Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20191611

Review Article

Neurosteroids: current perspective in therapy of neuropsychiatric disorders

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Received: 04 February 2019
Accepted: 03 March 2019

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ABSTRACT

Neurosteroids are natural or synthetic steroid derivatives which act locally in brain by modulating neuronal excitability. The objective of this study is to analyze available literature on classification, biosynthesis and mechanism of action, and therapeutic potential of neurosteroids. A review of literature pertaining to neurosteroids published from inception to 2018 was carried on data bases like PUBMED, Google Scholar and Science Direct. The search terms used were neurosteroids, neuro-active steroids, ganaxolone and GABA-A receptor modulators. Review of literature suggests neurosteroids are powerful neuro-modulators, involving rapid non-genomic and non-hormone receptor mechanisms. They are classified based on structure as pregnane, androstane and sulphated neurosteroids, and based on function as excitatory or inhibitory neurosteroids. They act via $GABA_A$ receptor (primarily), rho- GABA (ρGABA), NMDA-glutamate and sigma receptor modulation. The inhibitory neurosteroids demonstrate sedative, anxiolytic and anticonvulsant actions, whereas the excitatory agents produce memory enhancing and anxiogenic effects. They show efficacy in various CNS and psychiatric conditions like epilepsy, anxiety, depression, learning and memory disorders and substance abuse. Endogenous neurosteroids have limited clinical use due to low bioavailability, lack of specificity and unwanted effects. Hence, synthetic agents like alphaxalone, ganaxolone, sepranolone and brexanolone which have better bioavailability and specificity, are being investigated in various phases of clinical trials. Neurosteroids are novel endogenous compounds with neuro-modulatory function and show promising effects in therapy of various neurological and psychiatric conditions. Further studies that prove their long term efficacy and safety may revolutionize the clinical approach to therapy of these conditions.

Keywords: Alphaxalone, GABA-A receptor, Ganaxolone, Neurosteroids, Neuromodulators

INTRODUCTION

Neurosteroids are natural or synthetic steroid derivatives that act locally in the brain as neuroactive compounds modulating neuronal excitability.[1-3] The term neurosteroid was coined by Etienne-Emile Baulieu in 1981 to describe the steroids that accumulate in the brain, either through de novo synthesis from steroid precursors, or from endocrine glands.[1] They are thought to act by rapid non-genomic mechanisms not involving any hormone receptors.[2]

Classification

Neurosteroids can be classified in several ways based on structure as well as function as depicted in Figure 1.[2-4]

Based on structure, they are divided into three groups

- Pregnane derivatives: Allopregnanolone and Allotetrahydroxycorticosterone
- Androstane derivatives: Androstenediol and Etiocolanone

- Sulfated neurosteroids: Pregnenolone Sulfate (PS) and Dehydroepiandrosterone Sulfate (DHEAS)

Based on function, they are classified into two categories

- Excitatory neurosteroids which are the sulphated compounds
- Inhibitory neurosteroids which are the pregnane and androstane neurosteroids.

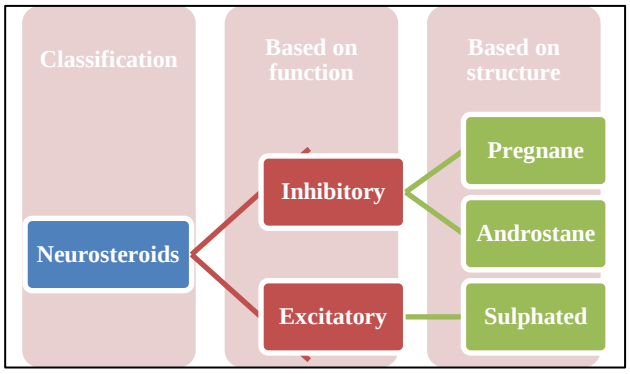

Figure 1: Classification of neurosteroids.

Neurosteroidogenesis and its regulation

The biosynthesis of neurosteroids occurs not only locally in the brain but also from peripheral sources which are later transported into the brain. The enzymes required for neurosteroidogenesis are found in neurons and glial cells in various regions of the brain.[5-8] Most of the neurosteroids are synthesized by A-ring reduction of steroid precursors by action of enzymes 5α-reductase and 3α-hydroxysteroid oxidoreductase (3α-HSOR) in a sequential manner. In the periphery these steps occur in tissues like reproductive endocrine tissues, liver, and skin.[5] In the brain they mainly occur in the neocortex and hippocampal tissues.[5,9] The precursors for this process being highly lipophilic readily enter the brain from peripheral tissues, as do the peripherally synthesized neurosteroids.[10-12]

The initial steps of neurosteroidogenesis involve the conversion of cholesterol to pregnenolone by the enzyme cytochrome P450 cholesterol side-chain cleavage enzyme (CYP450scc) which is expressed in neuronal cells and astrocytes.[13] Pregnenolone is further converted to progesterone by 3β-hydroxysteroid dehydrogenase. Progesterone is then converted to dihydroprogesterone by 5α-reductase which is then converted to allopregnanolone by 3α-HSOR. Progesterone is also converted to deoxycorticosterone (DOC) by CYP2D enzyme. DOC is further reduced to dihydroDOC by 5α-reductase which then forms tetrahydroDOC (THDOC) by action of 3α-HSOR. Androstane neurosteroids are also synthesized by similar A-ring reduction of androstenedione.[2]

Neurosteroidogenesis control is under the influence of a translocator protein (18KDa) which is located in the outer mitochondrial membrane. This protein which was previously known as peripheral or mitochondrial benzodiazepine receptor, is now known to favor the transport of cholesterol from outer to inner mitochondrial membrane, thus promoting neurosteroidogenesis.[14-16] The steps involved are given in the Figure 2.[4]

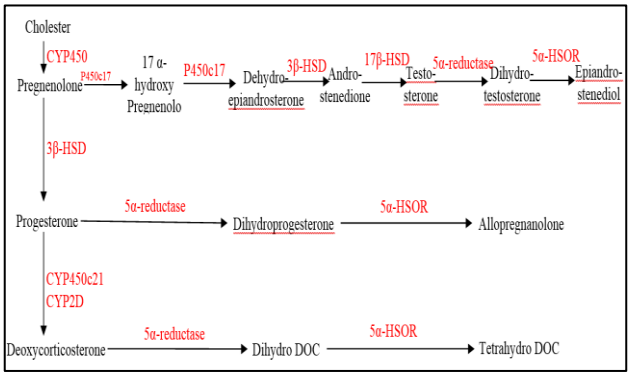

Figure 2: Biosynthesis of neurosteroids.

Mechanisms of neurosteroid action

The major difference in mechanism of action of neurosteroids from steroids is that neurosteroids do not act primarily through classical intracellular steroid receptor based genomic pathways, but mainly through ionic channel and membrane receptor based non genomic mechanisms. This non-genomic action is principally via regulation of the GABA-A chloride channel receptor action. The minor activity on steroid receptors is due to conversion of neurosteroids to classical steroids.[17-20]

GABA-A receptor modulation

As mentioned earlier, GABA-A receptor is a major site of action for neurosteroids which regulate its function by both positive and negative modulation. GABA-A receptors are ligand-gated chloride ion channel which are mainly inhibitory on synaptic transmission. GABA-A receptors are pentameric in structure with two α, two β and one γ or δ subunits which form the chloride ion channel.[21] GABA interacts with a specific binding site and mediates the opening of the chloride channel which allows the influx of chloride ions and hyper-polarization of cellular membrane. Phasic inhibition occurs as a result of activation of γ2-containing GABA-A receptors by synaptic release of large amounts of GABA whereas, tonic inhibition results from continuous interaction of ambient GABA released elsewhere on the δ-subunit containing GABA-A receptors.

The GABA-A receptors present in the hippocampal dentate gyrus granule cells contain the δ-subunit. There receptors have unique role in controlling the hippocampal excitability by setting a baseline excitability.[2] Both processes i.e. phasic and tonic inhibition are affected by neurosteroids by binding to a distinct site depending on the molecular structure of the GABA-A receptor involved, which is depicted in Figure 3 and 4 below.[2,17,22]

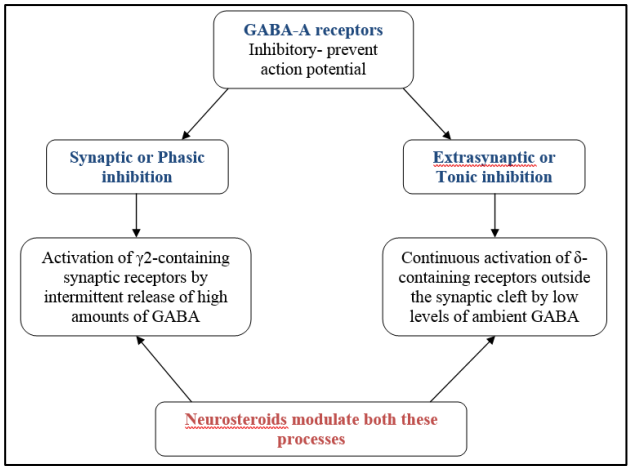

Figure 3: Neurosteroid modulation of phasic and tonic inhibition mediated through GABA-A receptors.

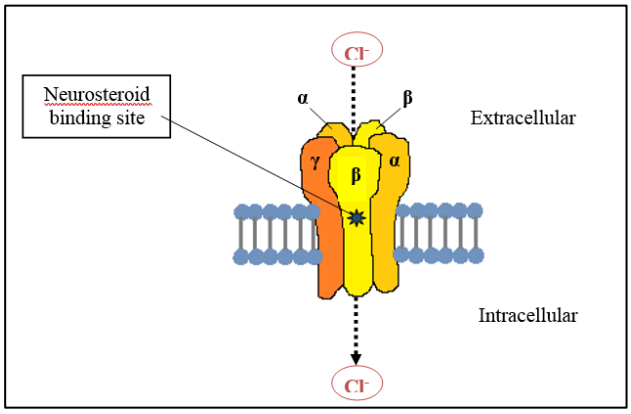

Figure 4: Neurosteroids mechanism of GABA-A receptor modulation.

The positive neurosteroid modulators of GABA-A receptors are allopregnanolone, THDOC and androstanediol.[23,24] The negative neurosteroid modulators are sulfated compounds like PS and DHEAS act by non-competitive mechanisms by binding to a site different from that of allopregnanolone and THDOC. Thus, at least three binding sites on GABA-A receptors are recognized for neurosteroids.

- Allosteric enhancement of GABA-evoked currents by allopregnanolone
- Direct activation by allopregnanolone
- Antagonist action of sulfated neurosteroids such as PS

Modulation of other GABA receptors

The rho-GABA receptors also called as GABA-C or GABA-Aρ receptors are also inhibitory specifically in the retina and other parts of nervous system. They modulate a variety of visual, sleep and cognitive disorders, and are implicated in apoptosis of hippocampal neuronal cells and pituitary hormonal regulation. Neurosteroids like allopregnanolone, 5α-THDOC and alphaxalone potentiate the ρ-GABA evoked currents whereas pregnanolone, 5β-dihydroprogesterone and 5β-THDOC inhibit their currents. Selective antagonists may delay or prevent the development of myopia and may enhance learning and memory.[25]

Glutamate receptor modulation

Pregnenolone sulphate (PS) and other sulphated neurosteroids like DHEAS have shown potent allosteric agonistic activity at N-methyl-D-aspartate (NMDA) glutamate channels. PS acts as a positive modulator at NMDA receptors by 1) selectively potentiating NMDA receptor mediated glutamate-induced depolarization, 2) Inhibiting the GABA, glycine and non-NMDA responses and 3) Augmenting the frequency and duration of opening of the NMDA-activated calcium channels.[2,26-28]

Sigma-1 receptor modulation

First described as a subset of opioid receptors, Sigma receptors exist as two types- sigma-1 and sigma-2 receptors.[29] Among these sigma-1 receptors were evaluated in various neurological conditions such as anxiety and depression, learning and memory, schizophrenia and drug abuse. Neurosteroids are considered as the endogenous ligands of these receptors with pregnenolone, DHEAS and their sulphates acting as agonists and progesterone acting as antagonist.[30]

Therapeutic role in Neuro-psychiatric disorders

Depending on their structure, neurosteroids either have neuro-inhibitory or neuro-excitatory effects. Accordingly, agents such as pregnenolone, allopregnanolone and THDOC are useful as sedative, anxiolytic agents and anti-epileptic agents whereas others like pregnenolone sulphate and DHEAS are useful as memory enhancing agents with excitatory and anxiogenic properties.

Neurological disorders

Epilepsy

The inhibitory neurosteroids which act as positive allosteric modulators of GABA-A receptors can be utilized therapeutically as anti-epileptic/anti-convulsant agents. They show a broad spectrum of activity being effective against various types of epilepsies including kindled seizures, pentylenetetrazol (PTZ) model of epilepsy, seizures due to drug-withdrawal, pilocarpine-induced seizures and at very high doses suppression of maximal electro-shock convulsion in animal models.[31] Though these agents differed in their relative potencies, synthetic pregnenolone derivatives showed similar anti-epileptic activity with a protective index that is comparable to conventional anti-epileptic agents that are clinically used.[2,32] Neurosteroids do not appear to be mired by limitations such as development of tolerance, which is a common problem with long term benzodiazepine

treatment. They also appear to be efficacious on many types of GABA-A receptors especially those containing the γ2 subunit. This makes them an ideal candidate for chronic treatment of epilepsies. Even though neurosteroids show promise as potent anti-epileptic agents, limitations with their bioavailability and metabolism leading to increased steroid receptor activity do not make them suitable agents to be used clinically.[2,33] In contrast, the sulfated neurosteroids act as proconvulsant agents at higher doses resulting in seizures and status epilepticus which can be counteracted by coadministration of allopregnanolone. Neurosteroids thus appear to have a regulatory role in epileptogenesis and seizure control.[4]

Anxiety and stress

As it is evident from the mechanism of action, excitatory neurosteroids are anxiogenic and inhibitory neurosteroids are anxiolytic in action.[34] Profound decrease in pregnenolone levels in the brain were observed in patients with induced anxiety. Hence increasing the synthesis of neurosteroids or external administration of the same may facilitate facilitate to abort anxiety and panic attacks.[35] In various animal model of anxiety such as lick suppression test and elevated plus maze, administration of 3α-reduced neurosteroids showed potent anxiolytic effects. It was also suggested that these neurosteroids may cause stress-induced activation of hypothalamo-pituitary-adrenal axis. Other genomic-mediated mechanisms such as inhibition of stress-induced CRH release and inhibition of CRH- gene expression was also suggested to be involved in their anxiolytic effects.[36] It is well known that corticosteroids have a significant role in stress management. Stress-induced release of hypothalamic corticotrophin releasing hormone (CRH) leads to stimulation and release of pituitary adrenocortico-tropic hormone(ACTH) which in-turn stimulates the release of adrenal corticosteroids. Similarly, neurosteroids are also released during states of acute physiological stress, especially THDOC and allopregnanolone whose levels rise rapidly in the plasma and brain.[17,30]

Depression

Deregulation of neurosteroid levels in the brain is thought to be involved in the pathophysiology of depressive illnesses. It was observed that there is reduced concentration of endogenous neurosteroids in the CSF of patients suffering from clinical depression. Treatment of these patients with selective serotonin reuptake inhibitors (SSRIs) resulted in an elevation of neurosteroids and exogenous administration of neurosteroids improved symptoms of depression. These findings consolidate the above theory. Both genomic and non-genomic mechanisms play a role in the anti-depressant effects of neurosteroids. These effects may likely be mediated through modulation of sigma-1 receptors which play an important role in pathophysiology of depression.[37] Neurosteroids such as pregnenolone, DHEA and their sulfated esters are agonistic whereas progesterone is antagonistic at these sigma-1 receptors.[30] The effects of DHEAS are mediated only through non-genomic mechanisms. DHEA and DHEAS which act as potent agonists at sigma-1 receptors, result in inhibition of noradrenaline reuptake and increase noradrenaline through NMDA evoked noradrenaline release which is mediated through sigma-1 receptors. On the other hand, allopregnanolone decreases noradrenaline induced corticotrophin releasing hormone (CRH) release and arginine-vasopressin (AVP) release which are both thought to have causal role in depression.[37] In addition to these, a disturbance in regulation of 3α-reduced neurosteroid synthesis was suggested to have a role in the physiochemical changes observed in certain mouse models of depression.[38]

Learning and memory

Neurosteroids are observed to modulate various learning and memory processes in animal models such as conditioned learning, special learning and simple associative learning. The excitatory neurosteroids act as enhancers of memory whereas the inhibitory ones depress learning and memory. In experimental animal models, PS enhanced memory when infused into the basal magnocellular nucleus while allopregnanolone inhibited memory functions.[39] Thus pregnenolone, DHEA and their sulphated compounds DHEAS and PS can be utilized as memory enhancers.[2] Various central receptors such as GABA-A, NMDA, cholinergic and sigma-1 receptors maybe involved in mechanism of memory enhancement of these agents.[39] These are also implicated in pathophysiology of diseases related to cognitive impairment and dementia.[40] The effects of the excitatory neurosteroids appear to be dose-dependent with extremes of doses (very low and very high) not significantly affecting learning and memory. Also, the actions of neurosteroids may be time-dependent, showing different actions on different phases of learning and memory. In various models of learning and memory, neurosteroids appeared to enhance memory consolidation more than acquisition and retrieval.[39]

Alcohol and other substance abuse

Neurosteroids are also implicated in drug acquisition, tolerance and withdrawal phases of drug abuse and dependence. Alterations in the levels of neurosteroids mediated by modulation of the hypothalamo-pituitary axis (HPA) may thus be involved in various phases of drug abuse. Exogenous allopregnanolone was shown to substitute for drugs due to reinforcing potential.[41,42] Involvement of neurosteroids in alcohol abuse, tolerance and withdrawal were correlated. There appears to be a time relationship between the behavioural effects of alcohol and the levels of alcohol-induced allopregnanolone in the brain. Moreover, the effects of alcohol could be blocked completely by blocking the endogenous neurosteroidogenesis. These effects may be mediated

through changes in GABA-A receptor sensitivity to neurosteroids during alcohol withdrawal.[2]

Limitations hindering the clinical use of neurosteroids

Clinical use of neurosteroids for treatment of the above mentioned conditions is precluded by certain limitations such as low oral bioavailability, lack of specificity and activity at the steroid receptors in the periphery leading to unwanted effects. To overcome these limitations synthetic derivatives of endogenous neurosteroids are being developed which are expected to possess improved bioavailability, specificity and reduced unwanted effects.

Synthetic neurosteroids and current perspective in therapy

Several neurosteroids with applications in important neuro-psyciatric disorders such as epilepsy, anxiety, anesthesia and Alzheimer's disease, have reached various stages of clinical development. Some of these compounds in relatively advanced stages have been discussed below (Table 1).

Table 1: Novel Synthetic Neurosteroids under development.

Drug name	Structure	Therapeutic use
Alphaxalone	Allopregnanolone	Anesthesia and sedation
Ganaxolone	3β methyl pregnane	Postpartum depression and infantile epilepsy
Sepranolone	Allopregnanolone	Premenstrual dysphoric disorder
Brexanolone	Allopregnanolone	Postpartum depression

Alphaxalone

It is a synthetic derivative of allopregnanolone. Alphaxalone is a known veterinary anesthetic agent and is now under evaluation for human use in a Phase 1c clinical study to evaluate the safety, efficacy and quality of recovery from anesthesia and sedation. The results of this study showed that Alphaxalone had "fast-onset, short-duration anesthesia with fast cognitive recovery similar to propofol, but with less cardiovascular depression, or airway obstruction and no pain on injection".[43]

Ganaxolone

This is a 3β methyl derivative of pregnane neurosteroid being developed as an antidepressant and anti-epileptic agent. A phase 2 double-blind placebo controlled study is underway evaluating the safety, tolerability and efficacy of ganaxolone in women with postpartum depression. Ganaxolone also has an FDA orphan drug designation (not FDA orphan drug approval) for the treatment of cyclin-dependent kinase-like 5 (CDKL5) gene-related early-onset infantile epileptic encephalopathy.[44,45]

Sepranolone

Also called as UC1010, it is a GABA-A receptor modulating steroid antagonist to allopregnanolone which is a metabolite from progesterone and a positive modulator of the GABA-A receptor. Allopregnanolone as an endogenous steroid may induce negative mood in sensitive women in premenstrual phase. Sepranolone as an antagonist of allopregnanolone is currently under evaluation for treatment of women with premenstrual dysphoric disorder (PMDD) in a randomized, double-blind, placebo controlled study. The results showed promising effect of sepranolone in treatment of PMDD.[46]

Brexanolone

It is also a synthetic derivative of allopregnanolone with positive allosteric modulatory effects on GABA-A receptors. Results of two randomized double-blind, placebo-controlled phase 2 and phase 3 clinical trials evaluating the efficacy of brexanolone in treatment of women with moderate to severe postpartum depression showed that brexanolone could be a novel therapeutic option for women with post-partum depression.[47,48]

CONCLUSION

Neurosteroids are endogenous steroidal compounds with multifarious neuro-modulatory function. They act through distinct non-genomic mechanisms involving various receptors in the CNS without involving the intracellular steroid receptors. They can be either excitatory or inhibitory in function which is mediated primarily through GABA-A receptor modulation by binding to a distinct site on this receptor. In addition to this neurosteroids also mediate their actions through other GABA receptors (GABA-C), NMDA-glutamate receptors and sigma-1 receptors. The pathways of biosynthesis, mechanism of action and clinical utility of neurosteroids are being elucidated in detail through 'animal and clinical studies. These agents show promise in therapy of various neurological and psychiatric conditions including epilepsy, disorders of learning and memory, anxiety, stress, depression and substance abuse. Development of synthetic analogues of neurosteroids with improved efficacy and safety is underway which if successful will revolutionize the clinical approach to the treatment of these complex neuropsychiatric conditions.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Baulieu EE, Robel P. Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate

(DHEAS) as neuroactive neurosteroids. Proc Natl Acad Sci. 1998 ;95(8):4089-91.
2. Reddy DS. Neurosteroids. Endogenous role in the human brain and therapeutic potentials. Progress in Brain Research. Elsevier B.V. 2010;(186):113-7.
3. Paul SM, Purdy RH. Neuroactive steroids. FASEB J. 1992;6(6):2311-22.
4. Reddy DS, Rogawski MA. Neurosteroids—endogenous regulators of seizure susceptibility and role in the treatment of epilepsy. Jasper's Basic Mech Epilepsies. 2012;9:258-80.
5. Mensah-Nyagan AG, Do-Rego JL, Beaujean D, Pelletier G, Vaudry H. Neurosteroids: expression of steroidogenic enzymes and regulation of steroid biosynthesis in the central nervous system. Pharmacol Rev. 1999;51(1):63-82.
6. Stoffel-Wagner B, Beyenburg S, Watzka M, Blümcke I, Bauer J, Schramm J, et al. Expression of 5alpha-reductase and 3alpha-hydroxisteroid oxidoreductase in the hippocampus of patients with chronic temporal lobe epilepsy. Epilepsia. 2000;41(2):140-7.
7. Petratos S, Hirst JJ, Mendis S, Anikijenko P, Walker DW. Localization of p450scc and 5alpha-reductase type-2 in the cerebellum of fetal and newborn sheep. Brain Res Dev Brain Res. 2000;123(1):81-6.
8. Do Rego JL, Seong JY, Burel D, Leprince J, Luu-The V, Tsutsui K, et al. Neurosteroid biosynthesis: enzymatic pathways and neuroendocrine regulation by neurotransmitters and neuropeptides. Front Neuroendocrinol. 2009;30(3):259-301.
9. Stoffel-Wagner B, Watzka M, Steckelbroeck S, Ludwig M, Clusmann H, Bidlingmaier F, et al. Allopregnanolone serum levels and expression of 5α-reductase and 3α-hydroxysteroid dehydrogenase isoforms in hippocampal and temporal cortex of patients with epilepsy. Epilepsy Res. 2003;54(1):11-9.
10. Schumacher M, Robel P, Baulieu EE. Development and regeneration of the nervous system: a role for neurosteroids. Dev Neurosci. 1996;18(1-2):6-21.
11. Mellon SH, Griffin LD, Compagnone NA. Biosynthesis and action of neurosteroids. Brain Res Rev. 2001;37(1-3):3-12.
12. Reddy DS, Kulkarni SK. Development of neurosteroid-based novel psychotropic drugs. In: Progress in medicinal chemistry. 2000;37:135-76. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0079646808700596.
13. Patte-Mensah C, Kappes V, Freund-Mercier MJ, Tsutsui K, Mensah-Nyagan AG. Cellular distribution and bioactivity of the key steroidogenic enzyme, cytochrome P450side chain cleavage, in sensory neural pathways. J Neurochem. 2003;86(5):1233-46.
14. Crawley JN, Glowa JR, Majewska MD, Paul SM. Anxiolytic activity of an endogenous adrenal steroid. Brain Res. 1986;398(2):382-5.
15. Wybraniec MT, Mizia-Stec K, Wiecek A. Contrast-induced acute kidney injury: the dark side of cardiac catheterization. Pol Arch Med Wewn Arch Intern Med. 2015;125(12):938-49.
16. Korneyev A, Pan BS, Polo A, Romeo E, Guidotti A, Costa E. Stimulation of brain pregnenolone synthesis by mitochondrial diazepam binding inhibitor receptor ligands in vivo. J Neurochem. 1993;61(4):1515-24.
17. Reddy DS. Pharmacology of endogenous neuroactive steroids. Crit Rev Neurobiol. 2003;15(3-4):197-234.
18. Reddy DS. Physiological role of adrenal deoxycorticosterone-derived neuroactive steroids in stress-sensitive conditions. Neuroscience. 2006;138(3):911-20.
19. Gee KW, McCauley LD, Lan NC. A putative receptor for neurosteroids on the GABAA receptor complex: the pharmacological properties and therapeutic potential of epalons. Crit Rev Neurobiol. 1995;9(2-3):207-27.
20. Lambert JJ, Belelli D, Peden DR, Vardy AW, Peters JA. Neurosteroid modulation of GABAA receptors. Prog Neurobiol. 2003;71(1):67-80.
21. Sieghart W. Structure, pharmacology, and function of GABAA receptor subtypes. Adv Pharmacol. 2006;54:231-63.
22. Majewska MD. Neurosteroids: endogenous bimodal modulators of the GABAA receptor. Mechanism of action and physiological significance. Prog Neurobiol. 1992;38(4):379-95.
23. Akk G, Covey DF, Evers AS, Steinbach JH, Zorumski CF, Mennerick S. The influence of the membrane on neurosteroid actions at GABA(A) receptors. Psychoneuroendocrinol. 2009;34 Suppl 1:S59-66.
24. Reddy DS, Rogawski MA. Ganaxolone suppression of behavioral and electrographic seizures in the mouse amygdala kindling model. Epilepsy Res. 2010;89(2-3):254-60.
25. Wang M. Neurosteroids and GABA-A receptor function. Front Endocrinol. 2011;2:44.
26. Sedlácek M, Korínek M, Petrovic M, Cais O, Adamusová E, Chodounská H, et al. Neurosteroid modulation of ionotropic glutamate receptors and excitatory synaptic transmission. Physiol Res. 2008;57(3):S49-57.
27. Wu FS, Gibbs TT, Farb DH. Pregnenolone sulfate: a positive allosteric modulator at the N-methyl-D-aspartate receptor. Mol Pharmacol. 1991;40(3):333-6.
28. Irwin RP, Lin SZ, Rogawski MA, Purdy RH, Paul SM. Steroid potentiation and inhibition of N-methyl-D-aspartate receptor-mediated intracellular Ca++ responses: structure-activity studies. J Pharmacol Experiment Therapeut. 1994;271(2):677-82.
29. Martin WR, Eades CG, Thompson JA, Huppler RE, Gilbert PE. The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. J Pharmacol Exp Ther. 1976;197(3):517-32.
30. Longone P, di Michele F, D'Agati E, Romeo E, Pasini A, Rupprecht R. Neurosteroids as neuromodulators in the treatment of anxiety disorders. Front Endocrinol. 2011;2(OCT):1-9.
31. Reddy DS, Castaneda DC, O'Malley BW, Rogawski MA. Anticonvulsant activity of progesterone and

neurosteroids in progesterone receptor knockout mice. J Pharmacol Exp Ther. 2004;310(1):230-9.
32. Carter RB, Wood PL, Wieland S, Hawkinson JE, Belelli D, Lambert JJ, et al. Characterization of the anticonvulsant properties of ganaxolone (CCD 1042; 3alpha-hydroxy-3beta-methyl-5alpha-pregnan-20-one), a selective, high-affinity, steroid modulator of the gamma-aminobutyric acid(A) receptor. J Pharmacol Exp Ther. 1997;280(3):1284-95.
33. Rupprecht R, Reul JMHM, Trapp T, van Steensel B, Wetzel C, Damm K, et al. Progesterone receptor-mediated effects of neuroactive steroids. Neuron. 1993;11(3):523-30.
34. Eser D, Baghai TC, Schüle C, Nothdurfter C, Rupprecht R. Neuroactive steroids as endogenous modulators of anxiety. Curr Pharm Des. 2008;14(33):3525-33.
35. Ströhle A, Romeo E, di Michele F, Pasini A, Hermann B, Gajewsky G, et al. Induced panic attacks shift gamma-aminobutyric acid type A receptor modulatory neuroactive steroid composition in patients with panic disorder: preliminary results. Arch Gen Psychiatry. 2003 Feb;60(2):161-8.
36. Eser D, Romeo E, Baghai TC, di Michele F, Schüle C, Pasini A, et al. Neuroactive steroids as modulators of depression and anxiety. Neuroscience. 2006;138(3):1041-8.
37. van Broekhoven F, Verkes RJ. Neurosteroids in depression: a review. Psychopharmacology (Berl). 2003;165(2):97-110.
38. Dong E, Matsumoto K, Uzunova V, Sugaya I, Takahata H, Nomura H, et al. Brain 5alpha-dihydroprogesterone and allopregnanolone synthesis in a mouse model of protracted social isolation. Proc Natl Acad Sci USA. 2001;98(5):2849-54.
39. Vallée M, Mayo W, Koob GF, Le Moal M. Neurosteroids in learning and memory processes. Int Rev Neurobiol. 2001;46:273-320.
40. Colciago A, Magnaghi V. Neurosteroids Involvement in the Epigenetic Control of Memory Formation and Storage. Neural Plast. 2016:1-10.
41. Concas A, Sogliano C, Porcu P, Marra C, Brundu A, Biggio G. Neurosteroids in nicotine and morphine dependence. Psychopharmacology (Berl). 2006;186(3):281–92.
42. Ginsburg BC, Gerak LR, McMahon LR, Roache JD. Neurosteroids in alcohol and substance use. In: Neuroactive steroids in brain function, behavior and neuropsychiatric disorders: Novel strategies for research and treatment. Ginsburg, Brett C. Springer Science. Business Media; 2008:509-538.
43. Monagle J, Siu L, Worrell J, Goodchild CS, Serrao JM. A phase 1c trial comparing the efficacy and safety of a new aqueous formulation of alphaxalone with propofol. Anesth Analg. 2015;121(4):914-24.
44. A Clinical Trial of Oral Ganaxolone in Women With Postpartum Depression. ClinicalTrials.gov[Internet].2019[Cited 8 January 2019]. Available at: http://clinicaltrials.gov/ct2/show/NCT03460756.
45. Search Orphan Drug Designations and Approvals. Accessdata.fda.gov. 2019. Available at: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=578017. Accessed 8 January 2019.
46. Bixo M, Ekberg K, Poromaa IS, Hirschberg AL, Jonasson AF, Andréen L, et al. Treatment of premenstrual dysphoric disorder with the GABAA receptor modulating steroid antagonist Sepranolone (UC1010)-A randomized controlled trial. Psychoneuroendocrinology. 2017;80:46–55.
47. Meltzer-Brody S, Colquhoun H, Riesenberg R, Epperson CN, Deligiannidis KM, Rubinow DR, et al. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet (London, England). 2018;392(10152):1058–70.
48. Kanes S, Colquhoun H, Gunduz-Bruce H, Raines S, Arnold R, Schacterle A, et al. Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. Lancet (London, England). 2017;390(10093):480-9.

Cite this article as: Tolety SB, Maity N, Anuradha HV. Neurosteroids: current perspective in therapy of neuropsychiatric disorders. Int J Basic Clin Pharmacol 2019;8:1119-25.