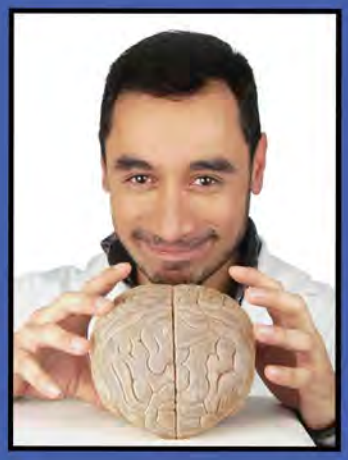

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