NEUROSTEROIDS: THE NOVEL NEUROMODULATORS

Tabassum N, Feroz A

Department of Pharmaceutical Sciences, University of Kashmir, Hazratbal, Srinagar-190006

Summary

The term neurosteroid applies to those steroids that are synthesized in the nervous system from cholesterol or other blood-borne steroidal precursors and accumulate in the nervous system. In general, they mediate their actions, not through classic steroid hormone nuclear receptors, but through ion-gated neurotransmitter receptors. The expression of the steroidogenic enzymes is developmentally regulated, with some enzymes being expressed only during development, while others are expressed in the adult. These enzymes are expressed in both neurons and glia, suggesting that these two cell types must work in concert to produce the appropriate active neurosteroid. Several of these steroids accumulate in the brain after local synthesis or after metabolism of adrenal steroids or gonadal steroids especially testosterone. These compounds can act as allosteric modulators of neurotransmitter receptors, such as $GABA_{A,}$ NMDA, and sigma receptors. Several synthetic neurosteroids (e.g. alphaxolone and alphadolone) have been used as sedatives for the purpose of general anesthesia for carrying out surgical procedures. Neurosteroid called ganaxolone has been developed and is currently under clinical trials for the treatment of epilepsy. The pharmacological actions of benzodiazepines at the $GABA_A$ receptor are similar to those of neurosteroids. Neurosteroids play a significant role in neurodevelopment and are involved in a wide variety of psychopathological processes. Current evidence points to important roles for neurosteroids in sexual and gender-typical behaviors control of ovulation and behaviors that strongly influence sexual interest and motivation like aggression, anxiety and depression.

Key words: Neurosteroids, Benzodiazepines, GABA, Neuromodulators

Introduction

Steroids, which are produced by the brain, are called neurosteroids. [1] They are also called 4th generation neuromessengers. Steroids and neurosteroids are very different from one another. Steroids are a class of natural and synthetic organic chemical compounds characterized by a particular molecular structure. They include the sex hormones, adrenal cortical hormones, bile acids, sterols, anabolic agents, and oral contraceptives. Most people recognize anabolic steroids, a synthetic version of the male sex hormone called testosterone. Neurosteroids are brain chemicals. Unlike most of the body's potent steroids, which are made in the sex glands, neurosteroids are only synthesized in the brain. Neurosteroids are known to be involved in behavior, stress, memory, depression, anxiety, aging of the brain, and neurodegenerative diseases.

Both glial cells and neurons participate in neurosteroid biosynthesis and metabolism. They rapidly alter neuronal excitability through interaction with neurotransmitter-gated ion channels. [2] In addition, these steroids may also exert effects on gene expression via intracellular steroid hormone receptors.

Biosynthesis:

Neurosteroids are synthesized in the central and peripheral nervous system, particularly but not exclusively in myelinating glial cells, from cholesterol or steroidal precursors imported from peripheral sources. They include 3 beta-hydroxy-delta 5-compounds, such as pregnenolone (PREG) and dehydroepiandrosterone (DHEA), their sulfates, and reduced metabolites such as the tetrahydro derivative of progesterone 3 alpha-hydroxy-5 alpha-pregnane-20-one (3 alpha,5 alpha-THPROG). These compounds can act as allosteric modulators of neurotransmitter receptors, such as $GABA_A$, NMDA, and sigma receptors. Neurosteroid synthesis in the brain might be catalyzed by biotransformation of cholesterol to various steroids by the cytochrome P450–containing monooxygenase systems. Cholesterol is transported into the mitochondria with steroidogenic acute regulating protein (StAR). In the mitochondria, cytochrome P450scc (CYP11A1) catalyzes the side–chain cleavage of cholesterol, resulting in pregnenolone formation, which is promoted by electron transfer from NADPH to P450scc through NADPH–adrenodoxin reductase (ADR) and adrenodoxin (ADX). PREG reaches the microsomes (endoplasmic reticulum), where cytochrome P45017α, lyase (CYP17) catalyzes the 17α–hydroxylation of pregnenolone, resulting in the formation of DHEA. After the transformation of DHEA to androstenedione by 3β-hydroxysteroid dehydrogenase (3β-HSD), cytochrome P450 aromatase (P450arom, CYP19) catalyzes the conversion of androstenedione to estrone. This is followed by a further transformation to 17β−estradiol by 17β−hydroxysteroid dehydrogenase (17β−HSD). Testosterone is also formed from androstenedione by 17β−HSD. The possible conversion of testosterone to17β−estradiol may be performed by P450arom. Hydroxysteroid sulfotransferase converts PREG and DHEA to their sulfate forms, PREGS and DHEAS. In another pathway in microsomes, PREG is metabolized to progesterone by 3β-HSD. Cytochrome P450c21 converts progesterone to deoxycorticosterone and deoxycortisol, which then reach the mitochondria, where P45011β converts them to corticosterone (CORT) and cortisol,

respectively. Cytochromes P45017α, P450c21 and P450arom accept electrons from NADPH–cytochrome P450 reductase. [1]

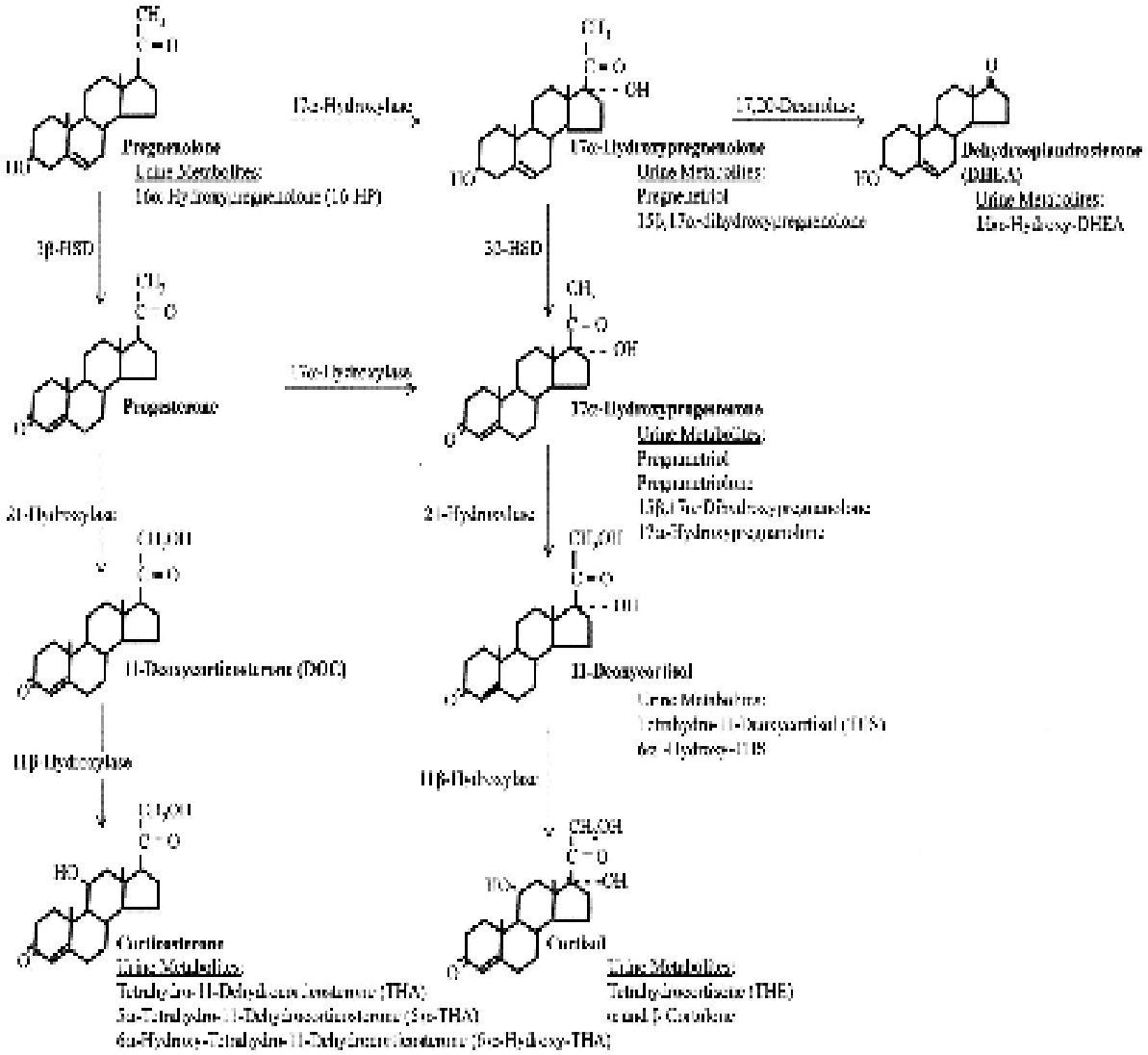


Fig: Biosynthesis of Neurosteroids

Mechanism of Neurosteroid Action:

These compounds can act as allosteric modulators of neurotransmitter receptors, such as $GABA_A$, [3] [4] NMDA, [5] and sigma receptors. [6] Progesterone (PROG) is also a neurosteroid, which activates progesterone receptors expressed in peripheral and central glial cells.[7] [8] [9] The 3α-hydroxy ring A-reduced pregnane steroids allopregnanolone and tetrahydro

deoxycorticosterone have been surmised to enhance GABA-mediated chloride currents, whereas pregnenolone sulfate and dehydroepiandrosterone (DHEA) sulfate display functional antagonistic properties at $GABA_A$ receptors.

Role of Neurosteroids in Different Pharmacological Actions

Role in antidepressant action:

Certain antidepressant drugs such as fluoxetine and fluvoxamine which were thought to act primarily as selective serotonin reuptake inhibitors have also been found to increase the levels of certain neurosteroids. Based on these studies, it has been proposed that increased levels of neurosteroids induced by fluoxetine or fluvoxamine may significantly contribute to or even be the predominate mechanism of action of these antidepressant drugs. [10]

Role in Development of Pediatric Psychopathology:

Neurosteroids play a significant role in neurodevelopment and are involved in a wide variety of psychopathological processes. There is accumulating evidence on their role in adult psychopathology. Little is known, however, about the possible role of neurosteroids in child and adolescent psychopathology although there is increasing evidence for their critical role from the early stages of brain development until adolescence. [11]

Role of neurosteroid in catamenial epilepsy:

Catamenial epilepsy is a menstrual cycle-related seizure disorder that affects up to 70% of women with epilepsy. It is characterized by an increase in seizures during particular phases of the menstrual cycle. The molecular mechanisms involved in the pathophysiology of catamenial epilepsy are not well understood. Recent studies suggest that cyclical changes of ovarian hormones estrogens (proconvulsant) and progesterone (anticonvulsant) appear to play a key role in the genesis of catamenial seizures. Progesterone reduces seizure susceptibility partly through conversion to neurosteroids such as allopregnanolone, which enhances $GABA_A$ receptor function and thereby inhibits neuronal excitability. In animal models, withdrawal from chronic progesterone and, consequently, of allopregnanolone levels in brain, has been shown to increase seizure susceptibility. Natural progesterone therapy has proven effective in women with epilepsy. Moreover, neurosteroids have been shown to be very effective inhibitors of catamenial seizures in animal models. Thus, synthetic neuroactive steroids, such as ganaxolone, which are orally active and devoid of hormonal side effects, represent a novel treatment strategy for catamenial epilepsy. However, their clinical efficacy in catamenial epilepsy has yet to be explored**.** [12]

Role in the modulation of diurnal changes:

The neurosteroid allopregnanolone has been shown to be a potent ligand of gamma-aminobutyric acid (GABA)-A receptors and enhances its receptor-mediated inhibitory events. Since central GABA plays a major inhibitory role, via GABA-A receptors, in hypothalamic–pituitary–adrenal (HPA) function in rats, the effect of passive immunoneutralization of allopregnanolone on diurnal

changes in corticosterone secretion and acute stress-induced corticosterone secretion in rats has been evalated. [13]

Role in sexual behavior and function:

Current evidence points to important roles for neurosteroids in sexual and gender-typical behaviors, control of ovulation, and behaviors that strongly influence sexual interest and motivation like aggression, anxiety and depression. At the cellular level, neurosteroids act through stimulating rapid changes in excitability and direct activation of membrane receptors in neurons. Thus neurosteroids can have immediate and specific effects on select neuronal pathways to regulate sexual function. [14]

Role in Alzheimer's disease:

It has been seen that a reduction of neurosteroids in the brain may initiate sporadic Alzheimer's disease (AD) which comprises >99% of all AD cases. AD research is currently focused on aberrant amyloid precursor protein processing and the hyper-phosphorylation of tau protein. It has also been established that neurosteroids provide a layer of protection from excessive excitation, and their age-related decrease may expose the vulnerability required to allow neuronal death by excitotoxicity and thereby initiate the disease. [15]

Role in treatment of Niemann-Pick Type C disease:

Endogenous and synthetic neurosteroids have been suggested for the treatment of Niemann-Pick Type-C (NP-C). NP-C is an autosomal recessive neurodegenerative disease caused by mutations in NPC1 (95%) or NPC2 (5%), resulting in lysosomal accumulation of unesterified cholesterol and glycolipids. It has been found that NP-C mice when treated with a single dose of allopregnanolone results in doubling of life span, substantial delay in onset of neurological symptoms, survival of cerebellar Purkinje and granule cell neurons, and reduction in cholesterol and ganglioside accumulation. [16]

Potential protective role in compromised pregnancies:

Complications during pregnancy and birth asphyxia lead to brain injury, with devastating consequences for the neonate. It has been found that the steroid environment, during pregnancy and at birth, aids in protecting the fetus and neonate from asphyxia-induced injury. Placental precursor support leads to remarkably high concentrations of allopregnanolone in the fetal brain and to a dramatic decline with the loss of the placenta at birth. These elevated concentrations influence the distinct behavioral states displayed by the late gestation fetus and exert a suppressive effect that maintains sleep-like behavioral states that are present for much of fetal life. This suppression reduces CNS excitability and suppresses excitotoxicity. With the availability of adequate precursors, mechanisms within the fetal brain ultimately control neurosteroid levels. These mechanisms respond to episodes of acute hypoxia by increasing expression of 5α-reductase and P450scc enzymes and allopregnanolone synthesis in the brain. This allopregnanolone response, and potentially that of other neurosteroids including 5α-tetrahydrodeoxycorticosterone (TH-DOC) has been found to reduce hippocampal cell death following acute asphyxia and suggests that stimulation of neurosteroid production may protect the fetal brain. [17]

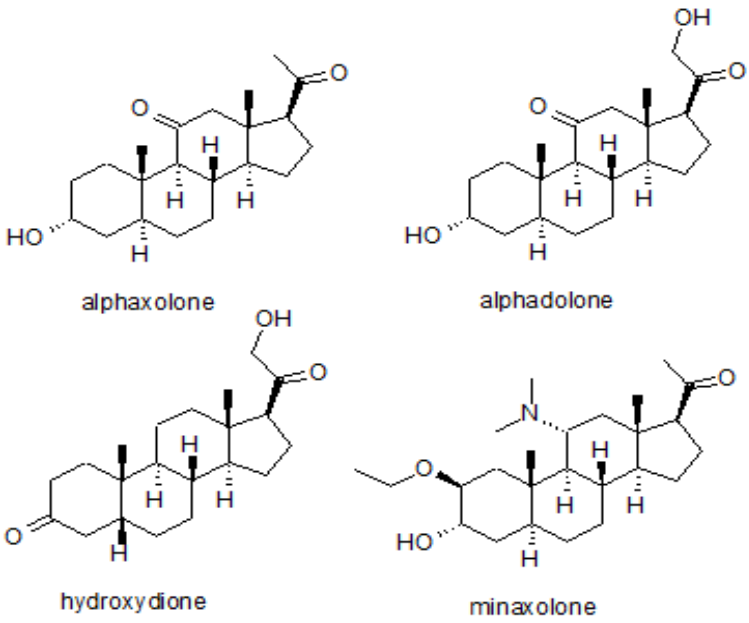
Therapeutic applications of Neurosteroids:

Several synthetic neurosteroids have been used as sedatives for the purpose of general anaesthesia for carrying out surgical procedures. The best known of these are alphaxolone, alphadolone, hydroxydione and minaxolone.

Hydroxydione was the first of these to be introduced, which is the esterified 21-hydroxy derivative of 5β-pregnanedione. It proved to be a useful anaesthetic drug with a good safety profile, but was fond to be painful and irritating when injected, probably due to poor water solubility. This led to the development of newer neuroactive steroids.

Althesin (a mixture of alphaxolone and alphadolone) was the next drug from this family to be marketed. Due to rare but serious toxic reactions this drug was withdrawn for human use. However, it is still used in veterinary medicine.

Minaxolone, the next neurosteroid anaesthetic introduced into human medicine, is around three times more potent than althesin and retains the favorable safety profile, without the toxicity problems seen with althesin. However this drug has also been withdrawn because it has been suggested as potential carcinogen in animal studies.



The neurosteroid ganaxolone, an analog of the progesterone metabolite allopregnanolone, has been extensively investigated in animal models and is currently in clinical trials for the treatment of epilepsy.[18] Neurosteroids, including ganaxolone have a broad spectrum of activity in animal models.[19] They may have advantages over other $GABA_A$ receptor modulators, notably benzodiazepines, in that tolerance does not appear to occur with extended use.[20][21] In clinical trials, ganaxolone has been found to be effective in the treatment of partial seizures in adults and is better tolerated.

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