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The interaction of estrogens and noradrenaline in depression

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Update by topics

SUMMARY

Depression refers to a mood disorder characterized by deep sadness and a loss of interest and pleasure. Epidemiologic studies show that this disorder represents a public health problem affecting 12% of the world population, while it is two times more likely to affect women than men. Depression is a complex disease in which, it has been observed, the noradrenergic system appears to play an important role. Thus, a decrease in the noradrenergic tone, changes in noradrenaline (NA) synthesis, reduction in its turn-over, and modulation of its receptors can induce this disease. Likewise, estrogens are a broad family of hormones with multiple biologic functions, which include those related to mood states. Clinical studies suggest that hormonal fluctuations, such as the premenstrual phase, puerperium and perimenopause, are associated with increased vulnerability to depression. Conversely, estrogens have shown antidepressant effects in different preclinical models. Binding and electrophysiology studies suggest that estrogens are able to modulate noradrenergic transmission, through an increase in NA neurons' firing rate, a regulation of noradrenergic receptors and the synthesis and catabolism of this neurotransmitter. Additionally, behavioral studies support the interaction of estrogens with the noradrenergic system. Thus, the purpose of this review is to analyze the role of noradrenalin, estrogens and their interaction in the treatment of depression in both clinical and preclinical studies.

Key words: Estrogens, adrenaline, depression.

RESUMEN

La depresión se define como un trastorno del estado de ánimo caracterizado por un estado de tristeza profunda y una pérdida de interés o placer. Este trastorno psiquiátrico afecta al 12% de la población mundial, siendo las mujeres quienes más la padecen. La depresión es una patología compleja, en la que se ha observado que el sistema noradrenérgico cumple un papel importante. Así, una disminución en el tono noradrenérgico, los cambios en la síntesis y el metabolismo de la noradrenalina (NA), así como en la modulación de sus receptores, pueden conducir a un estado depresivo. Por otro lado, los estrógenos son un grupo de hormonas gonadales con diversas funciones fisiológicas, incluidas las que se relacionan con los estados afectivos. Diversos estudios clínicos sugieren que las fluctuaciones hormonales, como la etapa premenstrual, el puerperio y la perimenopausia, se asocian con un aumento en la vulnerabilidad a presentar depresión y se ha demostrado que los estrógenos presentan efectos antidepresivos en diversos modelos conductuales. En estudios electrofisiológicos y de unión de ligando se reporta que los estrógenos son capaces de modular la transmisión noradrenérgica a través de diferentes mecanismos, los cuales incluyen un aumento en la frecuencia de disparo de las neuronas noradrenérgicas, la regulación de la densidad de los receptores noradrenérgicos, así como en los procesos de síntesis y metabolismo de este neurotransmisor. Además, diversos estudios conductuales han aportado información que apoya la participación de los estrógenos en la modulación del sistema noradrenérgico e incluso se ha propuesto que a través de esta vía podrían inducir sus efectos antidepresivos. De esta forma, el propósito de esta revisión es analizar, a nivel clínico y preclínico, la participación de la noradrenalina y de los estrógenos, y la relación entre ambos en el tratamiento de la depresión.

Palabras clave: Estrógenos, adrenalina, depresión.

1. DEPRESSION

Depression is an affective state of sadness which presents as a response to a variety of biological, genetic, and psychosocial factors.[1] According to the Diagnostic and Statistical Manual of Mental Disorders,[2] depression is defined as a mood disorder characterized by a state of deep sadness and a loss of interest or pleasure. These symptoms, which last for at

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least two weeks and are present during most of the day, tend to be accompanied by at least four of the following symptoms: a) cognitive, as a loss of interest, difficulty concentrating, low self-esteem, guilt, suicidal ideation; b) behavioral, as in psychomotor delay or agitation, reticence, crying; and c) somatic, as in sleep disorders (insomnia or hypersomnia), increased or decreased appetite, weight loss or gain, fatigue, and decreased sex drive.[1]

Epidemiological studies show that depression is public health problem affecting 12% of the global population, while women are two times more likely to suffer from depression than are men.[3,4] According to the World Health Organization, depression is the fourth most prevalent cause of morbidity worldwide, and it is estimated to be the second most prevalent cause of disability by 2020.[5]

2. NORADRENALINE AND DEPRESSION

2.1 Noradrenaline

Noradrenaline (NA) is the neurotransmitter for most of the postganglionic sympathetic fibers and for many central neurons. This catecholamine derives from the amino acid tyrosine, and it has L-3,4-dihydroxyphenylalanine (DOPA) and dopamine as its synthetic intermediates. The catalytic enzymes responsible for this process are tyrosine hydroxylase, dopa-decarboxylase, and dopamine β-hydroxylase. The NA is stored in the nerve endings within vesicles and released in the synaptic cleft by exocytosis. Some of the released molecules diffuse to attach to and activate postsynaptic receptors, thereby inducing a physiological response. Other NA molecules can occupy autoreceptors, and be recaptured by the transporter in presynaptic neurons to be restored or to be metabolized by monoamine oxidase A (MAO-A) or by cathecol-O-methyl transferase (COMT).[6]

The cell bodies and fibers containing NA originate in the *locus coeruleus* and other lower noradrenergic areas, such as the nucleus of the solitary tract or the lateral reticular nuclei. From these nuclei there are two large upward projection pathways: the dorsa noradrenergic pathway and the ventral noradrenergic pathway. Both pathways control the level of cortical/subcortical activity, primarily through projection to the cortex, to the limbic system (hippocampus, amygdala, and septum) and to the diencephalon (thalamus and hypothalamus).[7] As such, through these upward projections, it is thought that the NA is involved in controlling emotions and mood.[1]

2.2 Noradrenergic Receptors

The noradrenergic receptors are divided into two families: the α and the β.[8] The α1 receptor family is subdivided into α1A, α1B, and α1D, while the α2 family is subdivided into α2A, α2B, α2C, and α2D. Regarding the β receptor family, there are three known subtypes: β1, β2, and β3. The α1 and β receptors are located in the postsynapsis, while the α2 receptors are located in both the presynapsis and the postsyanpsis.[1,6]

When the noradrenergic neurons are stimulated, the NA is released towards the synaptic cleft, interacting with its α_1 or β postsynaptic receptors. When NA concentrations in the synaptic space are high, a portion of the released NA interacts with the α_2 presynaptic receptors (autoreceptors), resulting in a negative feedback or autoinhibitive process which serves to reduce noradrenergic transmission.[6]

The three families of adrenergic receptors are coupled to G proteins. The α_1 receptors are generally excitatory, coupled to phospholipase C (PLC), so that when stimulated, they induce the forming of inositol triphosphate (IP3) and Ca^{2+}. Meanwhile, the α^2 receptors decrease cAMP formation, as they are negatively coupled to adenylate cyclase. In turn, the β receptors are positively coupled to adenylate cyclase, so that their stimulation increases cAMP formation.[6,9]

2.3 Role of the Noradrenergic System in Depression

While the treatment of depression has focused in large part on the neurotransmitter serotonin (5-HT), it is known that the noradrenergic system is also involved in both the pathogenesis and treatment of this disease.[10-12] Regarding etiology, it has been observed that depressed patients show a reduction in NA activity, as the levels of the metabolite of this neurotransmitter (3-methoxy-4-hydroxyphenylglycol (MHPG) are reduced.[13,14] Additionally, patients treated with NA selective inhibitors show a drop in depressive effects when administered with an NA synthesis inhibitor.[14] Likewise, in *post-mortem* studies of suicide cases, it has been found that the *locus coeruleus* shows a marked increase both in the levels of the enzyme tyrosine hydroxylase and in the density of adrenergic α_2 autoreceptors,[15] which suggests depletion of NA in certain regions of the brain.[16] In addition, some studies show the existence of a polymorphism in the α_{2C} adrenergic receptor, which has been associated with changes in neuron activity, in the amygdala and cingulate, in response to emotional information (showing of sad faces) in depressed patients.[17]

In terms of treatment, it has been observed that administration of selective norepinephrine reuptake inhibitors, such as reboxetine, is as effective in treating depression as fluoxetine.[18,19] It has even been observed that reboxetine has had good results in depressed patients who do not respond to treatment with fluoxetine.[20] Likewise, duloxetine and venlafaxine (which are dual inhibitors, as they block reuptake of both norepinephrine and serotonin) have proven effective in treatment of major depression.[21-24] Furthermore, in the search for new strategies in treating depression, it has been suggested that simultaneous administration of adrenergic α_2 autoreceptor antagonists and noradrenaline reuptake inhibitors

increases the concentration of noradrenaline in several areas of the brain, inducing antidepressant effects.[25] This increase has been observed with both noradrenaline selective inhibitors (such as desipramine, reboxetine, and atomoxetine), as well as with the use of non-selective noradrenaline reuptake inhibitors (such as sibutramine, duloxetine, and venlafaxine). In fact, it has been suggested that this increase in NA could reduce the time in which the antidepressant effect is observed.[25]

3. ESTROGENS AND DEPRESSION

3.1 Estrogens

The term estrogen is used to describe the group of gonadal hormones with different physiological functions in various tissues and cell types. While initially it was thought that this was due to the hormones responsible for the functioning of the female reproductive system, today we know that estrogens are also involved in brain functions relating to affective states.[26,27]

Estrogens can be classified in three different groups:

1. *Natural Estrogens*: They are steroid compounds of 18 carbon atom, including estrone (E_1), 17 β-estradiol (E_2), and estriol (E_3). The ovaries are the main source of E_2 in premenopausal women, while most of the E_1 and E_3 is formed in the liver, using E_2, or in peripheral tissues, using androstenedione. In postmenopausal women, the main precursors of estrogen production in peripheral tissues are androstenedione, testosterone, and E_1.[27]
2. *Conjugated or Semi-synthetic Estrogens*: These compounds are a product of chemical alteration of natural estrogens. Synthetic estrogens include premarin (conjugated equine estrogen composed of E_1 sulfate and equilin and equilenin estrogens), ethinylestradiol (EE_2) (levonorgestrel), diethylstilbestrol (DES), chlorotrianisene, dienestrol, fosfestrol, mestranol, polyestradiol phosphate, and quinestrol.[27]
3. *Phytoestrogens*: These are nonsteroidal polyphenolic compounds which are extracted from plants and possess estrogenic activity. Phytoestrogens are found in a variety of plants and foods, such as soy (geistein and daidzein), wheat, red clover (Promensil), and peanuts. Based on their chemical structure, we can classify them as either flavonoids, stilbenoids, or lignans.[27,28]

3.2 Estrogen Receptors

The effect of estrogen is mediated by two intracellular estrogen receptors (ERα and ERβ) and a membrane receptor called GPR30. Activation of a gene for the ERα and ERβ receptors can result in multiple proteins from the same receptor. The mechanisms involved in this diversity include epigenetic changes and methylation of genes which encode these receptors, alternative RNA *splicing* which produces multiple isoforms of each mRNA receptor, and the multiple sites for initiation or translation of the mRNA of these receptors. In general, activation of ERα and ERβ receptors leads to transcriptional activation of target genes. Furthermore, the GPR30 receptor is a G-protein coupled seven-transmembrane receptor, and its activation is a result of the mobilization of intracellular Ca^{2+} and the synthesis of IP3.[27]

3.3 Role of Estrogens in Depression

Several lines of investigation indicate that estrogens play an important role in modulating depression.[29-31] Clinical evidence suggests that drastic hormonal fluctuations that occur throughout life, such as premenstrual, postpartum, and perimenopausal stages, are associated with increased vulnerability to the onset of psychiatric disorders, such as depression.[32,33] There is speculation that these psychiatric changes are associated with changes in the levels of sex steroids, such as estrogens, which significantly modulate brain functions, resulting in changes in mood and behavior.[31,33] In this regard, it has been observed that depressive episodes during menopause are accompanied by the drop in estradiol levels. Likewise, it has been observed that the elimination of hormone replacement therapy in postmenopausal women seems to be associated with onset of depressive symptoms.[31,34] Additionally, it has been proven that estradiol is useful in treating symptoms of postpartum depression.[35]

In line with clinical findings, preclinical studies have shown that estrogens, such as E2 and EE2, administered subcutaneously or in specific brain structures (such as the hippocampus), induce antidepressant effects in several animal models.[26,36-39] Likewise, this effect has been seen to be long-lasting, being maintained for 48 to 72 hours.[40] The effect of these compounds has been directly linked to the estrogen receptors, as the administering of specific antagonists for these receptors (such as RU 58668 and ICI 182-780) blocks the antidepressant effect.[41,42]

Similarly, *knockout* studies with rats on the ERβ[43] receptor and with selective modulators of these receptors, such as coumestrol or diarylpropionitrile, support the role of ERβ receptors in regulating depressive behaviors.[44]

4. INTERACTION BETWEEN ESTROGENS AND THE NORADRENERGIC SYSTEM IN DEPRESSION

Different studies, including ligand binding studies [45,46] electrophysiological recordings,[47,48] have shown that estrogen

can modulate noradrenergic neurotransmission throughout the Central Nervous System. This system is modulated through the release of NA, the regulation of its receptors, as well as the processes of synthesis and elimination of the neurotransmitter.

Regarding release of NA and regulation of receptors, it has been observed that E_2 administered to ovariectomized female rats increases the shot frequency of noradrenergic neurons projecting towards the preoptic area and the anterior hypothalamic area.[48] Likewise, E_2, DES, and mestranol reduced the density of α-adrenergic receptors in structures such as the hypothalamus, the frontal cortex, and the nucleus of the solitary tract.[45,46,49-51] Similarly, E_2 increases the activity of the α1 receptors in neurons from the preoptic area, while also decreasing the mRNA expression of the α2 receptor.[47] Finally, it has also been reported that chronic treatment with E2 reduces the response of the β-adrenergic receptors.[52]

Furthermore, with regards to NA reuptake, synthesis, and metabolism, *in vitro* studies have shown that E_2, EE_2, DES, and some cathecol estrogens, such as 2-hydroxy-EE_2 (2-OH-EE_2) and 2-hydroxy-E_1 (2-OHE), inhibit the NA reuptake sites in synaptosomes from the cerebral cortex and the hypothalamus of the rat,[53] resulting in an increase in NA levels in the synaptic space. In line with these findings, studies conducted by Hiemke et al.[54] show that acute administration to ovariectomized rats decreases the rate of NA reuptake in the hypothalamus and increases tyrosine hydroxylase mRNA levels in the *locus coeruleus*, thus increasing NA levels.[55] Finally, it has been reported that estrogens also increase NA levels by inhibiting the activity of the MAO.[56,57]

It is interesting that some preclinical studies (in the forced swimming model of depression) support the idea that estrogens induce antidepressant effects by modulating noradrenergic transmission. For example, it has been observed that EE_2 presents a behavioral profile similar to mixed noradrenalin and serotonin reuptake antidepressants, such as duloxetine and venlafaxine.[40,58,59] Similarly, it has been observed that EE2 estrogen facilitates the antidepressant effect of a selective NA reuptake inhibitor, desipramine.[60] These results have lead to the suggestion that the antidepressant effect of EE_2 is related to activation of the noradrenergic system, as well as the serotonergic system.

In the same line of research, it has been suggested that the interaction of EE_2 with the noradrenergic system could be mediated by α2-adrenergic receptors, given that idazoxan, a selective antagonist of these receptors, is able to block the antidepressant effect induced by EE_2.[42] Additional to these studies, it was recently found that DSP4, a neurotoxin that selectively destroys the noradrenergic nerve endings originating in the *locus coeruleus*,[61] was able to cancel out the antidepressant effect induced by the EE2 in the forced swimming test.[42]

Together, these findings suggest that estrogens can facilitate noradrenergic transmission by: 1. inducing the increase in NA synthesis; 2. reducing NA reuptake, thus improving NA availability; or 3. using a mechanism involving both 1 and 2. It is important to consider that, according to the foregoing information, it is clear that the antidepressant effect of estrogens is associated with a mix between its effect on the noradrenergic system, and its direct action on estrogen receptors.

In conclusion, depression is a complex pathology which involves neurotransmission systems like the noradrenergic system. Several researchers have confirmed the role of estrogens in modulating depression, and this research indicates that this regulation is carried out using noradrenergic neurotransmission. This set of information situates estrogens as new candidates in expanding our understanding of the physiopathology of depression, as well as in the discovery of new therapeutic strategies in treating this disease.

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