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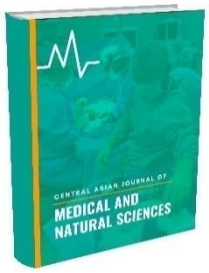

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Neurosteroids and Addictive Pathology

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Abstract: Biochemical, physiological and pharmacological aspects of hormonal regulation by endogenous chemical compounds of steroid structure have been well known for several decades. First and foremost, these are steroid hormones of the glucocorticoid group, which are the main chemical effector of stress and, thanks to the work of Sellier and his followers, are considered to be one of the key links in the pathogenesis of a wide range of diseases. Steroids originating in the central and peripheral nervous system have been discovered and intensively studied during the past 15 years. They have a different spectrum of biological activity and, in contrast to hormones, which have a discrete action, these substances, termed neurosteroids (NS), interact with targets located near the site of their synthesis.

Key words: dehydroepiandrosterone sulphate, androstenedione and pregnenolone, allopregnanolone and tetrahydro-deoxycorticosterone.

Introduction: Initially, the NS family consisted of one member, dehydroepiandrosterone sulphate (DHEAS), found in the brain after gonad and adrenal ectomy. Subsequently, androstenedione and pregnenolone (PREG) and their sulfated and lipid derivatives, as well as tetrahydrometabolites of progesterone (PROG) and deoxycorticosterone (DOC) were described.

NS are synthesized *de novo* in brain cells from cholesterol. A number of enzymes responsible for the conversion of different chemical groups are involved in the formation of different members of this family. Such enzymes include cytochrome P450, which modifies the cholesterol side chain, aromatase, 5α-reductase, 3α-hydroxysteroid dehydrogenase, and 17β-hydroxysteroid dehydrogenase .

In contrast to the intracellular receptors of steroid hormones, which act as transcriptional factors, the brain targets of NS are membrane receptors for neurotransmitters, with which these low molecular weight substances interact through allosteric regulation . For example, by binding to a specific "steroid site", other than the active site of the GABA receptor, allopregnanolone (ALLO) and tetrahydro-deoxycorticosterone (THDOC) enhance, and pregnenolone sulfate (PREGS) and DHEAS reduce the severity of the GABAergic signal. PREGS increases while ALLO-sulfate (ALLOS) reduces the efficiency of ligand interaction and functional activity of NMDA receptors. Nicotinic receptors are negatively affected by THDOC, ALLO and PROG sides and are positively modulated by estradiol. In

addition to the regulation of these receptors and the conduction of corresponding nerve impulses, NS are involved in many important functions of glial cells, in particular, the processes of myelination.

Based on this list of receptor NS targets, it would be reasonable to assume that steroids may be involved in the formation mechanisms of some types of addiction. However, the numerous experimental studies reviewed below and in progress point to a much more complex picture, and the results may contribute significantly to the development of theoretical models for the biological links in the pathogenesis of addiction to a wide range of chemical compounds, with associated diagnostic and therapeutic perspectives.

Neurosteroids and opioids

The concept of a possible role of NS in the pharmacological effects of opioids is based both on the above-described possibility of regulation of a wide range of neurochemical systems by these compounds and on experiments to determine the specific mutual action. In laboratory animals, the analgesic activity of PROG is known to be inhibited by naloxone, and the synthetic NS analogues alphadolone and alfaxalone potentiate the antinociception induced by morphine, fentanyl, or oxycodone. In a clinical study, alfadolone reduced the effective dose of morphine in patients after orthopaedic knee replacement, and the steroid did not cause sedation, respiratory depression, nausea or vomiting.

When administering addictive opioid alkaloids the content of NS in the brain changes: for example, when developing a conditioned place preference reaction with the help of morphine, animals show a decrease in the amount of dehydroepiandrosterone (DHEA) in n.accumbens and PREG in the hypothalamus. The average level of PREG, PREG-sulfate, and PROG in the brain is also significantly reduced in dependent animals, while the tissue concentration of DHEA, DHEAS, PREG, PREGS, PROG, and ALLO increases in naloxone- precipitated withdrawal syndrome.

In behavioral experiments, NS attenuate the physical phenomena of morphine dependence and even prevent their development by reducing the manifestations of tolerance to opioids. It is conceivable, on the basis of general considerations, that compounds acting in this way should have their own addictive potential. Indeed, in the methodological paradigm of discriminative stimuli, described in more detail below, a number of NSs are able to modify operant behavior, while morphine does not demonstrate the ability to substitute PREG. The latter circumstance provides a strong enough basis for the hypothesis that the described effects of the NSs are not caused by their interaction with opioid receptors or other components of the opioid systems, but are realized through other neurochemical pathways. This does not contradict the list of known receptor targets of NS.

Neurosteroids and cocaine

In contrast to opioids, at least one of the macromolecular targets of cocaine is common to this drug and some NS. In particular, both cocaine and PREGS directly interact with σ-1 subtype receptors involved in the formation of a heterotrimeric complex with IP(3)R inositol phosphate receptors and ankyrin, a cytoskeletal adaptor protein. It is interesting to note that the above trimer regulates the activity of intracellular Ca^{2+}-dependent signaling pathway, which is also activated by the "dopamine D_1 - receptor-phospholipase C" system, another target of cocaine . There may be other possible points of overlap between the pharmacological activity of cocaine and NS.

There are few studies reported in the literature on the effects of NS on the addictive properties of cocaine. Some pharmacological modifications of endogenous corticosterone synthesis (mainly subchronic exposure to synthetic analogues) are known to alter the expression of cocaine's addictive properties, although the steroid itself, as well as adrenalectomy, does not affect them. Interpretation of such results is difficult today, as numerous variants have been described, both for and against the

relationship between peripheral and central steroid pools. On the other hand, DHEA, even at low doses, significantly reduces cocaine self- administration in animals and decreases the intensity of drug-seeking operant behavior, without possessing cocaine-like properties of its own .

Neurosteroids and nicotine

Despite the fact that nicotinic receptors are one of the macromolecular structures on which NS have a direct regulatory effect, but, therefore, they are more likely to be involved in development of nicotine dependence, scientific literature only marginally confirms this possibility. Single or prolonged nicotine administration is associated with increased levels of ALLO and its precursors PREG and PROG in the brain and plasma. The effect persists in mecamylamine-precipitated nicotine withdrawal and has not been reproduced in adrenal/orchiectomized animals.

Direct injection of nicotine into the hippocampus causes extinction of conditioned reflex skills in alcoholic rats. This effect is not affected by ALLO, however, it is blocked by PREGS; according to the authors, the multidirectional effect of NS is due to negative or positive allosteric regulation of $GABAA_{receptors}$, respectively. The explanation probably needs to be complicated, as both NSs are capable of neutralizing the proconvulsant effect of nicotine, while ALLO also shows anticonvulsant activity in intact animals.

In addition, circulating blood DHEA concentration in patients with schizophrenia (as diagnosed by DSM-IV-TR) was found not to correlate with positive or negative symptomatology on the PANSS scale, but the steroid level was significantly lower in smoking patients compared to nonsmokers, suggesting that further research into the significance of NS in the pathogenesis of not only nicotine dependence, but also endogenous psychoses is warranted.

Neurosteroids and benzodiazepines

Studies on the interaction of NS and benzodiazepines (BDs) are based on a well-established view of the complex structure of the $GABAA_{receptor}$, which has specific allosteric binding sites for BDs and NSs, among others.

The positive modulator of the $GABAA_{receptor}$ ALLO inhibits the action of GABA, and this effect is not affected by the BD antagonist flumazenil. On the other hand, ALLO inhibits the spontaneous activity of GABAergic neurons, and although this effect of NS is independent of flumazenil, it is partially reversed by the PD partial agonist Ro15-4513. Prenatal diazepam application leads to abnormalities in NS metabolism, showing regional and gender specificity, which, however, are not accompanied by changes in GABAA- receptor sensitivity to steroid action. NS synthesis is also altered under the influence of endogenous ligands of the benzodiazepine binding site of the $GABAA_{receptor}$: octadecaneuropeptide (an 18-member fragment of the diazepam binding inhibitor molecule - DBI) and β-carbolines.

In behavioural experiments, PROG and ALLO have been shown to exhibit anxiolytic properties when administered on a single occasion, but their persistent use reveals an increase in anxiety in animals . Additional evidence for the modification of anxiety by NS is presented in the section on alcohol, but we note that no direct data on the interaction of steroids with addictive MDs are presented in the literature.

Neurosteroids and alcohol

Interest in the problem of "NS - alcohol" is supported by the same circumstances as in the BD, namely: the significant role assigned to GABA-receptors in the mechanisms of action of ethyl alcohol on the CNS. At the same time, a dose-dependence in the enhancement of alcohol consumption the CNS. Some researchers, considering the system "Ethanol-GABA effect", assess changes in NS

metabolism under the influence of ethanol as one of the mechanisms of its influence on the GABAergic system. Although the question of the "specificity" of the action of alcohol on GABAA receptors should probably be answered in the negative, their significant role in the formation of alcohol pathology cannot be doubted.

Three groups of processes involving GABA receptors are identified under the effect of ethanol: changes in the expression of the corresponding genes and receptor subunit composition, stimulation of steroidogenesis, and changes in the plasticity of GABAergic neurons. Probably the same can be proved by the data on the absence of ethanol stimulating effect on NS formation in female experimental animals. Acute alcohol intoxication results in increased levels of the major GABAA-receptor positive modulators ALLO and THDOC in rat cerebral cortex and hippocampus, and the effect is significantly more pronounced in the ethanol-preferring sardine line sP than in the ethanol-rejecting sNP.

When alcohol dependence is simulated using one of the most appropriate techniques, intermittent alcoholization, a decrease in seizure threshold and an increase in anxiety levels in animals are observed, cross-tolerance to GABAergic sedative-hypnotics; it is interesting to note that ethanol efficacy correlates with decreased levels of 3α-hydrosteroid-5α-pregnan-20-one (tetrahydro-PREG-pregnanolone) and is consistent with changes in the translation 5α-reductase and 3α-hydrosteroid dehydrogenase enzymes .

Central injection of ALLO into the hippocampus not only produces an anxiolytic effect, but also attenuates alcohol withdrawal symptoms and reduces its voluntary consumption in experimental animals. However, systemic administration of the NS, in contrast, increases its uptake. A detailed study in C57BL/6J mice revealed the ability of ALLO to modulate different phases of alcohol consumption. modulate the phases of alcohol consumption in mice: at low doses, it enhances, and at high doses, it inhibits alcohol intake in mice. mice. A dose-dependence in the enhancement of alcohol intake intensity was found in the first 5 min of observation and inhibiting the whole 2-hour experimental session. It is likely that ALLO is involved in the loss of control during ethanol abuse.

The NS are able to modify the effects of ethanol tolerance, for example, the anxiolytic effects of ethanol and anxiogenic withdrawal are enhanced by PROG but attenuated by DHEAS. PREGS enhances, and epipregnanolone prevents, the development of tolerance to the co-ordination- disrupting effects of ethanol. The effect of PREGS was not specific for the recorded parameters and was detected in the determination of the hypothermic effect of ethanol, which was similarly affected by DHEAS .

Although pharmacological analysis suggests differences between the additive taxane and hypnogenic effects of ethanol and BD or NS, i.e. indicating involvement of GABA receptors, the process may not be limited to the GABA system. For example, prenatal alcohol intoxication leads to a subsequent impairment of NS modulating activity towards NMDA receptors.

The addictive potential of neurosteroids

The above description of the interaction of NS with opioids pointed to the possibility of steroids having their own additive properties, as they can substitute for morphine in the discriminatory test. Other studies extend the possible crossover and suggest that ethanol, barbiturates or BDs may also be substituted agents. However, this quality is not shared by all NSs: the GABAA receptor positive modulator THDOC is able to replace ethanol in a discriminatory stimulus technique, whereas DHEAS, a negative modulator, has no intrinsic activity and does not reduce THDOC action. It should be noted that the substitution effect is partial, whereas full ethanol replacement can be achieved by using GABA mimetic agents interacting with different GABA receptor loci (diazepam, pentobarbital) or glutamate NMDA receptor antagonists. The presence of reinforcing properties in ALLO is demonstrated by a

two-bottle test under conditions of free choice between HC and water, however, this activity is not confirmed in operant behavior studies of pre-trained rats on self-injection of substances . Rare experimental molecular-biological manipulations have established the insignificance of the δ-subunit of the GABAA receptor for the discriminatory properties of ethanol or its scavenging agents - barbiturates, MDs or HCs.

Conclusion: From the material presented, it is not difficult to make some generalisations, although their semantics are not straightforward to understand. The reason for the difficulties should probably be sought not only and not so much in the diversity of NS targets in the brain and the specific mechanisms of the effects of addictive compounds on the body. In any case, the least definitive results are obtained when systems that are common targets for NS and addictive agents are examined; conversely, the greatest degree of modification of NS addictive processes is observed where common targets have not been proven.

This suggests that the analytico-synthetic attempt to create a synthetic picture of NS involvement in the formation of addictive behaviour and the implementation of the reinforcing properties of compounds by eliminating seeming contradictions is not well supported by evidence. We can only make a few assumptions.

Firstly, initially, different addictive mechanisms regulated by the NS via different targets may converge or integrate at a particular level, such as the dopamine system. There is some evidence for this: in particular, ALLO and PREG stimulate and are able to enhance morphine-induced dopamine release in n. accumbens.

Secondly, the NS may be involved in the formation of some phenomena, such as memory, which is now receiving increasing attention as a physiological substrate underlying the development of pathological processes in the CNS, including addictive behavior. Thirdly, there may be an additional target for NS, the pathogenetic significance of which is currently unknown; a specific pregnan X receptor PXR (NR1I2) could be such a target.

However, it is already clear that further research into the role of NS in addictive phenomena may have promising theoretical pathogenetic and diagnostic implications, while their therapeutic potential remains debatable.

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