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Review Article

The endogenic neurosteroid system and its role in the pathogenesis and therapy of mental disorders

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Abstract

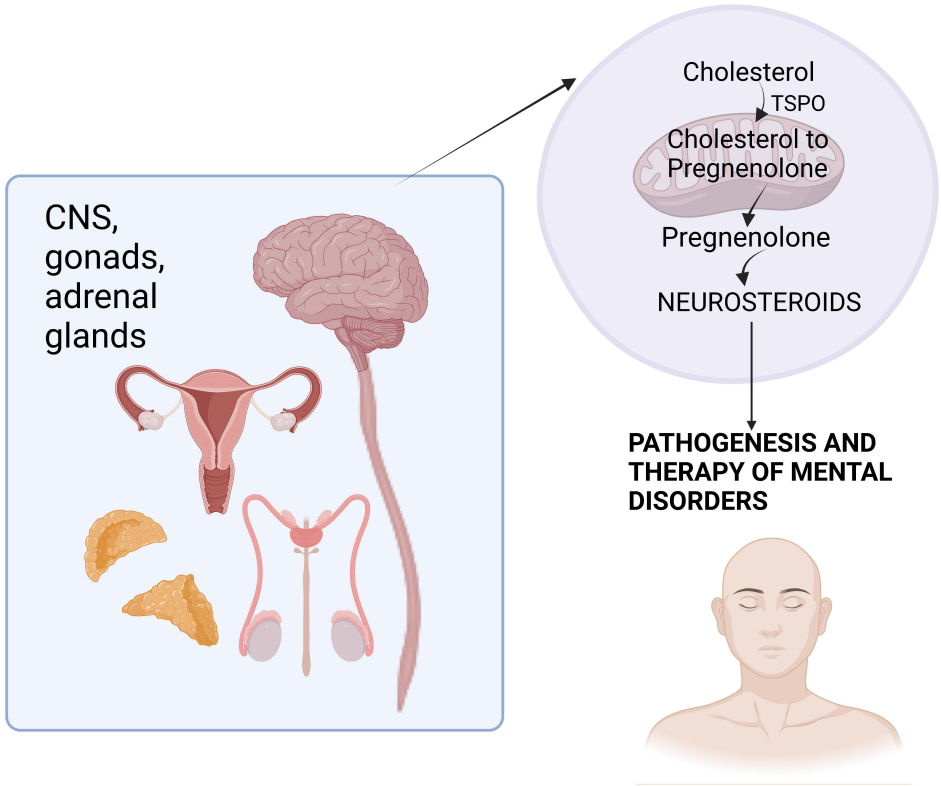
Introduction: Although neurosteroids have been relatively recently discovered, their significant role in the neurochemical processes and pathogenesis of a number of psychiatric and neurological disorders is now quite clear. First of all, it seems important to clarify the definition of the endogenous neurosteroids as a class of steroids, taking into account the variability of approaches to their description. Currently, neurosteroids include endogenous steroids synthesized in the central nervous system, gonads, or adrenal glands and interacting with $GABA_A$, NMDA, and sigma-1 receptors.

Neurosteroid biosynthesis: Biosynthesis of neurosteroids begins with rate-limiting reaction of TSPO binding cholesterol and transporting it into the mitochondria, where pregnenolone is synthesized following the cytochrome P450scc (CYP11A1) impact.

Interaction with $GABA_A$, NMDA and sigma-1 receptors: According to the experimental data, neurosteroids act as the most highly potent endogenous allosteric modulators of the GABA receptor; some types of neurosteroids (ALLO, DHEA, etc.) can produce a rapid anxiolytic and anticonvulsant effect. There is some experimental evidence for antipsychotic effects of some neurosteroids realized through NMDA receptors: intracerebral administration of ALLO to laboratory animals can prevent further appearance of motor agitation and other equivalents of psychosis after administration of high doses of amphetamines. It has also been proven in several studies on animal models that neurosteroids exhibit anxiolytic effects through sigma-1 receptors.

Conclusion: The article describes the process of neurosteroidogenesis and the effect of neurosteroids on listed receptorsin accordance with already available scientific data. In addition, this paper describes the specific role of various neurosteroids in the development of mental illnesses, including anxiety disorders, depression, and schizophrenia

Graphical Abstract



Keywords

allopregnanolone, GABA$_A$-receptors, DHEA, NMDA-receptors, pregnenolone, sigma-1 receptors, steroidogenesis, TSPO.

Introduction

About 40 years ago, the long-term presence of steroid hormones in the brain of rodents after adrenalectomy and castration was first discovered. In 1981, Corpéchot et al. (1981) demonstrated that some steroids are synthesized directly in the brain. Subsequently, in 1992, Paul and Purdy coined the term "neuroactive steroids" to include all natural or synthetic steroids that affect neuronal excitability via non-genomic mechanisms. The term was accepted in the literature, but Baulieu transformed the term which implied steroids with 3 properties: a) they are synthesized within the nervous system *de novo* from cholesterol; b) their presence in the nervous system after removal of steroidogenic tissues was demonstrated; c) the enzymes involved in their synthesis are expressed within the nervous system (NS) (Schumacher et al. 2009). Later, the original term included steroids synthesized within the NS, but from peripheral metabolic precursors. Currently, neurosteroids include endogenous steroids synthesized in the central nervous system (CNS), gonads, or adrenal glands and interacting with GABA$_A$, NMDA, and sigma-1 receptors. This term most often refers to 3α-hydroxy metabolites of progesterone, deoxycorticosterone and testosterone with a reduced A-aromatic ring, GABA$_A$ receptor agonists, and 3β-hydroxy pregnane with a reduced A-aromatic ring, GABA$_A$ receptor antagonists (Compagnone and Mellon 2000).

Neurosteroids biosynthesis

The CNS steroids can be conditionally classified into two types:

1. Neuroactive steroids which are synthesized in adrenal glands, gonads or placenta (i.e., in the peripheral steroid organs) and which penetrated blood-brain barrier;

2. Neurosteroids which are synthesized within the CNS *de novo* from cholesterol or *in situ* from steroid metabolic precursors circulating in the blood (Do Rego et al. 2012).

The vast majority of steroids, except for conjugated ones, easily pass through the blood-brain barrier by diffusion or via transport proteins, such as organic anion transporting polypeptides or monocarboxylate transporters (Schumacher et al. 2009; Banks 2012; Witt

et al. 2014). Steroid hormones from peripheral organs are transported to the brain in a complex with albumin, transcortin, and sex hormone-binding globulin (Diotel et al. 2018). It is important to understand in which structures of the NS and by what types of cells neurosteroids are synthesized, but this depends on a number of factors. For example, in the brain of adult rats, aromatase, which is involved in the transformation of androgens into estrogens, is expressed exclusively by neurons. However, in the case of excitotoxicity or injury, it can also be expressed by astrocytes, which can be considered as indirect evidence of the neuroprotective effect of some neurosteroids (Schumacher et al. 2009). It is possible to determine the origin of the steroid using the enzymes involved in its synthesis, since the expression and activity of the enzyme in certain areas indicate the corresponding metabolic pathways. Cytochrome P450scc activity was found in the spinal ganglia, dorsal horns of the spinal cord, and somatosensory cortex, indicating a broad area of expression (Schumacher et al. 2009). The literature data suggests that neurosteroids are synthesized both in the CNS and in the peripheral NS. The experiments with cell cultures demonstrated that the neuroactive progesterone metabolite allopregnanolone is synthesized mainly by glial cells and interacts with $GABA_A$-receptors of nearby neurons (paracrine). These data agree with the results of the *in vivo* studies: the activity of the enzyme 3α-hydroxysteroid dehydrogenase (3α-HSOR) in the olfactory bulbs of rats did not change after the administration of kainic acid, which destroys neurons, but does not damage glial cells (Schumacher et al. 2009). *De novo* synthesis from cholesterol in glial cells and the CNS neurons takes place predominantly in the hypothalamus and limbic structures (hippocampus, amygdala) (Kalinina et al. 2014). However, such a generalization of localizations can be found mainly in the works of the Russian authors.

The first step in steroidogenesis in any tissue is cholesterol transport into the mitochondria. Cholesterol is transported to the outer mitochondrial membrane mainly in 2 ways: via facilitated diffusion with soluble lipid transfer proteins or via diffusion across membrane contact sites (Elustondo et al. 2017). The data of molecular models and spectroscopic analysis demonstrated that the proteins involved in the cholesterol transport to the outer membrane are the proteins containing the START-domain (StAR-related lipid-transfer), presumably STARD1, STARD3 and STARD4 (Calderon-Dominguez et al. 2014; Elustondo et al. 2017), and oxysterol-binding proteins. However, there are many more mechanisms involved in this process, and this is an open field for study. The cholesterol transport from the outer to the inner mitochondrial membrane is an important rate-limiting step in steroidogenesis. Despite its importance, its mechanism is not completely clear. Presumably, it involves the 800kD multiprotein complex, which includes the translocation protein (TSPO), voltage-dependent anion channel (VDAC), P450scc cytochrome, ATP-binding domain AAA, and optic nerve atrophy protein 1 (McNeela et al. 2018). The other authors believe that StAR (Steroidogenic Acute Regulatory Protein)/STARD1, auxiliary proteins VDAC and adenine nucleotide translocator play the main role in the cholesterol transport to the inner membrane of mitochondria (Rodriguez-Agudo et al. 2006; Kraemer et al. 2017; Larsen et al. 2020). However, TSPO also forms protein complexes with them. Monomeric forms of TSPO were found on the outer membrane of mitochondria. Apparently, the monomeric TSPO binds cholesterol, and the protein polymeric forms are involved in cholesterol translocation. It is impossible to unambiguously determine the composition of the multiprotein complexes involved in cholesterol translocation; however, it is believed that the process of neurosteroid synthesis *per se* begins with the activation of the above-mentioned 18kD mitochondrial translocation protein, TSPO, previously referred to as the peripheral benzodiazepine receptor. It binds cholesterol and transports it into the mitochondria, where pregnenolone is synthesized following the cytochrome P450scc (CYP11A1) impact. This reaction is rate-limiting in the synthesis of neurosteroids. It is noteworthy that diazepam binding inhibitor (peripheral benzodiazepine receptor inhibitory ligand) at nanomolar concentrations stimulates the synthesis of pregnenolone from cholesterol (Costa et al. 1994). The regulation of steroid synthesis involves follicle-stimulating, luteinizing and adrenocorticotropic hormones. TSPO expression is elevated in degenerative and demyelinating diseases, as well as in response to trauma, suggesting the neuroprotective properties of TSPO ligands (Schumacher et al. 2009). Leaving the mitochondria, pregnenolone initiates two significant metabolic pathways in neurosteroid synthesis and can develop the sulfated form following sulfotransferase effect. Salman et al. (2011) reported that the SULT2B1b isoform may be the predominant sulfotransferase (SULT) isoform involved in neurosteroid conjugation. However, sulfation of pregnenolone to pregnenolone sulfate predominantly involves the SULT2B1a enzyme. The SULT1E1 and SULT2A1 isoforms did not participate in neurosteroid sulfation directly in the brain, since expression of these proteins was not revealed by immunohistochemical analysis (Salman et al. 2011). SULT2A1, for example, is involved in DHEA sulfation in the reticular zone of the adrenal cortex (Khvostova et al. 2012).

Considering neurosteroidogenesis in detail, it is also important to pay attention to the enzymes involved in biosynthesis (Fig. 1). Following cytochrome P450C17 effect, which acts as 17α-hydroxylase, 17-OH-pregnenolone is synthesized from pregnenolone, then with the same enzyme, but now acting as 17,20-lyase, DHEA is synthesized from 17-OH-pregnenolone. DHEA can also form the neuroactive sulfated form of

DHEA-S. The reverse reaction is catalyzed by the enzyme sulfatase (STS). The second important cascade of reactions is the synthesis of progesterone and its derivatives. Progesterone is synthesized from pregnenolone by the action of 3β-hydroxysteroid dehydrogenase (3β-HSD). Below we will describe the three main reactions. the first of which is the synthesis of deoxycorticosterone (DOC) by 21-hydroxylase P450C21. Deoxycorticosterone is further transformed into dihydrodeoxycorticosterone (DHDOC) by 11β-hydroxylase P450C11, from which tetrahydrodeoxycorticosterone (THDOC) can be synthesized. The next important progesterone derivatives are 5α-dihydroprogesterone (5α-DHP) and 5β-dihydroprogesterone (5β-DHP), synthesized by 5α-reductase type 1 and 5β-reductase type 1, respectively. 5α-DHP is transformed into allopregnanolone (ALLO) and epi-allopregnanolone (3b5aP). Selective serotonin reuptake inhibitors, such as fluoxetine, sertraline, paroxetine, increase the affinity of 3α-HSD (type III) for 5α-DHP and block the reverse conversion of ALLO to 5α-DHP, which increases the rate of allopregnanolone synthesis (Schumacher et al. 2009). 5β-DHP is in turn the precursor of pregnanolone and epipregnanolone.

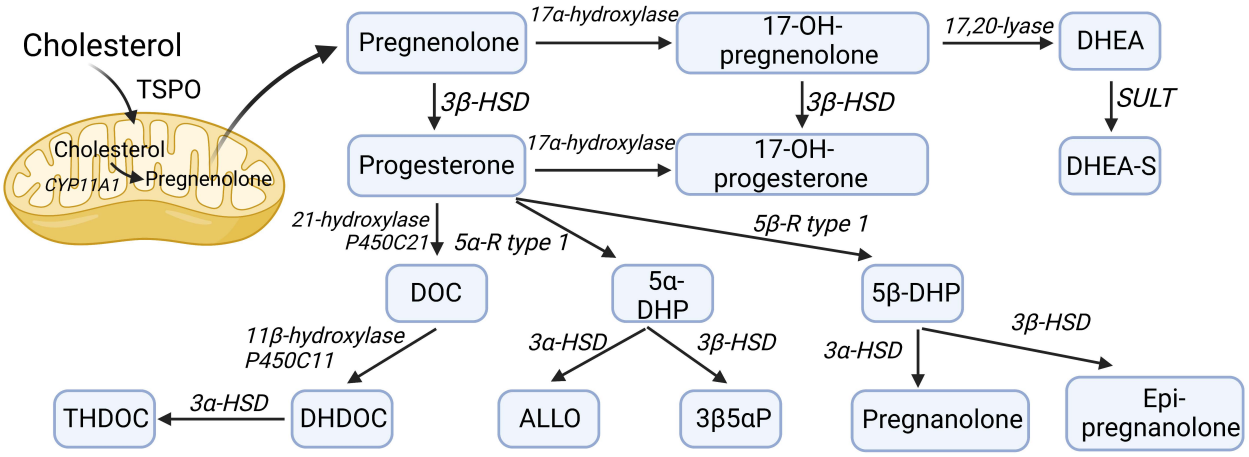


Figure 1. Neurosteroidogenesis and the enzyme system involved in the process. **Note:** Neurosteroids: DHEA – Dehydroepiandrosterone, DHEA-S – Dehydroepiandrosterone sulfate, DOC – Deoxycorticosterone, DHDOC – Dihydrodeoxycorticosterone, THDOC – Tetrahydrodeoxycorticosterone, 5α-DHP – 5α-dihydroprogesterone, 5β-DHP – 5β-dihydroprogesterone, ALLO – allopregnanolone, 3β5αP – epi-allopregnanolone. Enzymes: TSPO – Translocator protein, 20,22 Desmolase – P450C11 (CYP11A1), 17α-hydroxylase – P450C17 (CYP17A1), 17,20-lyase – P450C17 (CYP17A1), SULT – Sulfatase, 3β-HSD –3β-hydroxysteroid dehydrogenase, 3α-HSD – 3α-hydroxysteroid dehydrogenase, 21-hydroxylase –P450C21 (CYP21A2), 5α-R type 1 –5α-Reductase type 1, 5β-R type 1 –5β-Reductase type 1, 11β-hydroxylase – P450C11 (CYP11B1).

Interaction with $GABA_A$, NMDA and sigma-1 receptors

$GABA_A$ receptors are pentameric ligand-gated ion channels consisting of two α-subunits (α1-6), two β-subunits (β1-3), and one additional subunit (γ1-3, δ, ε, π, θ and ρ1–3) (Wang 2011). When ion channels open, the hyperpolarization resulting from the Cl^- ions flow leads to inhibition of neuronal activity (Joshi and Kapur 2019). Synaptic $GABA_A$ receptors are located within the synaptic cleft and contain γ-subunits. Often there are receptors with subunit composition: α1β2γ2 (60% of the total), α2β3γ2 (15-20%) and α3β2/3γ2 (10-15%) (Wang 2008). The expression of various $GABA_A$ receptors is specific for different regions of the nervous system. For example, the most common form of α1β2γ2 is found in most regions of the brain: cortex, hippocampus, and Purkinje cells. α2β3γ2 receptors are found in the cortex, hippocampus, amygdala, striatum, and hypothalamus (Wang 2008). Besides the main ligand, gamma-aminobutyric acid, $GABA_A$ receptors can bind many other compounds, including barbiturates, benzodiazepines, ethanol, zinc, and neurosteroids. It is noteworthy that each type of subunit has specific pharmacological properties and can only interact with certain molecules. The GABA binding sites are between the α and β subunits, and the benzodiazepine site is between the α and γ subunits (Sigel 2002). For neurosteroids, at least three binding sites were found. The receptor activation by neurosteroids, in particular allopregnanolone, occurs through a site located between the β3–α1 subunits (Sugasawa et al. 2020). Allopregnanolone and epi-allopregnanolone can induce receptor desensitization via sites on the β3 subunit, while binding of neurosteroids to the α1 subunit can lead to different effects depending on the molecular structure (Sugasawa et al. 2020). Allopregnanolone can potentiate the receptor effect both allosterically (through increased current) and directly, activating the receptor at high concentrations. $GABA_A$ receptor antagonists are pregnenolone sulfate and epi-allopregnanolone (Wang 2011).

The nature of the $GABA_A$ receptors interaction is determined not only by the neurosteroid structure and type (agonist/antagonist), but also by the GABA receptor structure (composition of subunits), as well as by the location of the receptor (synaptic and extrasynaptic). Synaptic (phasic) and extrasynaptic (tonic) inhibition are two types of inhibitory neurotransmission mediated through $GABA_A$ receptors. Neurosteroids can potentiate both phasic and tonic currents. The action kinetics of synaptic $GABA_A$ receptor neurosteroid agonists was studied by measuring the spontaneous inhibitory postsynaptic potential (sIPSP) in brain neurons. Neurosteroids may produce a small effect on the time of onset and peak amplitude of sIPSP, reducing the likelihood of a synaptic potential. Agonists prolong the decay time of the impulse. In hippocampal CA1 neurons, granule cells, and Purkinje cells, neurosteroids prolong sIPSP at relatively low (nanomolar) concentrations (Wang 2008). However, at >10μM concentrations, neurosteroids can activate $GABA_A$ receptors interacting directly with the binding site (Majewska et al. 1986). This so-called GABA-like effect of neurosteroids is able to suppress excitatory neurotransmission (Shu et al. 2004).

Extrasynaptic $GABA_A$ receptors containing the δ subunit have a very high affinity for some neurosteroids, which may indicate their importance as a target. At concentrations of 10–100 nM, 3α5α-THDOC selectively enhances tonic inhibition (Stell et al. 2003). Tonic inhibition was reduced in δ-subunit knockout mice (Mihalek et al. 1999). However, the extrasynaptic effects of neurosteroids vary in different areas of the CNS. 3α5α-THDOC at 250 nM concentration produced no effect on tonic inhibition in the thalamic ventrobasal complex (Porcello et al. 2003). On the other hand, tonic inhibition of CA1 in hippocampal neurons expressing α5-subunit $GABA_A$ receptors is affected by 3α5α-THDOC at ≥100 nM concentrations (Stell et al. 2003). This heterogeneity suggests that potential modulation depends on the specific local metabolism of particular neurosteroids.

According to the experimental data, neurosteroids act as the most highly potent endogenous allosteric modulators of the GABA receptor (Lambert et al. 1995). When administered parenterally, some types of neurosteroids (ALLO, DHEA, etc.) can produce a rapid anxiolytic and anticonvulsant effect, and, with increasing doses, they can also exhibit sedative and hypnotic properties (Longone et al. 2011). According to some data, the neurosteroid system may represent a part of the endogenous anxiolytic system. This point is supported, in particular, by data on a decrease in its activity in patients with panic disorder in whom a panic attack was induced by administration of lactate or cholecystokinin. In turn, administration of placebo to patients or administration of lactate or cholecystokinin to healthy volunteers had no effect on neurosteroid activity. On the other hand, the presence of neurosteroid effects has also been well documented with respect to first-line therapy for anxiety disorders – antidepressants from the SSRI group. In a number of studies, it was shown that by not fully established mechanisms most representatives of this class of antidepressants (first of all, fluoxetine, fluvoxamine and paroxetine) can increase the concentration of allopregnanolone and some other neurosteroid in the corticolimbic zones of the brain. As a result, the anti-anxiety effect is at least partially developed not due to modulation of serotonin receptors, but due to neurosteroid-mediated activation of GABA receptors (Rupprecht et al. 2010).

Finally, altered neurosteroid levels may be one of the most likely explanations for women's increased propensity for depressive disorders in general, and for postpartum depression in particular. It has been shown experimentally that a significant increase in peripheral blood progesterone (during pregnancy or the follicular phase of the menstrual cycle) leads to a compensatory decrease in the sensitivity of GABA receptors to neurosteroid (by reducing the expression of δ-subunits). A subsequent decrease in the neurosteroid level against the background of $GABA_A$ receptor activity decrease (during the luteal phase or after delivery) leads to the formation of affective symptoms (Brickley and Mody 2012). Currently, postpartum depression is the only reported indication for the use of Brexanolone (an artificially synthesized allopregnanolone). In addition to allopregnanolone, dehydroepiandrosterone, its sulfated form, and some others have also been shown to have antidepressant effects (van Broekhoven and Verkes 2003).

Some neurosteroids can act as allosteric modulators of NMDA receptors. Ligand-dependent, or rather co-controlled, ionotropic glutamate receptors are divided into subgroups according to their pharmacological properties: GluA (binds AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid), GluK (binds kainate), GluN (binds NMDA, N-methyl-D-aspartate) and GluD (binds d-serine) receptors. NMDA receptors are heterotetrameric ionotropic receptors consisting of two GluN1 subunits in combination with two GluN2 and/or GluN3 subunits (Vyklicky et al. 2014). NMDA receptors play a key role in the regulation of cognitive functions. NMDA receptor antagonism can occur through three pathways: competitive inhibition, blockade of ion channels, and noncompetitive inhibition through specific modulation sites (Vyklicky et al. 2014). Modulation of NMDA receptor activity can be either positive or negative. Positive modulators increase the affinity of the NMDA receptors agonist. Some neurosteroids, such as pregnenolone sulfate, are known to potentiate GluN2A and GluN2B-containing NMDA receptors, increasing the ability of the receptor to open the ion channel through phosphorylation (Vyklicky et al. 2014). However, the recent studies demonstrated that neurosteroids can also produce an inhibitory effect on this type of receptor. Pregnenolone sulfate is able to reduce the ability to open ion channels by a voltage-

independent mechanism. However, in this way, the inhibitory effect is produced only on previously activated (open) channels. The effect is less pronounced in GluN2A and GluN2B-containing receptors than in GluN2C and GluN2D-containing receptors (Adamusová et al. 2013). Apparently, the duality of the pregnenolone sulfate effect is explained by the different composition of the receptor subunits. The issue remains unresolved as the search for binding sites for neurosteroid inhibitors continues. DHEA can prevent NMDA-induced neurotoxicity to some extent, as well as increase the flow of Ca^{2+} ions into the cell through NMDA receptors (Li et al. 2009).

There is some experimental evidence for antipsychotic effects of some neurosteroids. In particular, intracerebral administration of ALLO to laboratory animals prevents the further appearance of motor agitation and other equivalents of psychosis after administration of high doses of amphetamines (Flood et al. 1992). This effect is probably related to the agonist effect of some neurosteroids on sigma-1 receptors, which can block dopamine release via NMDA receptors (which is consistent with the high efficacy of the sigma-1 receptor agonist fluvoxamine in psychotic depression, as well as with the presence of propsychotic effects when high doses of NMDA-receptor antagonists, such as ketamine, are taken) (Pabba and Sibille 2015).

Despite the fact that schizophrenia is not conceptualized as a classical neurodegenerative condition, a number of studies have shown the death of certain portions of neurons, mainly in the hippocampus (Cannon 2015). In this connection, the ability of a number of neurosteroid compounds to exert neuroprotective effect is of great interest. It is believed that neuroprotective effect of neurosteroids can be explained by three mechanisms – blocking of NMDA-receptors, stimulation of $GABA_A$-receptors, and modulation of polyunsaturated fatty acids metabolism. Moreover, many neurosteroids, according to experimental data, are also capable of enhancing neurogenesis and improving cognitive function through a variety of mechanisms, including action on NMDA receptors.

Presumably, sigma-1 receptors, along with NMDA receptors, affect neurocognitive functions. The administration of sigma-1 receptor agonists resulted in the increase in the GluN2A and GluN2B NMDA receptor subunits expression in the rat hippocampus (Pabba et al. 2014). Moreover, activation of sigma-1 receptor chaperones increased the of NMDA receptors presentation on the cell surface by stimulating the interaction between GluN2 subunits (Pabba et al. 2014). Sigma-1 receptors are involved in the transport and metabolism of ER lipids, the restoration of the lipid raft of the plasma membrane. Sigma-1 receptors are located in lipid raft-like microdomains of the endoplasmic reticulum membrane (Hayashi and Su 2010; Zhemkov et al. 2021). Sigma-1 receptors can modulate the transport of cholesterol into mitochondria and thereby regulate the processes of steroidogenesis. The hypothesis is supported by reduced pregnenolone levels in the mice with sigma-1 receptor gene knockout (Marriott et al. 2012). In addition, sigma-1 receptors are involved in many cellular mechanisms: the release of neurotransmitters, the inositol phosphate system, inflammation, synaptogenesis, neuroplasticity, etc. Neuroplasticity is an important process in neuropsychiatric diseases. Pregnenolone and DHEA may produce beneficial effects in some neuropsychiatric disorders as sigma-1 receptor agonists. The studies demonstrated that the sulfated form of dehydroepiandrosterone can attenuate phencyclidine-induced cognitive loss in mice (Hashimoto 2015), whereas progesterone, like testosterone, inhibits sigma-1.

First of all, the properties of sigma-1 receptor agonists were revealed in pregnenolone, DHEA, and their metabolites, which makes them some of the most probable endogenous ligands of this receptor subtype (Monnet and Maurice 2006). According to the existing data, activation of sigma-1 receptors leads to a number of favorable effects, among which an anxiolytic effect is traditionally mentioned. The realization of the anxiolytic effect of neurosteroids through sigma-1 receptors has been proved in several studies on animal models. Of greatest interest is the work by Noda et al (2000), who showed the ability of sulfated forms of pregnenolone and DHEA to block evoked fear conditioning reactions in mice, and the introduction of the selective sigma-1 receptor antagonist NE-100 significantly reduced the effectiveness of neurosteroids.

Influence on this type of receptors may be responsible not only for anxiolytic but also for antidepressant effects. Apparently, the antidepressant effect of sigma receptor stimulation may be related to the increased release of noradrenaline and dopamine, as well as to the indirect modulation of NMDA-receptors (Bergeron et al. 1996).

Conclusion

Although the discovery and study of neurosteroids have been relatively recent, there is now a common understanding of the role of these substances, as well as their significant impact on the human psyche, in scientific community. Nevertheless, now many issues still require further research, and the data are somewhat controversial. A better understanding of the neurosteroidogenetic pathways, as well as the interaction between neurosteroids, $GABA_A$-, NMDA- and sigma-1 receptors, will shed light on neurobiological processes, as well as open up new prospectives in the mental disorders treatment.

Conflict of interests

The authors declare no conflict of interests.

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