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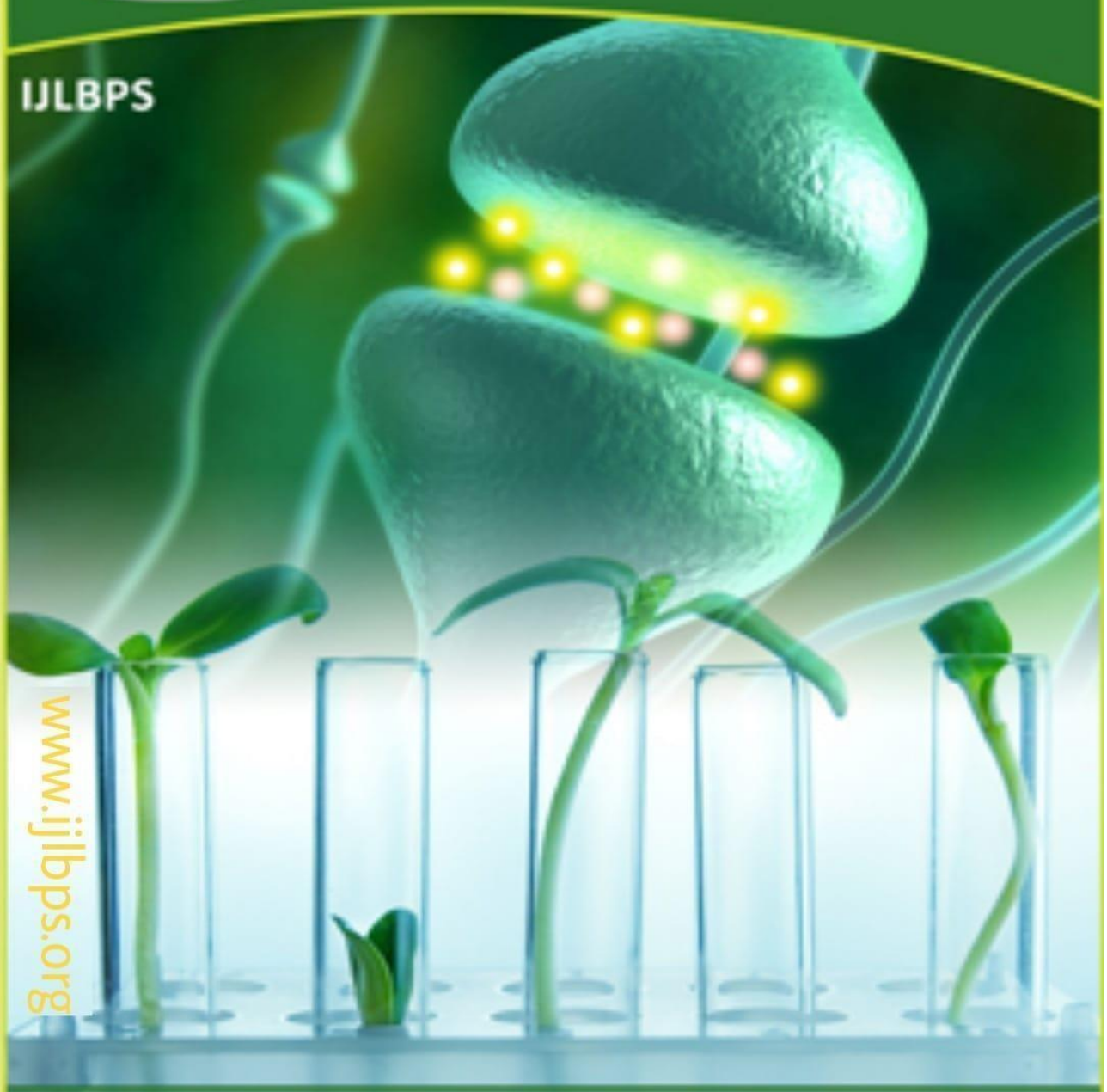

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Neuropharmacological Disturbance and Neuroactive Steroids

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Abstract

Like the adrenal glands, the testes, and the placenta, the brain produces steroids. In contrast to classic steroidogenic tissues, steroid synthesis in the nervous system requires the coordinated expression and regulation of genes encoding the steroidogenic enzymes in a number of cell types (neurons and glia) at different locations in the nervous system, often at a considerable distance from the cell bodies. Furthermore, the production of these hormones could be developmentally controlled and connected to their roles in the developing brain. The brain and neurological system produce a class of steroids known as neurosteroids, which serve a broad range of purposes. Common steroid hormone nuclear receptors aren't involved in mediating their effects; rather, they use ion-gated neurotransmitter receptors or direct/indirect regulation of other neurotransmitter receptors. We review the enzymatic biochemistry, pharmacological characteristics, and mechanisms of action of neurosteroids. Neurosteroids are examined in terms of their physiological significance and prospective use in treating certain human disorders.

Key-Words: Neurosteroid, Gaba, Dehydroepiandrosterone sulfate, CNS

Introduction

Dehydroepiandrosterone sulfate (DHEAS) is a steroid molecule that has been demonstrated to be generated by the brain and is thus referred to as a "neurosteroid" (NS) by Baulieu, who coined the word in 1981. Later, androstenedione, pregnenolone, their sulfates [1,2] and lipid derivatives as well as tetrahydro metabolites of progesterone (P) [3] and deoxycorticosterone (DOC) were discovered as neurosteroids [1]. It's not only the neurological system that generates Ring A reduced metabolites from P. Lymphocytes, for instance, also contribute to the production of THP [4]. Neuroactive steroids (NAS) are steroids that may affect neural functions notwithstanding where they were produced.Both the steroidogenic peripheral glands and the central nervous system (CNS) are responsible for the synthesis of these substances. Indeed, chemicals involved in steroidogenesis' first step—the conversion of cholesterol to pregnenolone—are expressed in the central nervous system.Proteins like steroidogenic acute regulatory protein and translocator protein 18 kDa (TSPO; also known as peripheral benzodiazepine receptor) move cholesterol into the mitochondria and catalyze cytochrome P450 side chain breakage, respectively. androstenedione, androsterone, and dehydroepiandrosterone (DHEA), andAffiliating Author

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Mailingaddress:
kapil752003@yahoo.comenzyme involved in the production of pregnenolone from cholesterol. Various neuronal and glial subpopulations also express steroid-metabolizing enzymes such 3-hydroxysteroid dehydrogenase, cytochrome P450c17, 5-reductase (5-R), 3-hydroxysteroid oxido-reductase,17-hydroxysteroid dehydrogenase, and aromatase [5].Brain-Activating Steroid SynthesisIt's been known for a long time that steroids play a crucial role in the formation and function of neuronal membranes, which is why the central nervous system contains so many of them. Recent research has shown that not only is there evidence of de novo synthesis and a steroid metabolic route in the brain, but also that these substances are carried into the brain from the periphery. Pregnenolone and its metabolites are synthesized from cho- lesterol by enzymes other than those in the adrenal glands [6-8]. This route is especially prominent in the glia. Many of these neurosteroids were discovered to have much greater concentrations in the central nervous system (CNS) and in certain brain areas than in the plasma, indicating an active involvement for these neuroactive steroids in brain cells.and their metabolites, are major compounds in the family' of neuroactive steroids found in the CNS. This family contains metabolites of progesterone, testosterone, and deoxycorticosterone, all of which are present in the brain in significant amounts [9-11]. Neuroactive steroids such as 5a-dihydroprogesteroneand3a- trahydroprogesterone were found to be synthesized by lymphocytes in a study [4] that focused on the peripheral, nonadrenal or gonadal, synthesis of neuroactive steroids. Synthesis of neuroactive steroids in the periphery may provide a convenient supply for their activities in non-central nervous system tissues.Epilepsypharmaceuticals that improve the action of GABAA receptors such as benzodiazepines and barbiturates as well as pharmaceuticals targeting the GABA binding's site of the GABAA receptor are often employed as efficient antiepileptic treatments. Therefore, anticonvulsant action should also exist in 3'-reduced neuroactive steroids. In fact, studies using a variety of animal models showed that these neuroactive steroids had significant anticonvulsant effects [12–15]. Epileptiform discharges were observed to diminish after progesterone treatment in the first clinical trials utilizing progesterone as a precursor molecule in women with catamenial epilepsy [16,17]. Antiepileptic research is being conducted on the first synthesized analogues of 3- reduced neuroactive steroids such ganaxolone [18–21]. Complex partial seizures and infantile spasms have shown promise in early phase II studies [22]. First animal studies with subchronic administration of ganaxolone suggest that this steroid induces anticonvulsant tolerance to benzodiazepines but not to itself [23], but long-term treatment with this new class of drugs must take into account putative side effects like sedation, altered sleep architecture, and development of tolerance. However, 3-reduced neuroactive steroids may provide a potential new alternative for treating many types of epilepsy.Insomnia is a common problem, and there is some evidence that neuroactive steroids may help. Progesterone decreases slow-wave sleep and promotes nREM sleep and decreases sleep latency in both rats and humans [24,25]. The neuroactive A-ring decreased metabolites of progesterone seem to mediate the effects of progesterone on these spectral alterations associated with sleep. Indeed, allopregnanolone decreases when delivered systemically.at brain concentrations similar to those induced by progesterone injection, it delays the onset of nREM sleep and lengthens pre-REM sleep [26]. As the nREM-specific effects of allopregnanolone on sleep are detected at brain allopregnanolone levels within physiological ranges [27], it has been postulated that neuroactive steroids might play a role in modifying physiological sleep [26]. While its 21-OH congener 3a-hydroxy, 5a-

tetrahydrodeoxycorticosterone (5a- THDOC) has been shown to considerably improve nREM sleep duration, other researchers have shown that allopregnanolone has no effect on nREM sleep [28]. Allopregnanolone8 has a low bioavailability, therefore the variation in results is likely attributable to variations in dosing. There are some documented discrepancies in the effects of benzodiazepines and neuroactive steroids on sleep-EEG power spectra [25, 26], but there are also numerous similarities.In rats tested at circadian time-18, pregnanolone and CCD3693 did not substantially enhance the amount of time spent in nREM sleep, in contrast to the therapeutically utilized benzodiazepine receptor hypnotics zolpidem and triazolam [29]. Rebound insomnia may be less of a concern with steroid hypnotics because, unlike benzodiazepines, these neuroactive steroids do not cause compensatory declines in nREM sleep when their nREM-promoting effects wane. Finally, unlike triazolam and zolpidem, pregnanolone and CCD3693 generate their sleep-related effects at non-myorelaxant dosages [29], and enhance nREM sleep-bout duration, which is thought to be a predictor of sleep quality in humans. These findings point to potential benefits of neuroactive steroids when used therapeutically. The clinical viability of some of these hypotheses is actually being tested right now (see: CCD3693).PsychosisPsychiatric symptoms may be linked to shifts in gonadal hormone production, according to epidemiological research [30,31]. Clinical symptoms of schizophrenia, for instance, have been demonstrated to fluctuate with the phases of the moon [30]. As an added note, postmenopausal women are more likely to experience the start of schizophrenia episodes compared to their younger counterparts [31]. It is thus plausible to postulate that an abrupt reduction in steroid concentrations may play a role in the development of such illnesses and that steroid restoration may be helpful. Male Wistar rats' locomotor activity was reduced after receiving progesterone [32], and this effect was dose-dependent. Neither haloperidol nor progesterone has been shown to cause produced catalepsy nor antagonized amphetamine- induced stereotypy. However, both progesterone and haloperidol but not 3α, 5α-THP effectively restored thedisruption of the prepulse inhibition (PPI) of the acoustic startle response (ASR) that was evoked by apomorphine. This behavioral profile of progesterone is compatible with the sedative properties of its metabolite 3α, 5α-THP via the $GABA_A$ receptor but also with the possibility that progesterone itself shares some properties with atypical antipsychotics, which may be relevant for the development and treatment of psychotic disturbances, e.g. postpartum psychosis. It has been recently demonstrated that the atypicalneuroleptic agent olanzapine may increase theconcentrations of 3α, 5α-THP in rat brain [33]. Also clozapine, in contrast to haloperidol, may enhance the concentrations of both the 3α, 5α-THP and progesterone in rat brain in a time- and dose-dependent fashion [34]. Thus, neuroactive steroids might also contribute to the pharmacological profile of atypical antipsychotic drugs. Clinical studies reporting a beneficial effect of progesterone in women with postpartum psychosis are only available on a case report basis. However, schizophrenic women improvedmore rapidly when receiving 17β-estradiol as an adjunct to neuroleptic therapy when compared with neuroleptic treatment alone in an open label study [35]. In a recent placebo controlled investigation a dose- dependent beneficial effect of adjunct treatment with 17β-estradiol on psychotic symptoms in schizophrenic women has been found [36]. Thus, adjunct treatment with gonadal steroids might help to reduce neuroleptic doses in women resulting in a more favorable side effect profile. Future studies should assess also the potential of selective estrogen receptor modulators (SERMs) which lack distinct peripheral side effectsinherent to estrogen therapy [37].

MemoryNeurosteroids have been implicated in memory acquisition and loss in rodents. Pregnenolone sulfate infused into the basal magnocellularis nucleusenhanced memory performance in rats, whereas allopregnanolone disrupted memory [38]. Consistent with this,

intracerebroventricular infusion of allopregnanolone decreased memory performances, whereas pregnenolone sulfate significantly increasedmemory performances [39]. Pregnenolone, DHEA and DHEAS also increased memory in mice when injected into cerebral ventricles. Pregnenolone sulfate is thought, in part, to act via increasing hippocampal acetylcholine release [40]. There is also increasing evidence that some of the memory-enhancing effects of neurosteroids might be through the modulation of sigma receptors [41], since these effects are counteracted by giving the patient haloperidol or another medication that acts on sigma receptors [42-44]. Again, it is intriguing to consider the possibility that altered neurosteroidogenesis contributes to the memory loss seen in many disorders and normal human developmental processes, including aging.AnxietyAnxiety as a symptom and anxiety as a mental condition are distinct concepts, and distinguishing between them is important when trying to grasp the connection between neurosteroids and anxiety. Unlike fear, which is targeted at a particular person, place, or thing, the tension associated with anxiety seems to have no obvious source. Anxiety may be a symptom even if the underlying physical cause has nothing to do with a mental disorder. Anxiety, on the other hand, may be a psychopathological sign of many other types of mental disease, such as schizophrenia, mood disorders, somatoform disorders, etc. Indeed, an entire chapter of the Diagnostic and Statistical Manual of Mental Disorders (DSM- IV-TR, A.P.A., 2000) is devoted to anxiety disorders. Anxiety disorders such as phobias, GAD, panic attacks with and without agoraphobia, OCD, and PTSD, among others, are covered here. However, human studies are few, and only a small number of research teams have attempted to reproduce previous findings on the same disease [45–47]. When it comes to anxiety disorders, panic disorder has been the subject of a great deal of research, with the majority of these studies having been conducted by the same team [48–50]. This may bode well for the reliability and repeatability of findings regarding diagnosis, psychometric testing, and steroid determination. The following findings are documented in the literature on anxiety disorders: Spivak et al. discovered increased levels of DHEA and DHEAS in males with PTSD, but in women DHEA levels were comparable to those of controls and 3a,5a-THP levels were lowered [52]. Pregnenolone sulfate (PREGS) was shown to be decreased in GAD [51]. Fear disorder has been linked to decreased PREGS levels while 3a,5a-THP and DHEA levels remained stable [53]. The majority of research on panic disorder and panic episodes has focused on these topics. Among women with panic disorder, progesterone (PROG), progesterone recombinase (PRG), tetrahydropyridine (THDOC), and thyrotropin-releasing hormone (TH) were all shown to be elevated [54]. Data are also available on levels of neurosteroids after pharmacologically induced panic episodes. Pentagastrin challenge was observed to raise DHEA levels [55], while cholecystokinin-induced fear increased THDOC levels. tetrapeptide (CCK-4) [56,57] found decreased levels of 3a,5a-THP after panic attack induction with both sodium lactate and CCK- 4 in panic disorder patients; however, no such changes were found in healthy controls after panic induction [58,59]. Therefore, based on the scientific evidence described above neurosteroids could become potential targets for therapeutic intervention in anxiety disorders

Conclusion

In animal models of CNS diseases, neuroactive steroids cause a range of effects that both overlap and vary from those produced by other positive allosteric modulators of the GABAA receptor. Therapeutic windows for neuroactive steroids match well to those of already used medications in clinical practice, and preclinical assessment has indicated their usefulness in treating a number of central pathophysiological conditions. The effectiveness of neuroactive steroids has been shown in several clinical investigations, and there have been no major adverse effects noted. Neuroactive steroids are a

potentially useful family of GABAA receptor modulators, and their new mechanism of action, together with its hypothesized effectiveness and overall absence of side effects, warrants further clinical investigation.

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