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SCIENTIFIC REVIEWS AND LECTURES

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CELL AND MOLECULAR MECHANISMS OF NEUROSTEROID ACTION IN DIFFERENT PARTS OF THE CENTRAL NERVOUS SYSTEM (Part 2)

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Neurosteroids (or neuroactive steroids) are a class of endogenous compounds which are synthesized in nervous tissue or\and able to modulate the brain functional activity, the class also includes steroids from gonads or adrenals, which are capable of migrating through the blood brain barrier to achieve their biological targets. The second part of the review is focused on describing multiply features of synthesis, functioning of such neurosteroids as progesterone, allopregnanolone, dehydroepiandrosterone and dehydroepiandrosterone sulfate as well as their targets, synthesized analogs. It also highlights the peculiarities of their production in different regions of rat central nervous system in ontogenical aspect. Many outstanding processes which depend on progesterone level were described: differentiation of oligodendrocytes precursors, changes in Schwann cells' activity, which lead to myelination intensification, stimulation of dendrite, motoneurons' growth - the basis of nervous tissue recovery; synaptogenesis in Purkinje neurons. Special emphasis was made on the modulation of GABAA receptors by allopregnanolone, anti-apoptotic and neuroprotective effects of dehydroepiandrosterone and dehydroepiandrosterone sulfate. Diverse and controversial data on changes in neurosteroid effects in dependency on the target's localization in the brain were systematized. Human and rat neurosteroid profiles were compared and contrasted in order to estimate the possibility of rat usage as a biological model in studies, which are focused on the correlation between changes in neurosteroid status and such diseases as epilepsy, schizophrenia, autism, anxiety, depression, posttraumatic stress disorder.

Keywords: neurosteroids, neurotransmitters, neuronal plasticity, progesterone, PROG, allopregnanolone, ALLO, dehydroepiandrosterone, DHEA, dehydroepiandrosterone sulfate, DHEAS, regions of central nervous system, ontogenesis.

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Abbreviations: ALLO – allopregnanolone; DHEA, DHEAS – dehydroepiandrosterone, dehydroepiandrosterone sulfate; PROG – progesterone; P450scc - cholesterol side-chain cleavage enzyme; P450c17 - steroid 17α-monooxygenase; ST – sulfotransferase; PKA – protein kinase A; AMPA – α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF – brain derived neurotrophic factor; GABAA – receptor of γ-aminobutyric acid type A; 3βHSD – 3β-hydroxysteroid dehydrogenase; NGF – nerve growth factor; NMDA – N-methyl-D-aspartate; PREG, PREGS – pregnenolone, pregnenolone sulfate; 5-HT-receptors – membrane 5-hydroxytryptamine or serotonin receptors; mIPSCs – miniature inhibitory postsynaptic currents; TSPO - translocator protein; LTP - long-term potentiation; MPA - medroxyprogesterone acetate; PXR - nuclear pregnane X receptor; MAP-2 - microtubule-associated protein 2.

Progesterone

Progesterone is derived from pregnenolone by the 3βHSD enzyme [20]. Maximum pregnenolone and progesterone levels in hippocampal tissue may be detected right after the birth and then their progressive decrease comes. Maximum enzyme's activity may be detected in ependymal cells of brain's ventriculars and in cerebellar Purkinje cells (0,717+\-0,37 c.u. and 0,400+\- 0,06 c.u. respectively). This level of activity is comparable to its level in cells of peripheral endocrine glands (zona fasciculata of adrenal glands, Leydig cells in testis [1]. Progesterone and 5α-dehydroprogesterone conduct their effects trough the progesterone nuclear receptor, whereas 3α-hydroxi-4-pregnen-20-on and allopregnanolone don't seem to have such a molecular mechanism. Moreover, 5α-dehydroprogesterone and allopregnanolone may interact with $GABA_A$ receptors, effect that progesterone lacks [7,15], in other words, the intracellular presence of 5α-reductase and 3α-hydroxysteroid-dehydrogenase may result in genesis of extra neuromodulators. Still, some of sources state that in unsaturated concentrations progesterone and androsterone interact with glycine and $GABA_A$ receptors, which leads to activation of ion transport [29].

Role in the myelination processes

Progesterone is synthesized by Schwann cells and considered to play

an important role in myelination in the peripheral nervous system, including the myelination stimulation after cold damage mediated by locally synthesized progesterone. This effect is mediated mainly by the interaction with nuclear receptor and more rarely by the neuroactive metabolites' formation. Showed that progesterone provokes the intensification of the main myelin's protein's expression, increase of myelin's expression's speed, reduction of time needed for the initiation of synthetic processes. [8]. Progesterone increases the expression level of myelin-specific proteins' mRNA, including mRNA of protein zero (P0), peripheral myelin protein 22 (PMP-22) [23], transcriptional factor Krox-20, which also regulates the myelination in the peripheral nervous system [8]. When Schwann cells and neurons are cultivated together, progesterone dose-dependently increases myelin formation speed, involving the increase in expression level of P450scc and 3βHSD. Consequently, progesterone modulates the process of myelin's formation directly in Schwann cells and indirectly by the nuclear receptors' activation and transcription's stimulation in neurons, which was proved by the elimination of neuronal progesterone's effect when the receptors were blocked by RU-486, progesterone's antagonist. The intensification of myelination takes place in the CNS as well [11].

Role in oligodendrocytes' differentiation

The level of enzymes' expression, needed for progesterone's and its metabolites expression, is different for oligodendrocytes and their progenitors, therefore it may be suggested that neurosteroids take part in progenitors' proliferation and their terminal differentiation [10]. Pre-progenitors, which have the highest concentrations of 3βHSD и 3αHSD, synthesize progesterone from pregnenolone actively. Mature oligodendrocytes are characterized by high level of 5α-reductase as well, but can not convert pregnenolone into progesterone due to the termination of 3βHSD expression [22].

Progesterone's influence on the spinal cord motoneurons' functional activity

Progesterone is involved in recovery of the spinal cord motoneurons' functioning [25]. The increase in pregnenolone and progesterone concentrations without significant changes in P450scc and 3βHSD expression levels was detected in the tissue of damaged spinal cord, but not in its serum, which implies the existence local neurosteroidogenesis [17]. Progesterone stimulates the mRNA's expression of such substances as acetylcholinesterase, Na^+,K^+-ATPase, GAP-43, synthesis of the main myelin's protein, proliferation of oligodendrocytes' progenitors [24] in damaged motoneurons. Nevertheless, another point of view states that classic progesterone's nuclear receptor's can't mediate recovery effects due to the fact that transcriptionally inactive ligand of the progesterone's receptor, enantiomer of progesterone, provokes the same recovery effect on the animals' damaged spinal cord [29]. Allopregnanolone, progesterone's metabolite, may also contribute positively to the recovery process as both 5α-reductase and 3αHSD are present in the spinal cord cells. Some of progesterone's effect may be mediated by the growth factors' stimulation, for instance, BDNF - brain-derived neurotrophic factor [6]. Spinal cord's damage leads to the decrease in BDNF's mRNA expression as well as in quantity of the BDNF protein itself. 3 days-long progesterone treatment doesn't change the BDNF's mRNA expression level in spinal cord motoneurons of animals in control group, whereas mRNA's and BFNF's levels increase significantly in motoneurons in dorsal horns of the spinal cord [24]. Nonetheless, progesterone stimulates the immune binding of BDNF in motoneurons of healthy animals, suggestively because of the increase in BDNF synthesis in non-neuronal cells.

Cerebellum as progesterone's target

Progesterone induces cerebellum's development [27]. Purkinje cells express P450scc, 3βHSD, 5α-reductase and 3αHSD, within their membrane, PREG, PREGS, PROG and ALLO are synthesized [13]. Purkinje neurons produce PROG and ALLO in the neonatal period, when the ecpression level and enzyme activity of 3βHSDare heightened. It is widely known that cortex formation in rodents is performed by the migration of external granular cells, neuronal and glial growth, synaptogenesis in the neonatal period, Purkinje cells also differentiate just after the birth, therefore, cerebellum's development coincides with the neurosteroidogenesis intensification [22]. Progesterone's influence on the Purkinje cells differentiation, which reveals itself in stimulation of dendritic growth, formation of dendritic spines, regulation of synaptic distribution density, is identified in cultivated cerebellar slices of rat pups and in mature rat's brain *in vivo* [25], [Table 1]. These effects may be mediated by classical nuclear receptor PGRMC1, undifferentiated receptors or progesterone's metabolites.

Allopregnanolone

Allopregnanolone's interaction with $GABA_A$- receptors leads to both tonic and phase generation of inhibitory currents, resulting in neuroprotective and anti-convulsant effects [14]. Nonetheless, PREGS acts as a $GABA_A$-receptors antagonist, and if the balance between PREGS and ALLO is upset, seizers may occur [19, 27].

Behavioral and electrophysiological effects of ALLO and all structurally similar compounds are specific for $GABA_A$ receptors: they have a low influence on or simply don't interact with glycine, AMPA, NMDA and 5-HT_3 receptors [18]. ALLO increases the frequency of mIPSCs – miniature inhibitory postsynaptic currents dose-dependently in preorbital zone of hypothalamus, probably, because of the stimulation of a spontaneous GABA release. This effect is strictly determined by extracellular concentration of Cl^- ions, in other words, it's determined by primary activation of presynaptic $GABA_A$ receptors followed by increased membrane's permeability for chorine ions [30]. Animal models showed that enhancing of 3α,5α-THP (ALLO) and 3α,5α-THDOC (allotetrahydrodeoxycorticosterone) expression during stress may be a homeostasis mechanism normalizing the activity of GABA-ergic system as well as hypothalamus-pituitary-adrenal system. Nevertheless, neurosteroids concentrations and actions are pathologically changed in the conditions of chronic stress, for instance, ALLO may be neurotoxic. It impairs long-term potentiation mechanism, which consequently leads to the disruption of short-term and long-term memory. It morphologically results in the reduction of hippocamp's mass. [5]. Moreover, ALLO in chronically high concentrations may increase the quantity of soluble Aβ-amyloid, which is a predictor of grave Alzheimer disease, in a synaptic gap.

If the exposure to high concentrations of ALLO is short-time and is interrupted by considerable breaks, ALLO intensifies the differentiation of the unipotent progenitor cells in the dentate furrow of the hippocampus, therefore, it enhances the recovery of nervous tissue. GABA plays the role of excitory mediator in those cells, as if they were embryonic, because of the increased chlorine's intracellular concentrations [16].

ALLO doesn't have influence on the spontaneous glutamate release in neurons of prefrontal cortex [Table 2], on the opposite, it inhibits this process, if it's induced by depolarizing agents and electrical stimulus [3]. Inactivation of Ca^{2+} ion channels of L, N, R, and P-types by

the formation of chelate complex with extracellular Ca^{2+}, inhibition of protein enzymes of vesicular transportation, blockage of signaling cascades, including calmodulin, adenylate cyclase and PKA underlies this process. The inhibitory effect of ALLO on the glutamate's release reduced the speed of neuronal death under conditions of oxygen-glucose deprivation and H_2O_2 in the experiment [14], which may determine such ALLO's neuroprotective effects as analgesic, anxiolytic, and antidepressant.

It is already known that ALLO increases spontaneous norepinephrine secretion in the cerebral cortex, this process is also menstrual phase-dependent. Interestingly that activating influence is maximum during estrus and I diestrus, decreases gradually during II diestrus, proestrus and 7 days after ovariectomy. ALLO potentiates K^+-stimulated norepinephrine secretion through α2-noradrenergic receptors throughout the estrus. As norepinephrine takes part in modulation of cortical neurons' excitability, its influence on ALLO may either enhance excitability or determine sex-dependent and menstrual phase-dependent features of modulation [26, 30].

Another mediator secreting under the ALLO's influence is dopamine. The animal model, striatum slices, isolated from rat's brain in estrus phase, demonstrated the enhancement of NMDA-induced dopamine secretion. Ovariectomy eliminates this effects, whereas subcutaneous injection of the combination of endogenous estrogen and progesterone regains it. ALLO triggers significant suppression of spontaneous dopamine secretion *in vivo* during the estrus, but still enhances it in animals after ovariectomy on hormone-replacement therapy with estrogen and progesterone [2]. Probably that stimulation of NMDA-induced dopamine secretion is a regulator of sensorimotor functions with sex and cycle features.

ALLO's microdialysis in nucleus accumbens of freely moving rats demonstrates controversial influence of the neurosteroid on the dopamine secretion, both activation and suppression of its spontaneous secretion, increase in secretion with morphine stimulation and decrease in stress-induced dopamine release were detected. Nucleus accumbens plays an important role in formation of mood and motivation, that is why, ALLO may be considered as a modulator for those processes as well as for drug addiction, depression and abstinent syndrome [30].

It was stated that ALLO inhibits spon-

Table 1

List of progesterone's (PROG) main effects in various regions of the central nervous system (without developmental characteristics)

Location	Basic effect	Required conditions	Receptors	Meaning
Hippocampus	NMDA-stimulated norepinephrine release (o)	-	NMDA-receptors	Increase of the intensity of mental processes and physical activity
Prefrontal cortex	1. Spontaneous release of glutamate (o) 2. 5-HT stimulated release of glutamate (o) 3. Dopamine-stimulated Glutamate Release (-)	-	Sigma-1 (-) Sigma-1/D1 synergy (-)	Impact on cognitive function, participation in the pathogenesis of neuropsychiatric diseases
Hypothalamus	Release of serotonin (-)	Ventromedial nuclei	5-HT receptors	Elimination of serotoninergic tonic inhibition, (+) lordosis behavior (arching of the back in mammals during estrus)
	Release of serotonin (o/+)	Preoptic zone		Blockade of the LG surge (peak lutropin concentration and stimulation of ovulation)
Cerebellum	Dendrite growth (+), dendritic spine formation (+), synaptogenesis (+)	Purkinje neurons	Nuclear progesterone receptor PGRMC1	Formation of the cerebellar cortex in the neonatal period, differentiation of Purkinje neurons
Spinal cord	1. Expression of myelin basic protein (+), protein 0 (P0) (+) 2. Peripheral myelin protein 22 (PMP-22) (+) 3. Transcription factor Krox-20 (+)	Schwann cells	Effect is mediated by PROG metabolites	Intensification of myelination processes and regeneration after damage
	Expression of nuclear progesterone receptors (+)	Dorsal root ganglia neurons	Nuclear receptor PROG	
	Expression of acetylcholine transferase, Na, K-ATPase, GAP-43, myelin basic protein, BDNF	Motoneurons	Metabolites, PGRMC1, nuclear receptor PROG (?)	Restoration of functions of damaged motoneurons

taneous dopamine secretion dose-dependently in neurons of prefrontal cortex, which take part in modulation of emotional state, whereas elimination of ALLO's effects by finasteride significantly increase stress-induced (foot shock) and drug-induced (anxiogenic druf FG7142) neurotransmitters' release [Table 2]. It was also stated that fluoxetine treatment in patients with depression and panic disorders stabilize neurosteroids' level in the CNS [2].

Dehydroepiandrosterone (DHEA) and Dehydroepiandrosterone sulfate (DHEAS)

The concentrations of DHEA and DHEAS change dynamically during the ontogenesis of the human body [12]. They decrease rapidly just after the birth due to the involution of the fetal zone of the adrenal cortex and then remain at a stable minimum level until individual is 7-8 years old. Adrenarche starts at this age due to the maturation of the adrenal cortex and therefore increased synthesis of DHEA and DHEAS in it, a process develops parallelly to puberty. The concentration of these neurosteroids continues to increase until 20-25 years of human's life, then the slow decline begins, subsequently, at the age of 60 years, the concentrations of DHEA and DHEAS barely reach 20-30% of their concentration at 20 years' age. These changes are directly related to the functions of these neurosteroids, which are vital in childhood,

Table 2

List of allopregnanolone's (ALLO) main effects in various regions of the central nervous system (without developmental characteristics)

Location	Basic effect	Required conditions	Receptors	Meaning
Hippocampus	K + -stimulated release of γ-aminobutyric acid (-)	-	Ca2+-canals L-type	Antipsychotic effect
	1. Spontaneous release of acetylcholine (-) 2. Stress-induced release of acetylcholine	Intraventricular injection	-	Modulation of memory, stress reactions
Prefrontal cortex	1.Spontaneous release of glutamate (o) K + -stimulated release of glutamate (-) 2.Spontaneous release of acetylcholine (-) 2.Spontaneous release of dopamine (-)	-	-	Modulation of cognitive processes, changes in emotional status during the menstrual cycle, pregnancy, menopause
Frontal cortex	1. Spontaneous release of norepinephrine: estrus, diestrus I (+); diestrus II and proestrus (o) 2.K + -stimulated release of norepinephrine: estrus (+)	-	α2 - noradrenergic receptors (+)	Regulation of excitability of cortical neurons, determination of sex differences in modulation of cortical functions
Striatum	1.Stimulated release of glutamate (o) 2.Spontaneous release of acetylcholine (-)	-	-	-
	1. Spontaneous release of dopamine: estrus (-) 2. NMDA-stimulated release of dopamine: est-rus (+); diestrus (o)	*In vivo* Striatum slices	-	Modulation of sensorimotor processes
Hypothalamus	1. Spontaneous release of γ-aminobutyric acid (+) 2.K + -stimulated release of γ-amino-butyric acid (o)	Preoptic zone	Primary activation of presynaptic GABAA receptors, Na + -K + -Cl-cotransporter, extracellular Ca2 +	GABA-ergic regulation of secretion of gonadotropin-releasing factors produced by neurons in the medial preoptic zone
	Spontaneous release of dopamine (-)	Ventromedial nuclei	-	Inhibition of the release of luteinizing hormone, reduction of reproductive activity

Table 3

CList of dehydroepiandrosterone's (DHEA) main effects in various regions of the central nervous system (without developmental characteristics)

Location	Basic effect	Required conditions	Receptors	Meaning
Hippocampus	NO production in response to NMDA receptor stimulation (-)		Sigma-1 (+)	Protection against glutamate, AMPA and kainate excitotoxicity, regulation of processes of syn-naptogenesis
Prefrontal cortex	Elongation of axons and dendrites (+) (+)	-	NMDA-рецепторы (+)	-
Forebrain	1. Spontaneous release of glutamate (+) 2. K + -stimulated release of glutamate (o) 3. Spontaneous release of glutamate (+) 4. K + -stimulated release of glutamate (+) 5. Spontaneous release of glutamate (-)	Synaptosomes Rats 12 months old Rats over 12 months old		Increase in physiological tonic glutamatergic impulses that regulate plastic processes

Table 4

List of dehydroepiandrosterone sulfate (DHEAS) main effects in various regions of the central nervous system (without developmental characteristics)

Location	Basic effect	Required conditions	Receptors	Meaning
Hippocampus	1. Strengthens the processes of dendrite formation 2. Spontaneous release of glutamate (+) 3. Spontaneous release of acetylcholine (+) 4. Release of norepinephrine: spontaneous (o); 5. K + -stimulated (o), in the presence of D2-antagonists (+); 6. NMDA-stimulated (+)	In nanomolar concentrations Microdialis *in vivo* Hippocampus slices	Sigma-1(+) Ca2 + -channels L, N-types Sigma-1(+)	Improving learning ability, memory
Prefrontal cortex	Spontaneous release of glutamate (+)		D1-receptors (+) Sigma-1 (+)	Providing cognitive processes

adolescence and adulthood: DHEA and DHEAS stimulate the development of the cerebral cortex [4], mediate neuronal plasticity, which underlies the adaptation to changing environmental conditions, through the influence on the amygdala reduce the level of fear and anxiety, which naturally increases due to the abundance of new impressions and experiences, are involved in providing hippocampal mechanisms of memory and learning by influencing synaptogenesis processes [Tables 3,4], have a protective function: decrease the ability of the GCS-receptor complex to affect the stress factors' transcription level in the cell; reduce GCS-mediated excess glutamate's release from neurons (reduce neurotoxicity, associated with excess glutamate); protect hippocampal neurons from AMPA and kainate excitotoxicity by inhibiting of NO-production stimulated by a NMDA-receptor mediated increase in the concentration of intracellular Ca2+, determine the development of sexual behavioral stereotypes before puberty, inhibit the mictoglia activation during the brain damage, reduce the activity of apoptosis and synthesis of proinflammatory cytokines [9], they are Sigma-receptor agonists that regulate Ca2+, Cl -, K+, NMDA-mediated ion currents, neurotransmitters' release, lipid neuronal transport, brain neurotrophic factor's signal transmission, myelination, neurogenesis and synaptogenesis [3], DHEA stimulates basal glutamate secretion and doesn't affect the K+ - stimulated release of the mediator in synaptosomes of the forebrain at the early stages of intrauterine ontogenesis both *in vivo* and *in vitro*. Since glutamatergic transmission of the forebrain provides

the plastic processes, which are necessary for learning and memorizing, it was assumed that DHEA increases the basal level of tonic impulsion of the forebrain cortex and confirmed by an improvement of rats' performances in the avoidance test.

It was shown that DHEA promotes elongation of τ-immunopositive axons in nanomolar concentration and insignificantly stimulates the growth of MAP-2 immunospecific dendrites, whereas DHEAS increases the formation of dendrites without affecting the length of the axon. DHEA dose-dependently increases calcium admission into cells in embryonic cortical neurons, apparently through interaction with NMDA receptors [Table 3], since this effect is blocked by MK801 and D-AP5 NMDA-receptors' antagonists, which may be one of the mechanisms underlying the regulation of axon growth. However, the fact whether such effects are limited to the period of intranatal development or persist in adult animals still remains unknown [21]. DHEAS can act as a DHEA depot [23].

DHEA microdialysis stimulates spontaneous acetylcholine secretion in the hippocampal neurons of anesthetized rats, a similar effect is observed when DHEAS plasma concentration increases, provoked by an inhibition of sulfatase activity. Cholinergic transmission provides the functional changes in hippocampal neurons that underlie memory, that is why enhancing of the spontaneous acetylcholine release may be one of the important mechanisms for improving memory under the action of DHEAS [30].

Conclusion. The spectrum of neuroactive steroids is specific to various parts of the CNS, their neurons and glial cells, and changes during the ontogenesis. Generally, steroidogenesis' intensification occurs in the pre- and neonatal periods of individual development, when these substances regulate the formation of the cerebellar cortex, elongation of processes, myelination, synaptogenesis, etc. Decrease or even the complete cessation of steroidogenesis enzymes' expression is observed then in adults. However, neurosteroids continue to influence learning and memorizing processes, emotional status, motivation as well as cognitive and motor functions of an individual. Increased steroidogenesis is observed in a number of physiological and pathophysiological conditions, such as cold and ischemic damage, pregnancy, stress, schizophrenia, Parkinson disease.

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