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NEUROSTEROIDS IN COGNITIVE DISORDER - FROM WELL-KNOWN PHARMACOLOGICAL ASPECTS TO A SOURCE OF CONTROVERSY

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Abstract: *The nervous system is not just a target organ for synthetic steroids. It is also controlled in a certain manner by steroids synthesized de novo in the brain, at the level of both neurones and glial cells. The impressive recent number of literature studies, clearly demonstrates the presence of enzymes necessary for syntheses of central neurosteroids and also the mechanism by which they act. Neurosteroids play a considerable part as an endogenous modulator of brain function and behaviour processes, and the decrease of their concentration can be associated with the pathophysiology of different neurological diseases accompanied by cognitive disorders such as depression, anxiety, schizophrenia, Alzheimer disease.*

INTRODUCTION

The last years' studies have certainly proven that the brain is a steroidogenic organ. The concept "*neurosteroid*" originally created by the French physiologist Etienne Baulieu is now widely used with reference to central synthesized steroids.(1,2) A significant progress in the understanding the role of neuroactive steroids is based on his studies, concerning the level of dehydroepiandrosterone (DHEA) sulphate in nervous system tissues (brain and peripheral nerves) in adult male rats at a higher concentration than in plasma. Evidence of possible endogenous synthesis of DHEA sulphate in the brain was obtained in this study, independent of the adrenal and testis secretions. The presence of enzymes involved in the classical steroid synthesis was identified at the central level as well.(1,2,3)

In the next years, the research continued to be aimed at determining their pharmacological action. One of the first neurosteroid effects was detected by *Selye H. et al*, more specifically the anesthetic effect of progesterone.(4) Studies showed that alphaxalone (synthetic neurosteroid) and barbiturates present a common mechanism of action, as they are allosteric modulators of the GABA-A receptors.(5,6) Other studies outline their involvement in the pathophysiology of acute and chronic pain.(7) Numerous studies performed by *Herzog A.* and other researchers demonstrated the effect of progesterone in the treatment of catamenial epilepsy, also linked with this mechanism (8,9,10) while ganaxolone is a neuroasteroid agent that has been evaluated in human clinical trials for the treatment of epilepsy.(11,12) Animal studies have shown that fluoxetine, a selective inhibitor of serotonin reuptake and a widely used antidepressant increases the level of allpregnenolone in the brain (13), while the direct administration of allpregnenolone improves the depressive behaviour in animal models.(14)

The discovery of endogenous neurosteroids has initiated many research directions in the neurological and biochemical fields, having an important clinical potential to be used from sedation to the treatment of epilepsy or brain injury, premenstrual syndrome, anxiety, maintenance of homeostasis, memory deficit and peripheral neuropathy.(15,16,17,18,19) Cognitive disorders are characterized by changes in brain structure and function that cause impairment of education, guidance, judgment, memory and intellectual abilities. Memory deficit is a common characteristic of neurological and neuropsychiatric disorders and therefore, the role of neurosteroids in the modulation of neurologic activity is a point of interest for scientists nowadays.

The purpose of this review is to emphasize the most important aspects regarding the biosynthesis of neurosteroids, their mechanism of action, the biological role, and their involvement in modulating the neurological disorders associated with cognitive disorders.

Biosyntesis

The nervous tissue has a steroidogenic activity and presents enzymes necessary for this process.(20) In contrast to classical steroidal tissues, the synthesis of steroids in the nervous system requires the expression and regulation of genes in coding steroidal enzymes in different types of cells (neurons or glia) in various locations in the nervous system, often at a certain distance from the cells.(21) The neuroactive steroids found in the nervous tissue are: pregnenolone and pregnenolone sulphate (PREG and PREGS), dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEAS), progesterone, deoxycorticosterone and tetrahydrodeoxycorticosterone (THDC).(22) The first stage in the central neurosteroids synthesis is to convert cholesterol into PREG, that phase, requiring the translocation of cholesterol from outer to inner mitochondrial membranes by means of a molecular complex, consisting of several proteins such as: translocator protein of 18kda (TSPO) (23), the steroidogenic acute regulatory protein (stAR), the adenine nucleotide transporter protein (ANT) and the voltage-dependent anion channel protein (VDAC).(24,25)

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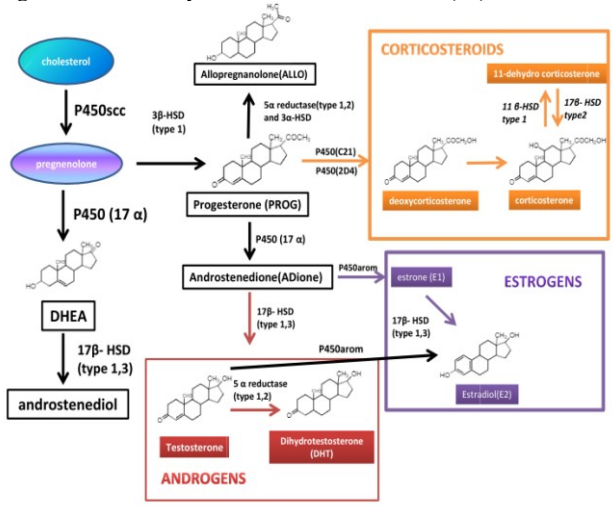
Several recent studies have considered the role of translocator protein (TSPO), formerly known as a peripheral or mitochondrial benzodiazepine receptor, proving that it has a high therapeutic potential (26,27) and the expression of this gene can increase in gliomas, neurodegenerative diseases, neurotoxin-induced inflammatory neurological diseases.(28) It is mainly located in the outer of mitochondrial membrane and favours the transport of cholesterol to the inner mitochondrial membrane, in order to enhance the sinthesys of neurosteroids. The selective ligands of the translocator protein can stimulate the biosynthesis of the neurosteroids in the brain, thereby confirming the key role of the protein in neurosteroidogenesis.(29)

Figure no. 1. The synthesis of neurosteroids (31)



Neurosteroids synthesis reactions are mediated by a number of enzymes such as: sulfatase, sulfotransferase, various isomers of the hydroxysteroid dehydrogenase (3α HSD III; 3β HSD 1/2; 17β HSD 1; 17β HSD 2/4), 5α reductase (type I and II) and different isosforms of cytochrome P450: p450scc (cholesterol side-chain cleavage enzyme) which mediates the cholesterol conversion into PREG and is found on human chromosome 15 (30), P450c17 (microsomal 17 hydroxylase) that mediates the conversion of PREG to dehydroepiandrosterone and progesterone to androstenedione, P450c21 (steroid 21 hydroxylase) which catalyzes the transformation reaction of progesterone in deoxicorticosterone, P450c11AS (mitochondrial aldosterone synthase) that mediates the deoxicorticosterone-corticosterone-aldosterone reaction and p450aro (gonadal aromatase enzyme) which catalyzes the transformation of testosterone into estradiol (figure no. 1).(21,31) The human brain expresses four types of 3α-HSD, which under different optimum conditions, either catalyzes 5α-dihidroprogesteronen reduction in allopregnenolone (ALLO) or reverses this reaction.(32) Two types of 5α-Rs (type I and type II) have been identified in the human and rodent tissue, which convert progesterone to 5α-dihydroprogesterone (5α-DHP) or convert deoxycorticosterone to 5α-dihydrodeoxycorticosterone (5α-DHDOC). These two types of enzymes are involved in the biosyntesis of ALLO and tetrahydrodeoxycorticosterone (THDC) and their presence in brain regions, such as cortex, hippocamp and amygdala, show that ALLO and THDC are synthesized from progesterone in the central nervous system.(17,32) Neurosteroids are frequently found in the sulphated form (PREGS). The sulphate or unsulfatated form, further influences the pharmacokinetics and pharmacological properties of neurosteroids.(33) The synthesis of the PREGS is mediated by the specific enzyme HST(sulfotransferase) cytosolic enzyme which catalyzes the transfer of the sulphate group from 3'-phosphoglyadenosine 5'-phosphfosulfate to the 3-hydroxy group of non-conjugated steroids.(34) The production of these enzymes is mediated by glutamate, amino butyric acid (GABA), gonadotrophin hormone inhibitors, melatonin, prolactin and glucocorticoids.(35)

Mechanism of action

The physiological effect of neurosteroids is explained both by direct action on neurotransmitters and indirectly by enhancing the neurotransmission.(17) Related to the mechanism of action, two types of mechanism are included, firstly, a genomic action, mediated through nuclear intracellular receptors (classical steroidal receptors) and secondly, a non-genomic action (ion channels and membrane receptors) in the brain.(36) Furthermore, the genomic effects of neurosteroids are mainly caused by their metabolic interconversion to traditional steroids.(37)

There is an increasing evidence that neurosteroids are not themselves active on classical steroidal receptors and they act predominantly through non-genomic mechanism.(29) Several studies in the literature support the above idea. A study by *Rupprecht R. et al,* shows that neurosteroids do not have an affinity for traditional steroid receptors (37), however, some metabolites of the neuroactive steroids form by intracellular oxidation of the 3α-hydroxy group may still be bound to the steroid receptors. From another point of view, the latency period presented by those mechanisms confirm that, the effect of the neurosteroids at central level is rapid, while steroids acting through the classic receptors are slow at the start and show a prolonged action.(38) Other studies by *Reddy et al*. on the progesterone receptor in mice, beyond doubt demonstrate that the classic steroid receptor is not necessary for sedation, anxiety and anticonvulsive activity of progesterone or related neurosteroids.(39,40)

Several studies have shown that neurosteroids act predominantly on two types of receptors: the GABA (5,41,42) and NMDA receptors (43), but also can influence other receptors, such as: serotonin, sigma 1 (type 1), nicotine receptors.(21)

The gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system, having an extremely important role in regulating neuroexcitation and muscle tone. Structurally, the GABA-A receptors are hetero-pentameric transmembrane receptors with a central Cl^- permeable pore. Most of the GABA-A receptors are composed of units α, β and γ or δ.(44) Neurosteroids are specifically binding on the α subunits of GABA receptors.(45) Stimulation of GABA-A receptors leads to the opening of ion channels, chlorine influx, followed by hyperpolarization. There are two types of inhibitory neurotransmission mediated by the GABA-A receptors: synaptic (phasical) and extrasapic (tonical) inhibitors. Neurosteroids modulate both GABA-A-synaptic and extrasynaptic receptors, in this way increasing the phasic and also the tonic currents.(12)

Starting from the responsible mechanism for the rapid effect of steroids on neuronal excitation, has been demonstrated that neurosteroids are selected allosteric and potent modulators of the GABA-A receptors which increase the channel opening time and frequency at low concentrations and can activate directly the GABA-A receptors at high concentrations.(46) They can act both as positive and negative modulators depending on their chemical structure.(47,48) The inhibitory neurosteroids with strong modulatory effects of the GABA receptors are: PREG, ALLO, 3α,5α-tetrahydrodeoxycorticosterone (THDOC), 3α,5β-androsterone, 5α-androstan-3α, 17β-diol, 5β-androsten-3α, 17β-diol.(49,50) These neuroasteroids present inhibitory actions on

neurotransmission. They act as positive allosteric modulators of the GABA-A receptors and have antidepressants, anxiety, sedatives, analgesic, anesthesic, anticonvulsive, neuroprotective effects and reduce stress. Other neurosteroids can present excitatory actions on neurotransmission and act as potential negative allosteric modulators of the GABA-A receptors, low allosteric positive modulators of the NMDA receptors and agonist of the receptor σ1 and mainly have antidepressant, anxiogenic, cognitive, memory growth, anticonvulsive and neuroprotective effects.(29)

NMDA receptors are ligand-dependent ion channels with essential roles in synaptic transmission and plasticity, thus shaping the learning and memory processes. The receptors are heteromers composed of a combination of gluN1 and gluN2 subunits that bind glycine and also glutamate.(52)

Neurosteroids, being strong lipophilic molecules, can easily pass the blood-brain barrier, those neurosteroids synthesized in peripheral tissues are accumulated in the central nervous system and can influence some of brain functions.(53)

Neuroateroids in cognitive disorder?

Several studies have shown that neurosteroids present a wide range of effects at central level from the embryogenesis to the adult age.(21) Modification in neuroactive steroids levels were associated with various neurological disorders such as: major depression, postpartum depression, schizophrenia, catamenial epilepsy, panic attacks.(54)

Current research on the effect of neurosteroids on the brain areas responsible for memory function have demonstrated that they present an important role in acquisition, consolidation and retrieval of information.(17) Neurosteroids can participate in memory enhancing, but also in the processes of memory loss, as presented in various studies performed on rats. Recent evidence has considered the positive effect of neurosteroids on cognitive processes. It is explained by the fact they interact with NMDA receptors, more precisely changes are made in their compositions, both subtype NR1 and subtype NR2 being found at the hippocamp level, the area of the brain involved in cognitive processes.(36)

A study performed by *Mayo W. et al* on rats through the perfusion of PREG-S and TH-PROG into the nucleus basalis magnocellularis demonstrates that PREGS increases cognitive performance while the administration of ALLO has caused memory loss.(55) Another important aspect, related to their administration shows that the acute administration improves the memory function (56) while the chronic administration can cause memory loss and lead to exacerbation of symptoms of an existing neurological pathology.(57,58) Also, prolonged intraventricular perfusion of PS has improved cognitive performance on mice.(59)

It is known that cholinergic transmission modulates the memory processes and degrades with age. Starting from this idea based on several studies which prove that the PREGS influences the release of acetylcholine, more exactly it is directly proportional to the dose of administered neurosteroid.(60) Based on the assumption that in Alzhrimer's disease is a decrease in the synthesis of acetylcholine and that neurosteroids have a positive influence on cholinergic transmission, we can admit that a low level of neurosteroids can be considered a risk factor for the disease (61) and PREGS, DHEA. DHEAS have reduced memory deficits induced by β-amyloid β25-35 associated with Alzheimer's disease in a dose-related manner.(62)

By understanding the fact that sigma receptors are involved in reward learning behaviour, another idea that demonstrates the beneficial action of neurosteroids on learning and memory processes could refer to his modular action on sigma receptors, because their effects are mitigated by the administration of the antagonist sigma receptors.(36). Cannabinoid receptors are also known as one of the neurosteroids class of receptors. Knowing that the activation of cannabinoid (CB1) receptors influence negatively the memory and the learning function (63), it has been demonstrated that the endogenous neurosteroids are claimed to be the negative allosteric modulators of the receptors CB1.(64)

Schizophrenia is a particular type of psychosis characterized by delirium, hallucinations and cognitive disorders. N-methyl D-aspartate (NMDA) receptors modulate the excitation synaptic transmission and play a foremost role in learning and memory processes. The low activity of NMDA was associated with schizophrenia pathophysiology (65) and the administration of NMDA agonists causes a decrease of these effects.(66) Altered neuroactive steroid levels have been also detected in schizophrenia. The treatment with PREG has been investigated as an adjuvant for cognitive and negative symptoms in schizophrenia patients. Patients who have received PREG have shown significantly higher improvements in cognitive scores, indicating the promising therapeutic potential of neurosteroids in these diseases.(67)

Literature data indicate that estradiol can improve memory deficits in schizophrenia, so far the mechanism has been slightly elucidated and the assumption that it is acting through the GABAergic neurotransmission is not yet investigated. An assumed mechanism is that estrogen inhibits through negative feedback the secretion of the luteinizing hormone, because a high level of this hormone has been associated with decreased memory.(68)

Steroid sulfatase inhibitors, an enzyme which converts sulphated steroids into free steroids, can alter the neurosteroid mechanism and affect cognitive function. They enhance the antiamnesiac effect of DHEAS by suggesting that an increase in the levels of endogenous-sulphate neurosteroids by inhibiting the steroid sulphatase activity can improve the learning and memory function.(69)

Endogenous neuroactive steroids play an important role in the learning deficit and memory associated with certain types of anxiety. The modulation of the GABAergic transmission in the central area a of the amygdala, explains their anxiety-based effect (70), that the amigdala has been involved in the processes of emotional memory, fear and anxiety. Neurosteroids such as ALLO and THDC are potent anxiolytic agents.(15) The treatment with fluoxetine, a selective inhibitor of serotonin reuptake, increases in response to the dose, the ALLO concentrations in the brain (13) suggesting that the increased neurological synthesis could be involved in the anxiety-based actions of the fluoxetine. For patients with induced panic attacks, there is also a sharp drop in the levels of ALLO.(71) Therefore, the replacement of neurosteroid by synthetic analogues or stimulation of endogenous neurosteroids syntheses can be a promising strategy for the treatment of anxiety disorders.

CONCLUSIONS

The aging-associated diseases have a substantial effect on the cognitive processes and are associated with the gradual decline in certain forms of memory. We can say that memory losses, along with the elderly advance and various neurologic diseases can be related with neurosteoidogenesis decay. Neurosteroids are considerable endogenous modulators of the neural circuits by involving them on central neurotransmissions, responsible for neuronal excitability, thus they can represent in the future potential therapeutic agents for the treatment of diseases accompanied by affective disorders. Although it is possible that neurosteroidal treatment may be useful in the treatment of anxiety, depression, schizophrenia, because not all

systemic administered neurosteroids pass easily the blood-brain barrier, some may be metabolized to steroids with different action (17) mechanisms and the mechanisms through which they act are not fully elucidated, the medical potential of these compounds is limited and requires further investigation. However, it is with optimism that this issue is being considered.

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