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Research Article

BIOSYNTHESIS OF NEUROSTEROID AND PHARMACOLOGYCAL ACTION

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ABSTRACT

Over the past decade, it has become clear that the brain, like the gonad, adrenal and placenta, is a steroid genic organ. Neurosteroids are synthetized in the central and the peripheral nervous system, in glial cells, and also in neurons, from cholesterol or steroidal precursors imported from peripheral sources. However, unlike classic steroid genic tissues, the synthesis of steroids in the nervous system requires the coordinate expression and regulation of the genes encoding the steroid genic enzymes in several different cell types (neurons and glia) at different locations in the nervous system, and at distances from the cell bodies. The steroids synthesized by the brain and nervous system, given the name *neurosteroids* Progesterone itself is also a neurosteroid, and a progesterone receptor has been detected in peripheral and central glial cells. At different sites in the brain, neurosteroid concentrations vary according to environmental and behavioural circumstances, such as stress, sex recognition, or aggressiveness. 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 through ion gated neurotransmitter receptors, or through direct or indirect modulation of other neurotransmitter receptors. Briefly summarized the biochemistry of the enzymes involved in the biosynthesis of neurosteroids. This article presents a review on some reporteddeals with the synthesis and biosynthesis of neurosteroids and it may be important to study the effects of abnormal neurosteroid concentration metabolism in view of the possible treatment of functional and trophic disturbances of the nervous system.

INTRODUCTION

The steroids synthesized by the brain and nervous system it can be called as term neurosteroids. Neurosteroids, also known as neuroactive steroids, are exogenous or endogenous steroids which rapidly alter neuronal excitability through interaction with ligand-gated ion channels and other cell surface receptors. Rupprecht R *et,al* 2003 feb. 28. Neurosteroids have wide range of potential clinical applications from sedation to treatment of epilepsy and traumatic brain injury. Neurosteroids are steroids hormones which are synthesized locally within nervous. Strous RD, et, al 2006 Apr 30. The term *neurosteroid* was coined by the French physiologist Étienne-Emil Baulieu in 1981 and refers to steroids synthesized in the brain. Zorumski CF, *et, al* 2013 Jan 31;

Steroids

A steroid is an organic compound which contains four rings that are arranged specific molecular configuration. the core structure of steroids composed of 17 carbon atom bounded in four "fused" ring in three six-member cyclohexane rings and one five-member cyclopentane ring. Terech P *et,al* 1997 Dec 18.Steroids may vary by functional groups attached to this four-ring core and by oxidation state of the rings. The brain is the mosttargeted organ for steroids hormones. Many steroids are found in plants, animals and fungi. All steroids are manufactured in cells from the sterols lanosterol (animals and fungi) or cycloartenol (plants).Vollhardt KP, *et,al* 2003.

Examples - cholesterol, sex hormones, testosterone.

Classification of Newrosteroids

Inhibitory Neurosteroids

These neurosteroids exert inhibitory actions on neurotransmission. They act as positive allosteric modulators of the $GABA_A$ receptor (especially δ subunit-containing isoforms), and possess, in no particular order, antidepressant, anxiolytic, stress reducing, rewarding, prosocial, antiaggressive, prosexual, sedative, pro-sleep, cognitive and memory-impairing, analgesic,

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anesthetic, anticonvulsant, neuroprotective, and neurogenic effects. Major examples include the pregnanes allopregnanolone (brexanolone), pregnanolone (eltanolone), and tetrahydrodeoxycorticosterone (THDOC), the androstane 3α-androstanediol, and the cholestane cholesterol.

Excitatory Neurosteroids

These neurosteroids have excitatory effects on neurotransmi - sion. They act as potent negative allosteric modulators of the $GABA_A$ receptor, weak positive allosteric modulators of the NMDA receptor, and/or agonists of the σ_1 receptor, and mostly have antidepressant, anxiogenic, cognitive and memory-enhancing, convulsant, neuroprotective, and neurogeniceffects.

Major examples include the pregnanes pregnenolone sulfate (PS), epipregnanolone, and isopregnanolone (sepranolone), the and rostanes dehydroepiandrosterone (DHEA; prasterone), and dehydroepiandrosterone sulfate (DHEA-S; prasterone sulfate), and the cholestane 24(*S*)-hydroxycholesterol (NMDA receptor-selective; very potent).

Pheromones

Pheromones are neurosteroids that influence brain activity, notably hypothalamic function, via activation of vomeronasal receptor cells.
They include the and rostanes and rostadienol, and rostadienone, and rostenol, and an rostenone and the estrane estratetraenol.

Other Neurosteroids

Certain other endogenous steroids, such as pregnenolone, progesterone, estradiol, and corticosterone are also neurosteroids. However, unlike those listed above, these neurosteroids do not modulate the $GABA_A$ or NMDA receptors, and instead affect various other cell surface receptors and non-genomic targets. Also, many endogenous steroids, including pregnenolone, progesterone, corticosterone, deoxycorticosterone, DHEA, and testosterone, are metabolized into (other) neurosteroids, effectively functioning as so-called *pro* neurosteroids.

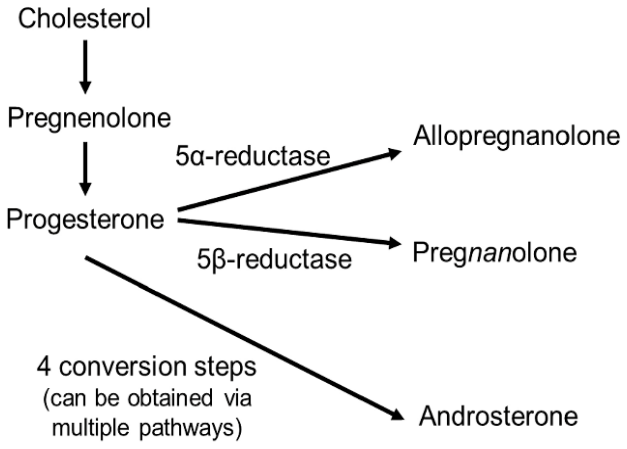

FIGURE 1. The neurosteroid synthesis pathway.

Biosynthesis of Neurosteroids

Neurosteroids are A-ring reduced metabolites of the steroid hormones progesterone, deoxycorticosterone or testosterone. The steroid precursors of neurosteroids are mainly synthesized by gonads, adrenal gland, and feto-placental unit. Numerous neurosteroids are generated by sequential reduction of the parent steroid by 5α-reductase and 3α-hydroxysteroid oxidoreductase. Including allopregnamolone and adrenostanediol. All this steps of conversions take place in peripheral tissues such as reproductive endocrine tissues, liver, and skin that are rich reducing activities. Reddy DS, *et,al* 2010.Neurosteroids are highly lipophilic so that it can readily cross the blood-brain barrier; neurosteroids which are synthesized in peripheral tissues accumulate in the brain and can influence brain function. Some evidence supported that neurosteroids biosynthetic enzyme are present in human brain. 5α-Reductase activity has been identified in both neurons and glial cells in the brain. In humans, the 5α-reductase and 3α-HSOR enzymes have been found in neocortex or subcortical white matter as well as in hippocampal tissues. Reddy DS, *et,al*2003,15. Thus the neurosteroids can be formed from their parent hormonal steroids directly in the target brain region. Steroid precursors readily enter the brain so that pools of peripherally synthesized precursors are readily available for local neurosteroid biosynthesis. Since the activity of the 3α-HSOR is far greater than that of the 5α-reductase, steroid 5α-reduction is the rate-limiting step in the biosynthesis of neurosteroids. The physiological significant of neurosteroidal PROG is clearly different from endocrine PROG. It mey act paracrinally and in particular site of formation of 3α, 5α-TH, PROG, might be different from either source. MacDonald PC, *et,al* 1991 Nov 1.

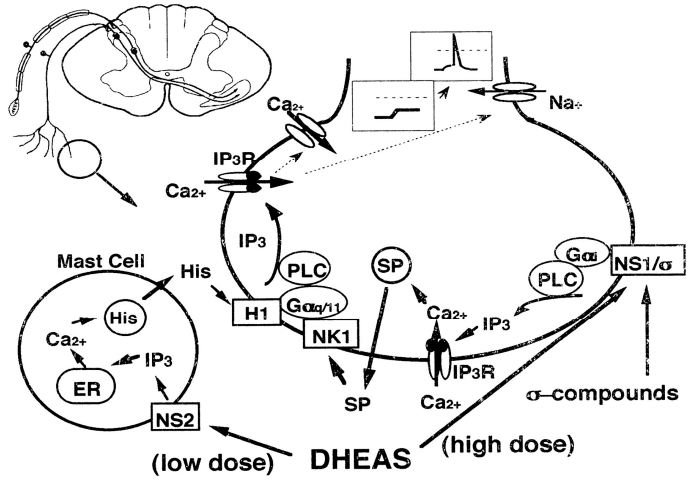

Fig Biosynthesis & Function of Neurosteroid

Physiological Role of Neurosteroid

Neurosteroids Work in Human Brain

The brain is a site of extensive metabolisms and case of andogens aromatizition and 5α-reductase give rise to active metabolites resoectively, estratiol, and 5α-dihydrotesterone, which influence neuroendocrine function and behaviors. Neurosteroids are synthetized in the central and peripheral nervous system, it is now recognized to the brain and other nervous system the ability of forming, “neurosteroids”, from cholesterol, testosterone, androstenedione and estradiol form cholesterol or steroidal precursors imported from peripheral source. Uzunova V *et,al* 1998 Mar 17. At different part in the brain, neurosteroid concentration differs according to ecological and behavioural conditions, such as anxiety, gender

gratitude and antagonism. A physiological function of neurosteroids in the central nervous system is powerfully recommended by the role of hippocampus PREGS with value to recall, observed in age rats. In the peripheral nervous system, a role for PROG synthesized in Schwann cells have be established in the renovate of myelin after cryolesion of the sciatic nerve in vivo and in culture of dorsal root ganglia neuritis.The peripheral steroids hormones cross the blood-brain barriers and act on cells through intracellular receptor-mediated mechanisms that regulate numerous important brain neuronal functions .the brain conventionally in to considered to be target site of peripheral steroid hormones. Uzunova V,*et,al* 1999 Jan 1.

Endogenous Role in the Human Brain

Neurosteroids such asallopregnanolone are promoting allosteric modulators of GABA-A receptors which influential antiseizure activity in animal models and this is endogenous regulators of convulsion inclination, anxiety, glooming and stress. Pregnenolone sulfate, the sulfate neurosteroids and have ingative GABA-A receptor modulators, are memory-enhancing agents. Reddy DS *et,al* 2010synthetic neurosteroids have batter bioavailability and efficiency and drugs that enhance neurosteroid synthesis include therapeutic potential in nervousness, epilepsy and other brain disorders. Neurosteroidogenic agents that lack benzodiazepine-like side effects show assure in the treatment of anxiety, stress, and depression. The allopregnanolone, androstanediol, deoxycorticosterone, epilepsy. Hosie AM *et,al* 2006 Nov 23.

Role of Neurosteroids as Antidepressant Agent

Certain antidepressant drugs such as fluoxetine and fluvoxamine, which are generally thoughtto affect depression by acting as selective serotonin reuptake inhibitors (SSRIs), andthey have also been known to normalize the levels of certain neurosteroids at doses that are inactive in affecting the reuptake ofserotonin. This suggests that other actions involving neurosteroids may also be at play in the effectiveness of these drugs against depression. This suggest so as to previous actions relating neurosteroids may also be play in the efficiency of drugs alongside depression. The revise point towards the possibility to SSRI's command mood via supplementary than the single pathway so as to has arriving most of our awareness, and it suggest to the steroids synthesized in the human brain can play a physically powerful physiological role in adaptable anxiety and depression.van Broekhoven F,*et,al* 2003 Jan 18.,Mellon SH,*et,al* 2002 Jan 1.

Neurosteroidsas A Regenerative Agent in Human Brain

Neurosteroids regulate both regeneration and repair systems in the brain, and among this class of molecules, allopregnanolone has been broadly investigated for its role to promote regeneration in both the central and peripheral nervous systems. In the brain, allopregnanolone induced generation and survival of new neurons in the hippocampus of both aged mice and mice with Alzheimer disease, accompanied by restoration of associative learning and memory function. Brinton RD *et,al* 2013 Apr 1**.**Therapeutic windows for efficacy of allopregnanolone were evident in the brains of mice with both normal ageing and Alzheimer disease. Allopregnanolone dose and a regenerative treatment regimen of intermittent allopregnanolone exposure were determining factors regulating therapeutic efficacy. Allopregnanolone serves as proof of concept for therapeutics that target endogenous regeneration, windows of therapeutic opportunity for regeneration, and critical system biology factors that will determine the efficacy of regeneration. Wang JM,*et,al* 2007 Dec 1.

Clinical Approche of Neurosteroids In Catamenial Epilepsy

Catamenial epilepsy is a menstrual cycle-related seizure disorder that affects up to 70% of women with epilepsy. Catamenial epilepsy is characterized by an increase in seizures during particular phases of the menstrual cycle. Three distinct patterns of catamenial epilepsy are - perimenstrual, periovulatory, and inadequate luteal phase - Currently, there is no specific treatment for catamenial epilepsy are available. The molecular mechanisms involved in the pathophysiology of catamenial epilepsy are not well understood yet. 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. Reddy DS, *et,al* 2001 Mar 9. Progesterone reduces seizure susceptibility partly through conversion to neurosteroids such as allopregnanolone, which in turn enhances GABA (A) receptor function and thereby inhibits neuronal excitability. In the study of many animal models, withdrawal from chronic progesterone and, consequently, of allopregnanolone levels in brain, has been shown to increase seizure susceptibility. Reddy DS,*et,al* 2004 Dec 31.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 as well. Some synthetic neuroactive steroids, like ganaxolone, which are orally active and devoid of hormonal side effects, have a novel approach in the treatment strategy for catamenial epilepsy. However, their clinical efficacy in catamenial epilepsy has yet to be explored. A greater understanding of the molecular mechanisms is clearly needed for designing effective treatment and prevention strategies of catamenial epilepsy in women at risk. Majewska, *et,al* 1986.

Clinical Potential of Neurosteroid for Cns Disorders

Neurosteroids are the basic endogenous molecules in the brain that affect many neural functions. The neuronal GABA-A receptor chloride channel is one of the prime molecular targets of neurosteroids. Allopregnanolone-like neurosteroids are potent allosteric agonists as well as direct activators of both synaptic and extrasynaptic GABA-A receptors. Hence, neurosteroids can maximally enhance synaptic phasic and extrasynaptic tonic inhibition. The resulting chloride current conductance generates a form of shunting inhibition that controls network excitability, seizures, and behavior. Such mechanisms of neurosteroids are providing innovative therapies for epilepsy, status epilepticus (SE), traumatic brain injury (TBI), fragile X syndrome (FXS), and chemical neurotoxicity. The neurosteroid field has entered a new era, and many compounds have reached advanced clinical trials. Synthetic analogs of neorosteroids have several advantages over natural neurosteroids for clinical use because of their superior bioavailability and safety trends. Reddy DS, *et,al* 2016 Jul 31.

Anaesthesia

Synthetic neurosteroids areused for the purpose of general anaesthesia as a sedative and forpurpose of surgical procedure. Alphaxolone, alphadolone, hydroxydione, and minaxolone are the best example for this. The first of these to introduce was hydroxydione, Hydroxydione proved to be a useful anaesthetic drug with a good safety profile, but due to its poor solubility it may be painful and cause irritation. Emerson DJ, *et,al* 2013 Mar 29. This led to the development of newer neuroactive steroids. The next drug from this family was the a mixture of alphaxolone and alphadolone, known asAlthesin but it may causes serious toxic reactions, due to which it has been withdrawal from human use but is still used in veterinary medicine. The next neurosteroid anaesthetic introduced into human medicine was the newer drug minaxolone, which is around three times more potent than althesin and have favourable safety profile, without the toxicity problems seen with althesin. However this drug was also ultimately withdrawn, not because of problems in clinical use, but because animal studies suggested that it may have potential of carcinogenicity and since alternative agents were available it was felt that the possible risk outweighed the benefit of keeping the drug on the market. Hammock BD,*et,al* 2009 Sep 11.

Ganaxolone

The neuerosteroid 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. Neurosteroids, including ganaxolone have a broad spectrum of activity indifferent animal models. They may have advantages over other $GABA_A$ receptor modulators, notably benzodiazepines, in that tolerance does not appear to occur with extended use.A randomized, placebo controlled, 10 week phase 2 clinical trial of orally administered ganaxolone in adults with partial onset seizure have been found safe in treatment, it is also well tolerated and efficacious. The drug continued to demonstrate efficacy in a 104-week open label extension. Data fromvarious non-clinical studies suggest that ganaxolone may have low risk for use in pregnancy. In addition to use in the treatment of epilepsy, the drug has potential in the treatment of a broad range of neurological and psychiatric conditions. Reddy DS,*et,al* 2010 May 31., Nohria V,*et,al* 2007 Jan 31.

Anxiety Disorders

Anxiety disorders are the most common psychiatric disorders. They are frequently treated with benzodiazepines, which are fast acting highly effective anxiolytic agents. However, their long-term use is impaired by tolerance development and abuse liability. In contrast, antidepressants such as selective serotonin reuptake inhibitors (SSRIs) are considered as first-line treatment but have a slow onset of action. Neurosteroids are powerful allosteric modulators of GABA (A) and glutamate receptors. However, they also modulate sigma receptors and they are modulated themselves by SSRIs. Both pre-clinical and clinical studies have shown that neurosteroid homeostasis is altered in depression and anxiety disorders andantidepressants may act in part through restoring neurosteroid misbalance. Greenberg PE, *et,al* 1999 Jul.

Moreover, novel drugs interfering with neurosteroidogenesis such as ligands of the Trans locator protein (18 kDa) may represent an attractive pharmacological option for novel anxiolytics which lack the unwarranted side effects of benzodiazepines. Thus, neurosteroids are important endogenous neuromodulators for the physiology and pathophysiology of anxiety and they may constitute a novel therapeutic approach in the treatment of these disorders. Beck A,*et,al* 2005 Jun 29., Zung WW,*et,al* 1971 Dec 31.

Steroidogenic Enzymes

Steroid genic enzymes, or steroid-metabolizing enzymes, are enzymes that are involved insteroidogenesis and steroid metabolism. They are responsible for the biosynthesis of the steroid hormones, including sex steroids (androgens, estrogens, and progestogens) and corticosteroids (glucocorticoids and mineralocorticoids), as well as neurosteroids, from cholesterol. These enzymes are also involved in the inactivation of steroids. Steroid genic enzymes are most highly expressed in classically steroid genic tissue such as the testis, ovary, and adrenal cortex and steroid-inactivating tissues like the liver, but are also widely present in other tissues in the body. Beck A *et.,al* 2005 Jun 29.

Neurosteroidogenesis Inhibitor

A neurosteroidogenesisinhibitor is a drug that inhibits the production of endogenous neurosteroids. Neurosteroids include the excitatory neurosteroids pregnenolone sulfate, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEA-S), and the inhibitory neurosteroids allopregnanolone, tetrahydrodeoxycorticosterone (THDOC), and 3α-androstanediol, among others. By inhibiting the synthesis of endogenous neurosteroids, neurosteroidogenesis inhibitors have effects in the central nervous system. Inhibitory neurosteroids are biosynthesized from steroid hormones by the action of two enzymes, 5α-reductase and 3α-hydroxysteroid dehydrogenase (3α-HSD).These enzymes can be inhibited by 5α-reductase inhibitors such as finasteride and dutasteride and by inhibitors of 3α-HSD such as medroxyprogesterone acetate. Contrarily, 3α-HSD is induced to varying extents by certain selective serotonin reuptake inhibitors (SSRIs), including fluoxetine, fluvoxamine, sertraline, and paroxetine, as well as by certain other antidepressants like venlafaxine and mirtazapine, and these antidepressants have been found to increase inhibitory neurosteroid levels. Inhibition of inhibitory neurosteroid biosynthesis by 5α-reductase inhibitors and 3α-HSD inhibitors has been associated with depression, anxiety, irritability, and sexual dysfunction, whereas enhancement of their biosynthesis has been implicated in the antidepressant and anxiolytic effects of some of the SSRIs. Inhibitors of cholesterol side-chain cleavage enzyme (P450scc), such as aminoglutethimide and ketoconazole, may block production of both excitatory and inhibitory neurosteroids, while CYP17A1 (17α-hydroxylase/17,20 lyase) inhibitors, such as abiraterone acetate, may mainly block production of excitatory neurosteroids. Antigonadotropins may also have the effect of lowering circulating neurosteroid levels. Terech P, *et.,al* 1997 Dec 18.

The Trans locator protein (TSPO), also initially described as the peripheral benzodiazepine receptor (PBR), is

a mitochondrial protein that is involved in neurosteroid biosynthesis. It is activated by certain benzodiazepines such as diazepam and midazolam, and via this action, inhibitory neurosteroid levels are increased. Selective TSPO activators, such as emapunil, are under investigation for clinical use as possible anxiolytics. Progesterone, which is the endogenous precursor to the inhibitory neurosteroids 5α-dihydroprogesterone and allopregnanolone, as well as, more distantly, THDOC, when administered exogenously, has been found to behave as a prodrug to these neurosteroids, with clinical signs of their action, such as sedation, readily evident in humans. Exogenous pregnenolonehas similarly been found to act as a prodrug of allopregnanolone. Metyrapone, a reversible inhibitor of the enzyme steroid 11β-hydroxylase, may increase inhibitory neurosteroid levels. Conversely, it may inhibit the production of cortisol-derived excitatory neurosteroids. Paracetamol (acetaminophen; Tylenol) has been shown to act at SULT2A1 (and potentially as SULT2B1) as an inhibitor of neurosteroidogenesis.[20] Specifically, the production of sulfate-containing neurosteroids, such as DHEA-S and pregnenolone sulfate, were decreased in patients taking paracetamol. Reddy DS,et., al 2003.

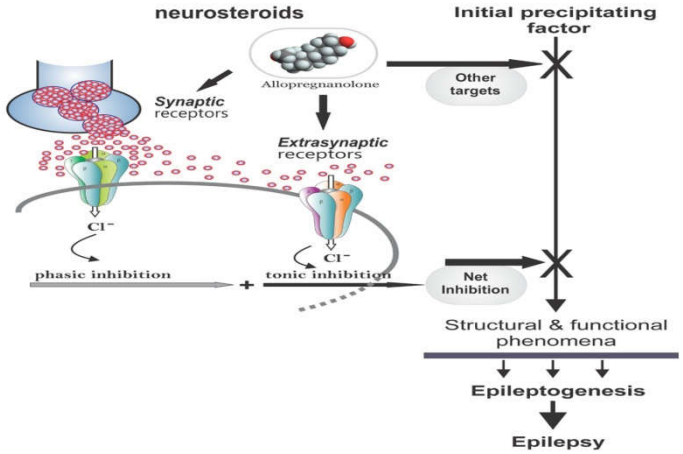

Fig Role of Hormone and Neurosyteroids

Life Style for Patient

1. Regular exercise. Walk for at least 40 minutes a day.
2. Avoid fried, oily, starchy foodstuffs, and coffee, sugar, refined flour and alcohol Eat smaller meals (low fat diet) five to six times a day instead of having three large meals.
3. Refrain from taking stress and tensions.

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CONCLUSION

Neurosteroids are endogenous modulators of neural excitability. The major pharmacological effects of neurosteroids occur largely as a result of their allosteric potentiation of GABA-A receptors. Experimental and clinical evidence suggest an endogenous role for neurosteroids in various neurological and psychiatric conditions such as epilepsy, anxiety and depression. Treatment of epilepsy, anxiety, depression and stress-sensitive conditions are among the clinical situations in which synthetic neurosteroid analogs may have clinical applications. Pathways of neurosteroid biosynthesis in the brain are better understood, but regulatory mechanisms are not 5iiujwell characterized. Much has been learned about the hormonal influence on brain function in females during puberty, menstrual cycle and menopause, but there is much more that is yet to be learned. Gender-related differences in epileptogenesis and epilepsy therapy are not well studied. The role of neurosteroids in gender-specific brain conditions certainly deserves further investigations. Although steroid hormones and sexually dimorphic brain structures play an important role in gender-related seizure susceptibility, the precise mechanisms underlying such sex differences in brain disorders remain unclear. Neurosteroid-based treatments are being developed for gender-specific conditions such as catamenial epilepsy. An NIH-funded study is currently determining progesterone efficacy in women with epilepsy. The main challenge in neurosteroid research is lack of specific antagonist(s) for neurosteroid sites on GABA-A receptors. Further studies are, therefore, clearly warranted to establish the molecular mechanisms of neurosteroid actions and their impact on the human brain.

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