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Neuroactive steroids and neuropharmacological disorder

Aruna Badoni[1]*, Jyoti Maithani[1] and Kapil Kalra[2]
1, Siddhartha Institute of Pharmacy, Dehradun, (UK) - India
2, Department of Pharmacy, Alpine College of Management & Technology, Dehradun, (UK) - India

Abstract
The brain, like the adrenals, gonads and the placenta, is a steroidogenic tissue. However, unlike classic steroidogenic tissues, the synthesis of steroids in the nervous system requires coordinated expression and regulation of genes encoding the steroidogenic enzymes in several different cell types (neurons and glia) at different locations in the nervous system, often at some distance from the cell bodies. Furthermore, the synthesis of these steroids might be developmentally regulated and related to their functions in the developing brain. The steroids synthesized by the brain and nervous system, given the name 'neurosteroids', have a wide variety of diverse functions. In general, they mediate their actions not through classic steroid hormone nuclear receptors, but through other mechanisms, such as ion-gated neurotransmitter receptors or direct/indirect modulation of other neurotransmitter receptors. We summarize the biochemistry of the enzymes involved in the biosynthesis of neurosteroids, their pharmacological properties and modes of action. The physiological relevance and potential uses of neurosteroids in certain human diseases are discussed.

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

Introduction
The term ''neurosteroid'' (NS) was introduced by Baulieu in 1981 to name a steroid compound, dehydroepiandrosterone sulfate (DHEAS), that was found at high levels in the brain long after gonadectomy and adrenalectomy, and later shown to be synthesized by the brain. Later, androstenedione, pregnenolone, their sulfates [1,2] and lipid derivatives as well as tetrahydro metabolites of progesterone (P) [3] and deoxycorticosterone (DOC) were identified as neurosteroids [1]. Production of Ring A reduced metabolites from P is not restricted to nervous systems. For example, THP is also produced by lymphocytes [4]. The term ''neuroactive steroid'' (NAS) refers to steroids that, independent of their origin, are capable of modifying neural activities.

These molecules are synthesized either in the steroidogenic peripheral glands (i.e., hormonal steroids) or directly in the CNS (i.e., neurosteroids). Indeed, molecules involved in the conversion of cholesterol into pregnenolone, the first step of steroidogenesis, are expressed in the CNS.

These molecules include translocator protein 18 kDa (TSPO; also known as peripheral benzodiazepine receptor) and steroidogenic acute regulatory protein, which are involved in the transport of cholesterol to the mitochondria and cytochrome P_{450} side chain cleavage, the enzyme that converts cholesterol into pregnenolone. In addition, enzymes involved in steroid metabolism, such as 3-hydroxysteroid dehydrogenase, cytochrome P450c17, 5-reductase (5-R), 3-hydroxysteroid oxido-reductase, 17-hydroxysteroid dehydrogenase and aromatase are also expressed by different neuronal and glial populations [5].

Synthesis of neuroactive steroids

The central nervous system has long been known to contain substantial amounts of steroids as part of their key function in the structure and function of neuronal membranes. However, only fairly recently has it become evident that not only they are transported into the brain from the periphery, but de novo synthesis, as well as a steroid metabolic pathway, are present in the brain. This pathway is most notably found in the glia where synthesis of pregnenolone and its metabolites, from cho- lesterol, is by enzymes other than those in the adrenal [6-8]. The concentration of many of these neurosteroids, in the CNS in general, and in specific regions of the brain, was found to be much higher than in the plasma, defining an active role for these neuroactive steroids in brain cells. Both cholesterol and cholesterol-sulphates have been found to be cleaved by specific brain enzymes, resulting in the sequential formation of pregnenolone, dehydroepiandrosterone (DHEA), androstenedione and androsterone, and similarly the formation of pregnenolone-sulphate, and DHEA-S, from cholesterol-sulphate. These steroids,

*** Corresponding Author**
E.mail: kapil752003@yahoo.com

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 the latency to nREM sleep and increases the duration of pre-REM sleep at brain concentrations comparable to those generated by progesterone administration [26]. As the nREM-specific effects of allopregnanolone on sleep are observed at brain allopregnanolone levels within physiological ranges [27], it has been suggested that neuroactive steroids could play a role in modulating physiological sleep [26]. Conversely, others have reported that allopregnanolone does not affect nREM sleep, although its 21-OH congener 3a-hydroxy, 5a-tetrahydrodeoxycorticosterone (5a-THDOC) significantly increases nREM sleep duration [28]. Given the generally poor bioavailability of allopregnanolone8, this discrepancy is probably due to differences in dosage preparation. Although the effects of benzodiazepines and neuroactive steroids on sleep architecture and sleep-EEG power spectra are similar in many respects [25, 26], differences have also been reported. In contrast to the clinically used benzodiazepine receptor hypnotics zolpidem and triazolam, pregnanolone and CCD3693 do not measurably interfere with REM sleep in rats tested at circadian time-18 at doses that significantly increase time spent in nREM sleep [29]. In addition, unlike the benzodiazepines, these neuroactive steroids do not produce compensatory decreases in nREM sleep after their nREM-promoting effects subside, leading to the suggestion that rebound insomnia might be less of a problem for steroid hypnotics. Finally, in contrast to triazolam and zolpidem, pregnanolone and CCD3693 increase nREM sleep-bout length, which is considered to be a determinant of sleep quality in humans, and produce their sleep-related effects at non-myorelaxant doses [29]. These data suggest that neuroactive steroids might offer certain advantages when employed therapeutically. Indeed, these ideas are currently under clinical scrutiny (e.g. CCD3693).

Psychosis

Epidemiological studies suggest that the onset of psychiatric symptoms may be related to changes in the secretion of gonadal hormones [30,31]. For example, the occurrence of clinical symptoms in schizophrenia has been shown to vary across the menstrual cycle [30]. Moreover, there is a difference between pre- and postmenopausal women with an increased vulnerability for the onset of schizophrenic episodes after the menopause [31]. Thus, it may be hypothesized that a sudden drop of steroid concentrations may contribute to the development of such disorders and a steroid replacement might be of therapeutic value. Progesterone administration dose-dependently decreased locomotor activity in male Wistar rats [32]. In contrast to haloperidol, progesterone neither

produced catalepsy nor antagonized amphetamine-induced stereotypy. However, both progesterone and haloperidol but not 3α, 5α-THP effectively restored the disruption 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 atypical neuroleptic agent olanzapine may increase the concentrations 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 improved more 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 effects inherent to estrogen therapy [37].

Memory

Neurosteroids have been implicated in memory acquisition and loss in rodents. Pregnenolone sulfate infused into the basal magnocellularis nucleus enhanced memory performance in rats, whereas allopregnanolone disrupted memory [38]. Consistent with this, intracerebroventricular infusion of allopregnanolone decreased memory performances, whereas pregnenolone sulfate significantly increased memory 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], 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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