SRYAHWA PUBLICATIONS

Archives of Neurology and Neuro Disorders
ISSN: 2638-504X | Volume 6, Issue 1, 2026
https://doi.org/10.22259/2638-504X.0601001

REVIEW ARTICLE

Role of Neurosteroids on Hippocampal-dependent Memory: A Mini Review

Sumi Borah[1], Girishya Bollyamoni[1], Sikha Agrawalla[1], Sanat Kr Nath[1], Prakash Seppan[1], Monica Manivannan[2]

[1]Department of Anatomy, Dr. Arcot Lakshmanasamy Mudaliar Postgraduate Institute of Basic Medical Sciences, University of Madras, Taramani Campus, Chennai 600 113, Tamil Nadu, India.
[2]Neuberg Diagnostic, Royapettah, Chennai 600014. India.

Received: 11 April 2026 Accepted: 27 April 2026 Published: 01 May 2026

Corresponding Author: Prakash Seppan, Department of Anatomy, Dr. Arcot Lakshmanasamy Mudaliar Postgraduate Institute of Basic Medical Sciences, University of Madras, Taramani Campus, Chennai 600 113, Tamil Nadu, India.

Abstract

Neurosteroids are steroidal hormones synthesized within the central or peripheral nervous tissues, either *de novo* from cholesterol or steroid hormone precursors, and that accumulate in the nervous system and have the ability to modulate neuronal excitability by rapid non-genomic effects on membrane receptors (including those of neurotransmitters) and conventional genomic actions involving both regulation of target gene expression. In the hippocampus, neurosteroids may be the primary mediators of steroid-induced synaptic plasticity. Studies indicate that the depletion of neurosteroids can create learning and memory disorders. The findings are derived from an online literature search across reputable databases, including Google Scholar, PubMed, and Scopus. A literature survey indicates that the neuro-modulatory role of neurosteroids in regulating anxiety, memory, cognition, and age-dependent changes in the nervous system requires further investigation. Although the rapid modulatory action of sex steroids on synapses has been studied in hippocampal neurons for several decades, the essential molecular mechanisms underlying neurosteroid action, as an endogenous source of steroids, remain poorly understood. Our previous study indicated that neural repair can be facilitated through androgens. Additionally, testosterone depletion alters androgen receptor expression in the hippocampus, leading to downregulation of dendritic spine-related proteins and learning disorders. The prospects and potential of neurosteroids as therapeutic agents or targets in neurogenerative disorders and aging remain largely underdeveloped, and more work is needed to fully elucidate their roles in maintaining healthy hippocampal synaptic plasticity.

1. Introduction

Human and animal studies have indicated the neuroprotective effect of gonadal hormones. Male sex steroid depletion has been proven to cause oxidative stress (Sakthi and Prakash, 2022) and could play an important role in the pathogenesis of Alzheimer's disease (Ref). Our previous study demonstrated that neural repair can be facilitated through the androgen receptor (Prakash et al., 2019), indicating a hormonal influence on nervous tissue. Furthermore, our recent studies have shown that sex steroid deprivation, such as testosterone, induces microtubule dysregulation and neurotrophin depletion in hippocampal tissue, leading to learning and memory disorders in male rats (Sakthi, Ganesh, & Prakash et al., 2021; 2022). Interestingly, neural tissue produces its own steroidal factors, i.e., Neurosteroids (not sex steroids). Neurosteroids are steroids synthesized within the central or peripheral nervous system and can modulate neuronal excitability through rapid, non-genomic actions, as well as exert genomic effects within neurons (Reddy, 2017). Neurosteroids, including pregnenolone, dehydroepiandrosterone and their sulphated esters and progesterone and its reduced metabolites,

Citation: Sumi Borah, Girishya Bollyamoni, Sikha Agrawalla, *et al.* Role of Neurosteroids on Hippocampal-dependent Memory: A Mini Review. Archives of Neurology and Neuro Disorders. 2026; 6(1): 01-05.

are synthesized in neural tissue (Brinton, 2013). Neurosteroidogenesis occurs in brain regions such as the cortex, hippocampus, and amygdala via enzymes that catalyze the *in situ* synthesis of progesterone from cholesterol (Raciti et al., 2023). Reports show that neurosteroids can exert genomic effects by activating intracellular steroid receptors. The degree to which neurosteroids produce genomic and non-genomic effects depends on the extent of their metabolism, i.e., from parent molecules to neuroactive molecules. The role of neurosteroids in normal and pathological conditions is not clearly understood.

2. Methods

The findings are derived from an online literature search across reputable databases, including Google Scholar, PubMed, and Scopus.

2.1 Neurosteroids on the Hippocampal Synaptogenesis

The hippocampal neurons, the pyramidal cells in the CA1–CA3 regions, and the granule cells in the dentate gyrus have been shown to biosynthesize sex steroids, including 17β-estradiol (17β-E2), testosterone (T), and dihydrotestosterone (DHT) (Hojo and Kawato, 2018). Interestingly, the importance of these endogenous steroids in controlling both the central nervous system (CNS) and the peripheral nervous system (PNS) has increased. Specifically, the enzymatic complex comprising 5α-reductase (5α-R) and 3α-hydroxysteroid dehydrogenase (3α-HSD) has been localized in several regions of the human brain (Steckelbroeck et al., 2001). Besides, the presence of P450 cholesterol side-chain cleavage enzyme P450SCC (in the inner membrane of mitochondria); 17α-hydroxysteroid-dehydrogenase, 17α-HSD, 3β-hydroxysteroid-dehydrogenase, 3β-HSD and other enzymes demonstrated in the CNS, which are required to convert or synthesize neuroactive metabolites, i.e., Neurosteroids. Though glial cells possess all the enzymatic pathways and the synthetic machinery for neurosteroids, neurons seem to have significantly higher amounts of 5α-R activity than astrocytes and oligodendrocytes (Faroni and Magnaghi, 2011).

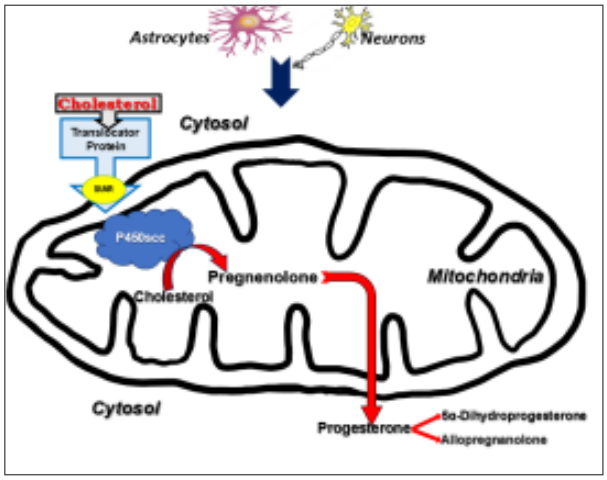

Figure 1. *Neurosteroids Synthesi*

In the hippocampus, neurosteroids have been shown to exert trophic effects and may be *s*the primary mediators of steroid-induced synaptic plasticity. They can modulate the activity of a variety of neurotransmitter receptors and ion channels, including type A gamma-aminobutyric acid (GABA) receptors, N-methyl-D-aspartate (NMDA) receptors, sigma receptors and N- and L-type Ca2+ channels (voltage-gated calcium channels) (Racit et al., 2023). There is evidence that neurosteroids strongly influence learning and memory processes, most likely by regulating neurotransmission (Ratner et al., 2019; Rossetti et al., 2022) and regulators of neuroinflammation in the Hippocampus (Yilmaz et al., 2019). Thus, neurosteroids can be a prospective therapeutic agent or target for treating age- and disease-related cognitive impairments and other neurodegenerative disorders.

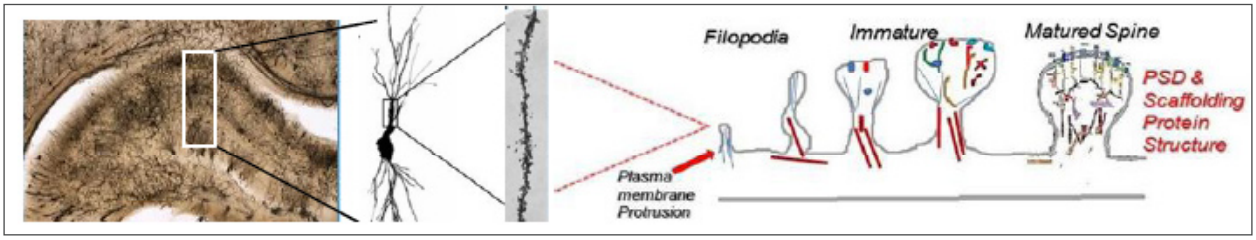

Figure2. *Hippocampal Synaptogenesis-Image depicting postsynaptic dendritic spine morphogenesis*

Sensory stimulation from various brain centers is relayed to hippocampal neurons. The repeated relay results in long-term potentiation and is the primary factor inducing dendritic spine proliferation, a hallmark of synaptic plasticity (Bastrikova et al., 2008). Furthermore, synaptic plasticity depends on the stability, size, and number of dendritic spines and is an important process in memory consolidation (Jungenitz et al., 2018; Olive & Gipson, 2018).

However, the possible role of neurosteroids in the expression of postsynaptic density proteins during synaptogenesis (Fig. 1: Golgi-Cox section and schematic image) remains unclear, as there is no strong experimental evidence. It has been reported that increased expression of GABAA receptors in CA1 pyramidal hippocampal cells is influenced by neurosteroids, leading to an optimal level of spine density, which is crucial for optimal learning and memory function in adulthood (Afroz et al., 2017). Thus, the physiological functions of neurosteroids are mediated through direct interactions with neurotransmitter receptors and indirectly through the activation of second-messenger signaling cascades. Their rapid non-genomic effects involve inhibitory and excitatory receptors (2023; Zorumski et al., 2025).

3. Concluding Remarks

The mitochondria play an important role in neurosteroid synthesis, which is accomplished by the movement of cholesterol across the mitochondrial membrane (i.e., from the outer to the inner membrane) mediated by the steroidogenic acute regulatory (StAR) protein. Subsequent conversion of cholesterol to pregnenolone (a key player, as its metabolites give rise to other neurosteroids) by cytochrome P450 side-chain cleavage (P450scc) represents the initiation of steroidogenesis. Mitochondrial dysfunction leads to neurosteroid depletion and may affect synaptic plasticity. The delineation of the influence of neurosteroids on memory function in association with neural/glial mitochondria function would be an interesting future therapeutic prospect for memory and cognition disorders.

Well-planned experiments are essential for advancing neurosteroid research. Understanding the genomic and non-genomic effects of neurosteroids on neural tissue underscores the need for credible, practical experimental animal models for research. Unfolding the puzzles of neurosteroid actions at a deeper level can be achieved by stereotaxic administration of neurosteroids into brain areas such as the hippocampus, thereby revealing their potential in spinal morphogenesis and memory consolidation. Literature has indicated the potential therapeutic use of neurosteroids like progesterone, allopregnanolone, and allotetrahydroxycorticosterone (THDOC) in epileptic disorders, probably by their GABA-A receptor-related or glutamatergic activity-related anticonvulsant effects (Perucca et al., 2023;

Walsh et al., 2025). More than four decades of research on neurosteroids and accumulated knowledge on their role in brain function still have not been fully translated into human therapy; this can be largely due to the difficulty in establishing the proper experimental model, a lack of knowledge on the dosage-dependent mechanism of neurosteroids, and ethical issues when it comes to human subjects. However, based on available data, neurosteroids are promising therapeutic agents for various nervous system diseases, particularly those associated with learning and memory. It is crucial to uncover the molecular mechanisms behind neurosteroid actions and their profound effects on the human brain. Understanding these processes can significantly enhance our knowledge of brain function and potentially lead to groundbreaking advancements in treatment strategies.

Like sex steroids, neurosteroids play a critical role in influencing memory-related regions of the brain, yet their specific molecular mechanisms remain elusive. Moreover, the dynamic interplay between sex steroids and neurosteroids in brain function—particularly in terms of sex-dependent effects—remains poorly understood and warrants further investigation. Addressing these knowledge gaps could unlock significant insights into the brain's complex workings.

Abbreviations

CA - Cornu Ammonis

17β-E2-17β-estradiol

T - testosterone

DHT – dihydrotestosterone

CNS - Central nervous system

PNS - Peripheral nervous system

5α-R - 5α-reductase

3α-HSD - 3α-hydroxysteroid-dehydrogenase P450 - Cytochrome P450

P450SCC – Cholesterol side-chain cleavage enzyme 17α-hydroxysteroid-dehydrogenase,

17α-HSD - 17-alpha-hydroxysteroid dehydrogenase

3β-HSD - 3β-hydroxysteroid-dehydrogenase\ GABA - gamma-aminobutyric acid

GABAA- gamma-aminobutyric acid A receptor NMDA - N-methyl-D-aspartate receptor

Declarations

Statement of Animal Ethics

Not Applicable.

Statement of Human Ethics and Consent to Participate Declarations

Not Applicable.

Consent for Publication

Not Applicable.

Availability of Data and Material

Not Applicable.

Competing Interests

The authors declare that they have no competing interests.

Funding

This work was funded by the Science and Engineering Research Board (SERB) Order No.EEQ/2021/001080. Dt:19.05.2022.

Authors' Contributions

SB, GB, SA, SN, MM, PS-consolidated literature data, designed and wrote the manuscript. All authors participated in interpreting and reviewing manuscript drafts and approving the final version submitted for publication. In addition, all authors read and approved the final manuscript. PS- Conceived the study idea. Sumi Borah (SB), Girishya Bollyamoni (GB), Sikha Agrawalla (SA), Sanat KR Nath (SN), Monica Manivannan (MM), Prakash Seppan (PS)

4. References

1. Afroz S, Shen H, Smith SS (2017) α4βδ GABAA receptors reduce dendritic spine density in CA1 hippocampus and impair relearning ability of adolescent female mice: effects of a GABA agonist and a stress steroid. Neuroscience 347:22–35. doi: 10.1016/j.neuroscience.2017.01.051.
2. Bastrikova N, Gardner GA, Reece JM, Jeromin A, Dudek SM (2008). Synapse elimination accompanies functional plasticity in hippocampal neurons. Proc Natl Acad Sci U S A. 105(8):3123-3127. doi:10.1073/pnas. 0800027105
3. Biagini G, Panuccio G, Avoli M. Neurosteroids and epilepsy (2010) Curr Opin Neurol 23:170- 6. doi: 10.1097/WCO.0b013e32833735cf.
4. Brinton LA, Felix AS, McMeekin DS, Creasman WT, Sherman ME, Mutch D, Cohn DE, Walker JL, Moore RG, Downs LS, Soslow RA, Zaino R (2013). Etiologic heterogeneity in endometrial cancer: evidence from a Gynecologic Oncology Group trial. Gynecol Oncol. 129(2):277-84. doi: 10.1016/j.ygyno.2013.02.023.
5. Faroni A, Magnaghi V (2011). The neurosteroid allopregnanolone modulates specific functions in central and peripheral glial cells. Front Endocrinol (Lausanne) 2:103.doi:10.3389/fendo.2011.00103
6. Foster Olive M, Del Franco AP, Gipson CD (2018). Diolistic Labeling and Analysis of Dendritic Spines. Methods Mol Biol 1727:179-200. doi: 10.1007/978-1-4939-7571-6_14.
7. Hojo Y, Kawato S (2018). Neurosteroids in Adult Hippocampus of Male and Female Rodents: Biosynthesis and Actions of Sex Steroids. Front Endocrinol (Lausanne) 9:183. doi:10.3389/fendo.2018.00183.
8. Jungenitz T, Beining M, Radic T, et al (2018). Structural homo- and heterosynaptic plasticity in mature and adult newborn rat hippocampal granule cells. Proc Natl Acad Sci U S A. 115(20): E4670-E4679. doi:10.1073/pnas.1801889115
9. Muthu SJ, Lakshmanan G, Seppan P (2022). Influence of Testosterone Depletion on Neurotrophin-4 in Hippocampal Synaptic Plasticity and Its Effects on Learning and Memory. Dev Neurosci. 44(2):102-112. doi:10.1159/000522201
10. Muthu SJ, Lakshmanan G, Shimray KW, Kaliyappan K, Sathyanathan SB, Seppan P (2022). Testosterone Influence on Microtubule-Associated Proteins and Spine Density in Hippocampus: Implications on Learning and Memory. Dev Neurosci. 44(6):498-507. doi:10.1159/000525038
11. Olive M, Del Franco AP, Gipson CD (2018) Diolistic labeling and analysis of dendritic spines. Methods Mol Biol 1727:179–200.
12. Perucca E, Bialer M, White HS (2023) New GABA-Targeting Therapies for the Treatment of Seizures and Epilepsy: I. Role of GABA as a Modulator of Seizure Activity and Recently Approved Medications Acting on the GABA System. CNS Drugs. 37:755-779. doi:10.1007/s40263-023-01027-2.
13. Prakash S, Muhammed I, Mohanraj KG, Lakshmanan G, Premavathy D, Muthu SJ, W Shimray K, Sathyanathan SB (2018) Therapeutic potential of *Mucuna pruriens* (Linn.) on ageing induced damage in the dorsal nerve of the penis and its implication on erectile function: an experimental study using albino rats. Aging Male 15:1-14. Doi: 10.1080/13685538.2018.1439005.

14. Raciti L, Formica C, Raciti G, Quartarone A, Calabrò RS (2023). Gender and Neurosteroids: Implications for Brain Function, Neuroplasticity and Rehabilitation. Int J Mol Sci. 24(5):4758. doi:10.3390/ijms24054758.

15. Ratner MH, Kumaresan V, Farb DH (2019). Neurosteroid Actions in Memory and Neurologic/ Neuropsychiatric Disorders. Front Endocrinol (Lausanne) 10:169. doi:10.3389/fendo.2019.00169

16. Reddy PH. Rajmohan R (2017) Amyloid-Beta and Phosphorylated Tau Accumulations Cause Abnormalities at Synapses of Alzheimer's disease Neurons. J Alzheimers Dis 57:975-999. doi:10.3233/ JAD-160612.

17. Rossetti MF, Varayoud J, Ramos JG (2022). Steroidogenic enzymes in the hippocampus: Transcriptional regulation aspects. Vitam Horm. 118:171-198. doi:10.1016/bs.vh.2021.11.004.

18. Sakthi Jothi M and Prakash S (2020) Apoptosis in Hippocampal tissue induced by Oxidative Stress in Testosterone Deprived Male Rats. Aging Male. 23: 1598–1610 https://doi.org/10.1080/13685538.2021.1892625.

19. Stephan Steckelbroeck, Matthias Watzka, Birgit Stoffel-Wagner, Volkmar H.J Hans, Lioba Redel, Hans Clusmann, Christian E Elger, Frank Bidlingmaier, Dietrich Klingmüller (2001) Expression of the 17β-hydroxysteroid dehydrogenase type 5 mRNA in the human brain, Mol Cell Endocrinol 171: 165-168,

20. Walsh, R., Doherty, C. P., & Doran, E. (2025). The use of steroids in adult epilepsy: A systematic review. Epilepsia open, 10:398–410. https://doi.org/10.1002/epi4.13019.

21. Yilmaz C, Karali K, Fodelianaki G, et al (2019) Neurosteroids as regulators of neuroinflammation. Front Neuroendocrinol. 55:100788. doi:10.1016/j.yfrne.2019.100788.

22. Zorumski CF, Covey DF, Izumi Y, Evers AS, Maguire JL, Mennerick SJ (2025) New directions in neurosteroid therapeutics in neuropsychiatry. Neurosci Biobehav Rev 172:106119. doi:10.1016/j.neubiorev.2025.106119.