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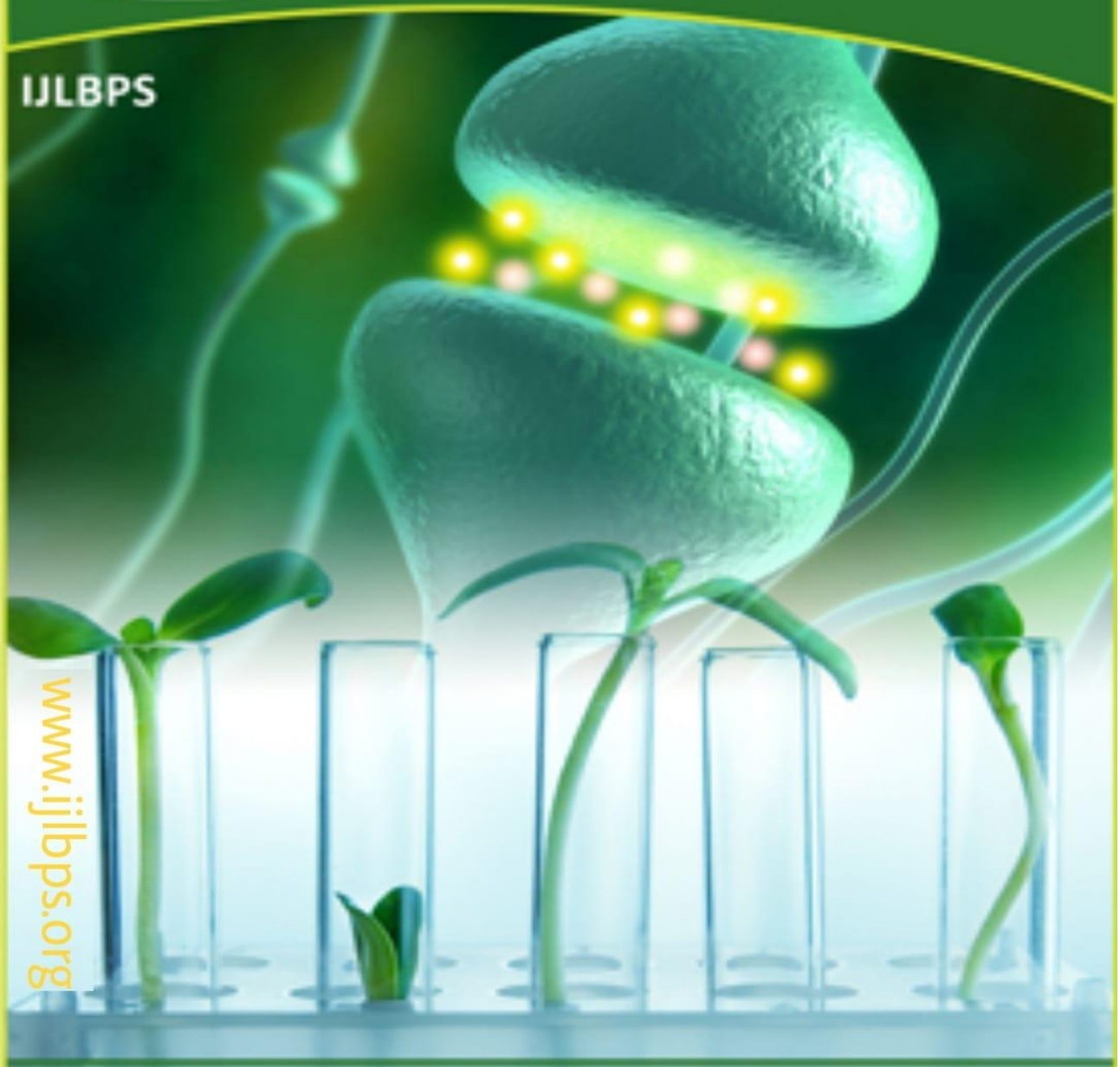

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Neuroactive steroids and neuropharmacological disorder

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Abstract

The brain, like the adrenal glands, testicles, and the placenta, produces steroids. Steroid synthesis in the nervous system differs from that in classic steroidogenic tissues in that it requires the coordinated expression and regulation of genes encoding the steroidogenic enzymes in multiple cell types (neurons and glia) at different locations in the nervous system, often at a considerable distance from the cell bodies. There may be a connection between the creation of these steroids and their roles in brain development. Neurosteroids, which are produced in the brain and nervous system, serve many different 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. We explore the physiological significance and possible use of neurosteroids in treating certain human disorders.

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

Introduction

In 1981, Baulieu used the term "neurosteroid" (NS) to describe the steroid molecule dehydroepiandrosterone sulfate (DHEAS), which was proven to be generated by the brain and persist in high quantities in the brain even after gonadectomy and adrenalectomy. Later, androstenedione, pregnenolone, and their sulfates [1,2] and lipid derivatives were recognized as neurosteroids [1], along with tetrahydro metabolites of progesterone (P) [3] and deoxycorticosterone (DOC) [4]. 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. The steroidogenic peripheral glands produce the hormonal steroids, whereas the central nervous system produces the neurosteroids. Indeed, chemicals involved in steroidogenesis' first step—the conversion of cholesterol to pregnenolone—are expressed in the central nervous system. Cholesterol transport to mitochondria and cytochrome P450 side chain cleavage are respectively mediated by the molecules translocator protein 18 kDa (TSPO; also known as peripheral benzodiazepine receptor) and steroidogenic acute regulatory protein.

cholesterol-to-pregnenolone converting enzyme. Different neuronal and glial populations also express enzymes implicated in steroid metabolism, including 3-hydroxysteroid dehydrogenase, cytochrome P450c17, 5-reductase (5-R), 3-hydroxysteroid oxido-reductase, 17-hydroxysteroid dehydrogenase, and aromatase [5]. Steroids have long been recognized to have a crucial role in the formation and function of neuronal membranes in the central nervous system. 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

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This route is especially prominent in the glia. Researchers discovered that the central nervous system (CNS) and some brain areas had much greater concentrations of neurosteroids than plasma, suggesting that these neuroactive steroids play an important function in brain cells. Cholesterol and cholesterol-sulphates are broken by different enzymes in the brain to produce different hormones in a precise order: pregnenolone, dehydroepiandrosterone, and testosterone. (DHEA), androstenedione and androsterone, andimilarly the formation of pregnenolone-sulphate, and DHEA-S, from cholesterol-sulphate. These steroids,

and their metabolites, are major compounds in the family' of neuroactive steroids found in the CNS. This family also includes: progesterone, testosterone and deoxycorticosterone, and their metabolites, also found in substantial quantities in the brain [9-11]. An interesting study on the peripheral, nonadrenal or gonadal, synthesis of neuroactive steroids was carried out [4], in which they demonstrated the effective metabolism of progesterone by lymphocytes and the production of the neuroactive steroids 5a- dihydroprogesterone and 3a-tetrahydroprogesterone. This peripheral synthesis of neuroactive steroids could be a useful source for them for their actions in a variety of tissues outside the CNS.

Epilepsy

Drugs that enhance the function of $GABA_A$ receptors such as benzodiazepines and barbiturates as well as drugs targeting the GABA binding's site of the $GABA_A$ receptor are commonly used as effective antiepileptic agents. Therefore, 3α-reduced neuroactive steroids should also possess anticonvulsant activity. Indeed, these neuroactive steroids exerted pronounced anticonvulsant effects in various animal models [12- 15]. First clinical experiences using progesterone as a precursor molecule in women suffering from catamenial epilepsy reported a decrease in epileptiform discharges following administration of progesterone [16,17]. Currently, first synthetic analogues of 3α- reduced neuroactive steroids, e.g. ganaxolone, are under investigation for antiepileptic activity [18-21]. In first phase II trials promising results have been obtained in complex partial seizures and infantile spasms [22]. Although first animal studies with subchronic administration of ganaxolone suggest that this steroid induces anticonvulsant tolerance to benzodiazepines but not to itself [23], putative side effects such as sedation, alteration of sleep architecture and development of tolerance have to be taken into account, especially when considering long-term treatment with this new class of drugs. Nevertheless, 3α-reduced neuroactive steroids may constitute a promising new treatment option for distinct forms of epilepsy.

Insomnia

Both preclinical and clinical evidence suggest a use for neuroactive steroids in insomnia. Progesterone shortens sleep latency, increases non-rapid-eye-movement (nREM) sleep duration and slightly suppresses slow- wave sleep in both rats and humans [24,25]. Effects of progesterone on these sleep-associated spectral changes appear to be mediated by the neuroactive A-ring reduced metabolites of progesterone. Indeed, systemically administered allopregnanolone reduces decreases the time it takes to enter nREM sleep and lengthens pre-REM sleep at brain concentrations similar to those produced by progesterone treatment [26]. Brain allopregnanolone levels within physiological ranges [27] show nREM-specific effects of allopregnanolone on sleep, suggesting a role for neuroactive steroids in modifying physiological sleep [26]. The length of non-rapid eye movement (nREM) sleep has been shown to be greatly increased by the 21-OH congener 3a-hydroxy, 5a-tetrahydrodeoxycorticosterone (5a- THDOC) [28], whereas other researchers have shown that allopregnanolone has no effect on nREM sleep. Allopregnanolone8 has a low bioavailability, therefore the variation in results is likely attributable to variations in dosing. Benzodiazepines and neuroactive steroids have been found to have comparable and distinct effects on sleep-EEG power spectra and sleep architecture [25, 26].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. Based on these findings, neuroactive steroids may have useful therapeutic applications. Such concepts are indeed undergoing clinical testing at the present time (see, for example,

CCD3693).

Psychosis

Changes in gonadal hormone production have been linked to the development of mental symptoms, according to epidemiological research [30,31]. Clinical symptoms of schizophrenia, for instance, have been demonstrated to fluctuate with the phases of the moon [30]. Furthermore, postmenopausal women are more susceptible to developing schizophrenia than their younger counterparts [31]. Therefore, it is possible to postulate that a quick decline in steroid concentrations may contribute to the development of such illnesses and that steroid replacement may be helpful. Male Wistar rats' locomotor activity was reduced after receiving progesterone [32], and this effect was dose-dependent. Progesterone, in contrast to haloperidol, neither created catalepsy or blocked the stereotypy caused by amphetamines. The acoustic startle response (ASR) prepulse inhibition (PPI) was disrupted by apomorphine, but both progesterone and haloperidol, but not 3, 5-THP, efficiently restored it. It is possible that progesterone shares some properties with atypical antipsychotics, which may be relevant for the development and treatment of psychotic disturbances, such as postpartum psychosis, because of its behavioral profile, which is consistent with the sedative properties of its metabolite 3, 5-THP via the GABAA receptor. Recent research in rats has shown that the atypical neuroleptic olanzapine may elevate 3', 5'-THP levels in the brain [33]. Clozapine, unlike haloperidol, may increase the concentrations of both 3', 5'-THP and progesterone in the rat brain in a time- and dose-dependent manner [34]. This suggests that the pharmacological profile of atypical antipsychotics may be influenced by neuroactive steroids. Progesterone has been shown to help women with postpartum psychosis in case reports, but no large-scale clinical trials have been conducted. In contrast, an open label trial [35] found that the rate of improvement in female patients with schizophrenia who also received 17-estradiol in addition to neuroleptic medication was much higher than in the control group. A dose-dependent positive impact of adjunct therapy with 17-estradiol on psychotic symptoms in schizophrenic women was identified in a recent placebo-controlled experiment [36]. As a consequence, a better side effect profile may be achieved with lower neuroleptic dosages if gonadal steroids are used as an adjunct therapy in women. Selective estrogen receptor modulators (SERMs), which treat estrogen deficiency without the usual estrogen therapy's negative peripheral effects [37], need further investigation.

Memory

Memory formation and disruption in rats may be related to neurosteroids. When injected into the basal magnocellularis nucleus, pregnenolone sulfate improved memory function in rats, but allopregnanolone had the opposite effect [38]. Consistent with this, intracerebroventricular infusion of allopregnanolone impaired memory performances, but pregnenolone sulfate dramatically boosted memory performances [39]. Memory was also improved in mice after injections of pregnenolone, DHEA, and DHEAS into the cerebral ventricles. Hippocampal acetylcholine release is hypothesized to be increased by pregnenolone sulfate [40]. More and more research suggests that neurosteroids may improve memory by influencing the expression of certain genes. sigma receptors [41], because these effects can be blocked by concurrent administration of haloperidol and other sigma receptor antagonists [42–44]. Again, it is interesting to speculate that memory loss associated with many diseases and normal developmental processes in human beings, including aging, might be the result of altered neurosteroidogenesis.

Anxiety

To understand the relationship between neurosteroids and anxiety, it must be considered that anxiety as a symptom and anxiety as a mental disorder are different entities. In the first case, anxiety indicates tension, a sensation of awareness with no apparent reason (different from fear, which is directed against a specific object or situation). As a sign, anxiety may be present in physiological conditions not linked to a specific psychopathological state or to a mental illness. Instead, as a psychopathological symptom anxiety can be a component of many kinds of mental illnesses including schizophrenia, mood disorders, somatoform disorders, etc. Indeed, a whole chapter of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, A.P.A., 2000) is dedicated to anxiety disorders. This chapter includes phobia, generalized anxiety disorder, panic disorder with and without agoraphobia, obsessive–compulsive disorder and post-traumatic stress disorder (PTSD). However, there are few studies on humans and few research groups have tried to replicate results on the same type of pathology [45-47]. Regarding anxiety disorders, there are many studies on the panic disorder; most of them have been carried out by the same group [48-50], which could be an advantage for the accountability and reproducibility of results (diagnosis, psychometric measurements and method of steroid determination). If we look at the studies on anxiety disorders, the following results

are reported: in generalized anxiety disorders, pregnenolone sulfate (PREGS) was found decreased
[51]; in post-traumatic stress disorder (PTSD), Spivak et al. measured higher levels of DHEA and DHEAS in men, while in women DHEA levels were similar to those of controls and 3a,5a-THP levels were decreased [52]. In phobia, the levels of PREGS were significantly lower, whereas 3a,5a-THP and DHEA were unchanged [53]. Most available data regard the panic disorder and panic attacks. In the panic disorder, PROG, PREG, 3a,5a-THP and THDOC were found generally increased in women, and PROG and DHEA in men [54]. Data are also available on levels of neurosteroids during pharmacologically induced panic attacks. Increased DHEA levels were found following pentagastrin challenge [55] and THDOC levels increased after panic induction with cholecystokinin-

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

Neuroactive steroids produce a spectrum of effects in animal models of CNS disorders that both overlap with those of other positive allosteric modulators of the GABAA receptor and exhibit quantitative and qualitative differences. Preclinical evaluation has predicted the efficacy of neuroactive steroids in the treatment of several central pathophysiological states and neuroactive steroids have predicted therapeutic windows that compare favourably with those of drugs currently available for clinical practice. Clinical studies have generally confirmed both the efficacy of neuroactive steroids as well as the absence of significant side-effects produced by these compounds. The novel manner in which neuroactive steroids are thought to transduce their effects in conjunction with their predicted efficacy and general lack of side-effects establishes these compounds as a novel class of GABAA receptor modulators and encourages additional clinical scrutiny.

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