https://jrhm.org/

Journal of
Reproductive Healthcare
and Medicine

Indian Society for the Study of Reproduction & Fertility

Review Article

Implicating transforming growth factor-β and sex steroids in the regulation of brain-gonadal functions

Sajwan Khatri Mamta

Department of Animal Biology, School of Life Sciences, University of Hyderabad, Hyderabad, Telangana, India.

***Corresponding author:**
Mamta Sajwan Khatri,
Department of Animal Biology,
School of Life Sciences,
University of Hyderabad,
Hyderabad, Telangana, India.

mamtasajwan13@gmail.com,
mamta@uohyd.ac.in

Received : 31 July 2022
Accepted : 18 October 2022
Published : 09 December 2022

DOI
10.25259/JRHM_12_2022

Quick Response Code:

ABSTRACT

Transforming growth factor-beta (Tgf-β) significantly mediates TGF signals in the brain and gonadal development. The present study insights into the implication of novel factor Tgf-β and sex steroids in coordination with catecholaminergic activity; moreover, the influence on catecholamines, gonadotropin-releasing hormone (GnRH1), and related transcripts/genes by implanting osmotic pump-mediated mismatches sex steroids in the teleost. The outcome collectively showed the severe effect of estrogenic compounds at the nominal dose over androgenic to alter reproductive conditions. In addition, the differential pattern of key transcription factors/genes revealed significantly higher expression in the brain and gonads than in other organs, which seem to have a role in the hypothalamic-pituitary-gonadal (H-P-G) axis to regulate brain-gonadal functions in catfish. Furthermore, the abundance of crucial factors mRNA and protein expression in the brain suggests a significant role in this correlation. Collectively, the study provides an understanding of the growth factors and sex steroids through dopaminergic system, where upregulated expression levels of GnRH1 vis-a-vis certain brain-related genes, that is, *GnRH1, Tgf-β, Gfrα-1, cyp19a1b, tph,* and *th* in teleost revealed their regulatory influence more importantly on the H-P-G axis.

Keywords: Transforming growth factor-beta, GDNF, Sex steroids, Brain, Gonads, Sexual development

INTRODUCTION

Growth factors typically act as signaling molecules, transforming growth factor-beta (Tgf-β), glial cell line-derived neurotrophic factor (GDNF), and sex steroids are vital regulators for growth, neuronal differentiation, and gonadal functions in response to reproduction, also many other biological processes.[1,2] TGF-β is essential for the development of the persistence and mediator of midbrain dopaminergic (DA-ergic) neurons and also upsurges the tyrosine hydroxylase (Th) expression levels in the brain.[3] Defective signaling pathway regulation transduces the Tgf-β signals, leading to several disorders, such as cancer, cardiovascular, metabolic, neurodegeneration, and other neurological disorders in the central nervous system (CNS).[4] A previous study reported the neuroprotective effects of Tgf-β, receptors (1-3), activin A, and GDNF for DA-ergic neurons *in vitro*, protein expression increases the survival of Th-immunoreactive DA-ergic in mice and catfish.[5,6] Tgf-β is an essential growth factor involved in various functions, that is, apoptosis, sex differentiation, cellular proliferation, and growth also act as a paracrine factor which plays key roles in gonadal functions[7] such as stimulation of follicular development and steroid hormone 17β-estradiol (E_2) and androgen (T) production in mammals.[8] In rainbow trout, Tgf-β stimulates the proliferation of spermatogonial and primordial germ cells[9] and prevents the maturation of oocytes in zebrafish.[10,11] Some members of the Tgf-β exhibit vital functions in reproduction by regulating gonads.[8,12] However,

it also upsurges the potency of particular Tgf-β, neurotrophin, fibroblast growth factor-2, brain cell-derived neurotrophic factor (BDNF), ciliary neurotrophic factor, and GDNF which regulate cellular processes during embryogenesis and support DA-ergic system in teleost.[3,13,14] Eliminating the Tgf-β type 2 receptor in DA neurons interrupt Tgf-β1 expression and GABAergic neurons, elevating mammals' inhibitory input.[15] Prominently, several neurotrophic factors, neurotransmitters/neuropeptides, and sex steroids are known to regulate gonadotropin (GTH), modulating the gonadotropin-releasing hormone (GnRH), and/or catecholaminergic (CA-ergic) systems at the level of the brain, to succeed reproduction.[16] In CNS sex steroids, E_2 and methyltestosterone (MT) are strong regulators of various diseases that occur in organ systems and also regulate the gonadal development and maintain a reproductive system in both sexes.[17,18] Sex steroid E_2 controls DA-ergic activity in many ways, that is, neurotransmission in combination with enzymes and anti-DA-ergic producing effects that involve neuron degradation.[19] In addition, DA is the significant inhibitory neurohormone that regulates GTH, whereas the stimulatory influence of norepinephrine (NE) and serotonin (5-HT) on GnRH release.[20,21] Moreover, natural sex steroids are altered by exogenous steroids that can mimic and disturb the neuroendocrine system.[22] McEwen[23] reported that gonadal steroids regulate diverse physiological functions in developing and mature neural targets by the hypothalamic-pituitary-gonadal (H-P-G) axis which further provides access to brain function organizational dealing with neuronal circuits and response capabilities, together with sex differences. The present review highlights the interactions of key growth factors and sex steroids and their regulation in the H-P-G axis and associated vital transcripts/genes, influencing regulatory pathways, and expression profiling to understand the regulation of brain over gonadal functions.

INVOLVEMENT OF GROWTH FACTORS AND OTHER KEY FACTORS IN THE BRAIN AND GONADAL FUNCTIONS

Tgf-β

Tgf-β is a crucial growth factor for developing midbrain DA-ergic neurons *in vitro* and *in vivo*.[2] However, in deficient mice, Tgf-β isoform and its receptor have not yet shown a role in CNS development.[24,25] Previously, human immunohistochemical analyses have been observed using specific polyclonal antibodies of Tgf-β1 and Tgf-β2 to identify cellular localization in ovarian tissues of various reproductive stages.[26] Further, ovarian tissue produces Tgf-β1 and Tgf-β2, though Tgf-β1 exists in main ovarian cell types; however, Tgf-β2 is produced by only follicular theca cells and luteal cells.[26] The Tgf-β1 signaling extensively regulates biological responses and various regulatory mechanisms at the molecular level of Tgf-β signaling in the modulation of specific physiological processes also brain and gonadal functions.[3,27] In goldfish, *Tgf*-β expression of the ovary showed a reduction in androgen production and its vital role in gonadal development at two different stages.[28] The significance of *Tgf-β* in reproductive function suggests the implication of cytokines in infertility and other sexual dysfunction.[29] Based on this premise, it is worthwhile to investigate the impact of *Tgf-β* and the modulatory action of a brain-pituitary-gonadal axis. The earlier report investigated *Tgf-β* as a vital molecule that regulates the survival of neurons synergistically with neurotrophic factors GDNF, BDNF, neurotrophin, and neuropeptides[6,30] in turn, these factors regulate the release of active TGF also modulation of Leydig cell steroidogenesis with androgenic steroids. Our recent finding revealed that the prominent *Tgf-β* mRNA and protein expression appear to propose a significant impact on growth factor signaling at the level of the brain. Further, TGF-β protein expression in the preoptic area of hypothalamus (POA-HYP) by immunolocalization indicates its role in neuronal development through GnRH and GTH axis which might support gonadal functions.[3]

GDNF/GDNF family receptor α-1 (GFRα-1)

Neurotrophic factors typically act as signaling molecules that influence the development and differentiation of many central and peripheral neuronal cells in response to reproduction. GDNF predominantly binds to GFRα-1 by modulating several central neurons including DA-ergic neurons in the brain[31] and protects against neurodegeneration. The complex GDNF-GFRα-1 recruits the tyrosine kinase transmembrane protein to upshot DA-ergic neurons differentiation.[32-34] In the neuroendocrine system brain, glial cells are an abundant cell type[35,36] that produces neurosteroids[37] such as estradiol-E_2, T, and neurotrophic factor GDNF in teleost.[6,38] Earlier studies confirmed that GDNF upsurges the DA uptake and Th expression and promotes the growth of midbrain DA-ergic neurons. Furthermore, GDNF acts as a neurotrophic factor in motor neurons and noradrenergic neurons in the CNS.[39,40] Our previous findings reported immunolocalization of GFRα-1 which exposed its presence in preoptic POA-HYP in adult catfish. Furthermore, siRNA transient silencing showed a lower expression level of *Gfrα-1* and down-regulated the brain-related gene expression. In catfish brains, *Gfrα-1* expression declined on the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP treatment triggering neurodegeneration, when further correlated with catecholamines (CAs), L-3,4-dihydroxyphenylalanine, DA, and NE levels, which conceivably entrains GnRH and GtH axis, by targeting CA-ergic activity moderately.[6] In addition, GDNF has neurotrophic and anti-apoptotic properties, which delay homeostasis of DA at different levels, that is, stimulation of the DA-ergic system, which inhibits the DA transporter activity, and Th transcription.[34] Neurochemical effects mediated by GDNF supplement the DA-ergic function, which might play a key role in motor symptoms possibly in pre-clinical or

clinical studies.[41,42] In GDNF-transgenic mice, motor neurons are located in the spinal cord; however, GDNF-deficient mice showed a significant decrease in motor neurons.[43] The earlier study by Viglietto *et al.*[44] shows that GDNF secrets from Sertoli cells to undifferentiated spermatogonia which proves to be a paracrine factor in mouse testes. Moreover, in rodents, proliferation, and suppression of differentiation of undifferentiated spermatogonia are promoted by GDNF.[33,45]

Th and CAs

Th is the rate-limiting enzyme involved in the biosynthesis of CAs, DA, NE, and epinephrine (E) which are the products of pathways that act as neurotransmitters and hormones in the CNS. Growth factors affect CA-ergic differentiation by evidence of Tgf-β, supporting the biosynthesis and expression of CA enzymes which indicate phenotypic expression possibly regulated in the CA-ergic cells, *in vitro* and *in vivo*.[46] In female catfish brain, Th and CAs expression levels[47] along with the 5-HT validated that Tph-5-HT[48,49] vis-à vis Th-CA may have a substantial role in brain sex differentiation consequently, on gonads.[50] *In vitro*, within 24 h treatment of cells with TGF, upsurges significantly the number of Th-positive DA-ergic neurons in rat embryonic day 12; however, neutralization of TGF entirely eradicates the DA-ergic neurons induction.[2] The key molecule, TGF-β, regulates neuronal survival and the Th-CAergic system synergistically with neurotrophic factors, that is, neurotrophin, GDNF, Gfrα-1, and BDNF.[6,30] Our previous study revealed that certain brain-related genes including *th, tph,* and *cyp19a1b* possibly have a key role in brain sex differentiation orchestration which regulates gonadal development.[50] The Intrastriatal GDNF target GDNF signaling which protect DA-ergic neuron content and Th activity in postnatal rats.[51] Taken together, affected DA-ergic neurons induce depletion of Th and DA also causing neurodegeneration in the brain and impairment of reproduction partially in catfish supported by the evidence of lower expression level sex steroids and gonad-related genes (*Unpublished*).

Sex steroid and GnRH

Sex steroids are essential in sexual functions and regulating many neuroendocrine activities. Our recent study highlighted the controlled release of sex steroids through an osmotic pump intraperitoneally implanted with E_2 and MT as opposed to the gender-regulated differential GnRH-GTH

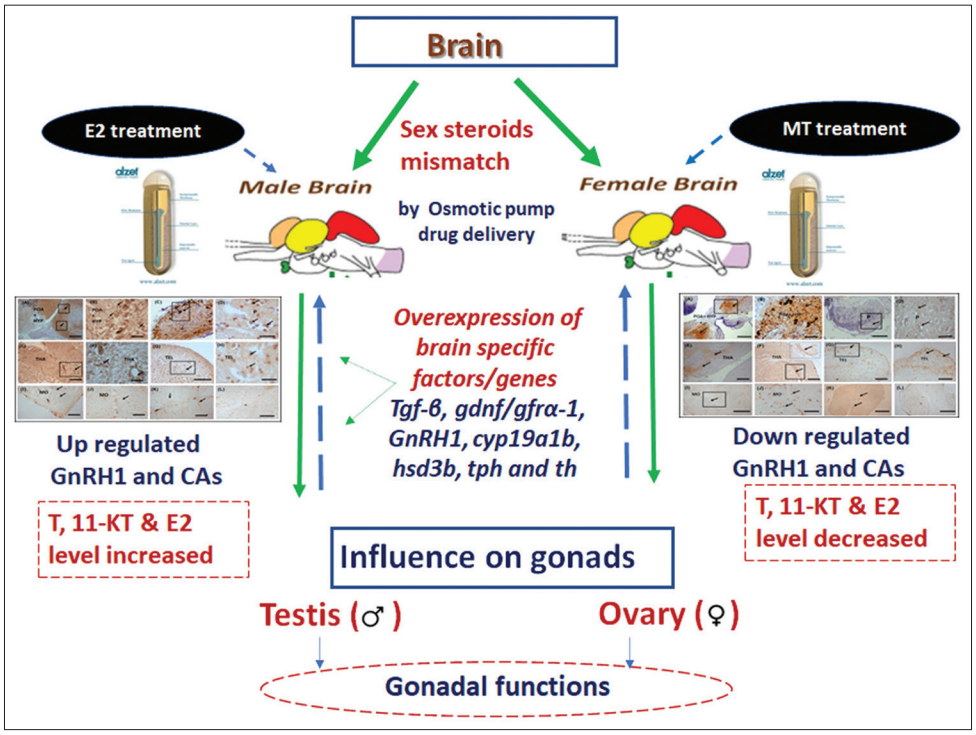

Figure 1: The schematic diagram represented the role of mismatched sex steroids treatment, drug delivery through an osmotic pump in the male and female brain using the catfish model and overexpression of transcripts/genes and their influences on the brain-gonadal functions. T: Testosterone, 11-KT -E_2: Estradiol-17b, MT: Methyltestosterone, CAs: Catecholamines, gdnf/gfrα-1: Glial cell line-derived neurotrophic factor/gdnf family receptor alpha-1, GnRH1: A gonadotropin-releasing hormone, tph: Tryptophan hydroxylase, th: Tyrosine hydroxylase, Tgf-β: Transforming growth factor-beta, Cyp19a1b: brain aromatase, and hsd3b: 3β-hydroxysteroid dehydrogenase.

axis and CA-ergic system. In addition, sex steroid treatment control CA-ergic activity and expression of brain-related genes, that is, *catfish GnRH1, Gfrα-1, hsd3b, cyp19a1b, tph,* and *th* consequently mismatched treatment of sex steroids showed estrogenic effect over androgenic at a lower dose which altered reproductive activity at the level of the brain by targeting CAs and GnRH1 in catfish [Figure 1].[18] The teleost brain produces several neurosteroids such as E_2 and neurotrophic factors, that is, GDNF, BDNF, and other neurotransmitters involved in DA neuron development also maintenance of the nervous system and reproduction. In the previous study, sex steroids play a pivotal role during sexual differentiation[52,53] where DA action modulated by E_2 combinations with enzymes at different levels produced anti-DAergic effects in teleost.[19] The regulatory role of steroids illustrates the interface between sex steroids, neurodegeneration, regeneration, and neuroinflammation through neurogenesis.[54] Besides, sex steroids regulate the morphology and many neural cells such as neuronal cells, glial cells, and endothelial cells which modulate neural activity, growth factor expression, and their function at the level of the brain in mammals and teleost.[18,54,] A previous study reported that in the nucleus through estrogen receptors (ERs) activity, E_2 directly controls transcription at the promoter region of various growth factors, BDNF, TGF-α, and NT-4. Instead, in the dendritic spines, sex steroids can bind androgen receptors and ERs to develop translation of BDNF through MAPK/ERK and PI3K/AKT activation.[55,56] It has been reported that the brain is influenced by sex hormones T, E, and progesterone; moreover, the nervous system has receptors for sex hormones during fetal development.[57,58] In mice, both prenatal and postnatal administration of non-steroidal antiandrogen (flutamide), T affected sexually dimorphic nuclei development in the hypothalamus.[59] In some species including catfish, sex steroids modulate the secretion of GTH which affects the activity of DA neuron in POA and HYP.[16,60,61] These variations influence the collaboration of gonadal steroids with CAs and GnRH in regulating GTH-II secretion.[21]

CONCLUSION AND FUTURE RESEARCH PERSPECTIVES

This review concludes that the growth factor Tgf-β with coordination of sex steroids and other crucial factors GDNF has a significant impact to regulate brain and gonadal functions by targeting DA-ergic neurons and signaling. Moreover, TGF-β immunolocalization protein expression in the POA-HYP and higher expression in the developing brain by tissue distribution and ontogeny exhibited its possible role in brain development through GnRH and GTH axis, plausibly supporting gonadal functions in catfish. In addition, administration of sex steroid E_2 in male catfishes through osmotic pump caused elevated expression of GnRH1 along with CAs resulting in estrogenic impact, whereas MT treated of opposed sex resulted in reverse, although gonadal function yet to study in depth. Importantly, plausible mechanisms of TGF-β with coordination of neurotrophic factors predominantly GDNF/Gfrα-1 and sex steroids, also their manifest neurotrophic effects on midbrain DA-ergic neurons raise expectations for a therapeutic approach to neurological diseases and impairment of reproduction.

Acknowledgment

MSK is grateful to A Grant-in-Aid (SR/WOS-A/LS-303/2017) from the Department of Science and Technology, Government of India, through the Women Scientist Program (WOS-A) which supported this work completely. MSK is thankful to Professor B. Senthilkumaran, Department of Animal Biology, the University of Hyderabad for providing laboratory facilities and guidance.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Department of Science and Technology (DST).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Dünker N, Krieglstein K. Targeted mutations of transforming growth factor-β genes reveal important roles in mouse development and adult homeostasis. Eur J Biochem 2000;267:6982-8.
2. Farkas LM, Dünker N, Roussa E, Unsicker K, Krieglstein K. Transforming growth factor-βs are essential for the development of midbrain dopaminergic neurons *in vitro* and *in vivo*. J Neurosci 2003;23:5178-86.
3. Mamta Anusha N, Senthilkumaran B. Transforming growth factor β: Cloning and expression profiling in the brain of catfish model. J Eng Res 2022;26:23-31.
4. Kashima R, Hata A. The role of TGF-β superfamily signaling in neurological disorders. Acta Biochim Biophys Sin 2018;50:106-20.
5. Krieglstein K, Suter-Crazzolara C, Fischer WH, Unsicker K. TGF-beta superfamily members promote survival of midbrain dopaminergic neurons and protect them against MPP+ toxicity. EMBO J 1995;14:736-42.
6. Mamta SK, Senthilkumaran B. GDNF family receptor α-1 in catfish: Possible implication to brain dopaminergic activity. Brain Res Bull 2018;140:270-80.
7. Itman C, Mendis S, Barakat B, Loveland KL. All in the family: TGF-β family action in testis development. Reproduction 2006;132:233-46.

8. Knight PG, Glister C. TGF-β superfamily members and ovarian follicle development. Reproduction 2006;132:191-206.
9. Sawatari E, Shikina S, Takeuchi T, Yoshizaki G. A novel transforming growth factor-β superfamily member expressed in gonadal somatic cells enhances primordial germ cell and spermatogonial proliferation in rainbow trout (*Oncorhynchus mykiss*). Dev Biol 2007;30:266-75.
10. Kohli G, Hu S, Clelland E, Di Muccio T, Rothenstein J, Peng C. Cloning of transforming growth factor-β1 (TGF-β1) and its Type II receptor from zebrafish ovary and role of TGF-β1 in oocyte maturation. Endocrinology 2003;144:1931-41.
11. Kohli G, Clelland E, Peng C. Potential targets of transforming growth factor-beta1 during inhibition of oocyte maturation in zebrafish. Reprod Biol Endocrinol 2005;3:1-11.
12. Ingman WV, Robertson SA. Defining the actions of transforming growth factor beta in reproduction. Bioessays 2002;24:904-14.
13. Krieglstein K, Strelau J, Schober A, Sullivan A, Unsicker K. TGF-β and the regulation of neuron survival and death. J Physiol Paris 2002;96:25-30.
14. Zheng S, Long J, Liu Z, Tao W, Wang D. Identification and evolution of TGF-β signaling pathway members in twenty-four animal species and expression in Tilapia. Int J Mol Sci 2018;19:1154.
15. Luo SX, Timbang L, Kim JI, Shang Y, Sandoval K, Tang AA, *et al*. TGF-β signaling in dopaminergic neurons regulates dendritic growth, excitatory-inhibitory synaptic balance, and reversal learning. Cell Rep 2016;17:3233-45.
16. Trudeau VL. Neuroendocrine regulation of gonadotrophin II release and gonadal growth in the goldfish, Carassius auratus. Rev Rep 1997;2:55-68.
17. Juntti SA, Coats JK, Shah NM. A genetic approach to dissect sexually dimorphic behaviors. Horm Behav 2008;53:627-37.
18. Mamta SK, Sudhakumari C, Kagawa H, Dutta-Gupta A, Senthilkumaran B. Controlled release of sex steroids through osmotic pump alters brain GnRH1 and catecholaminergic system dimorphically in the catfish, *Clarias gariepinus*. Brain Res Bull 2020;164:325-33.
19. Zhou W, Cunningham KA, Thomas ML. Estrogen regulation of gene expression in the brain: A possible mechanism altering the response to psychostimulants in female rats. Mol Brain Res 2002;100:75-83.
20. Peter RE, Trudeau VL, Sloley BD. Brain regulation of reproduction in teleosts. Bull Inst Zool Acad Sin Monogr 1991;16:89-118.
21. Goos HJ, Senthilkumaran B, Joy KP. Comparative Endocrinology and Reproduction. New Delhi, India: Narousa Publishing House; 1999. p. 113-36.
22. Zubeldia-Brenner L, Roselli CE, Recabarren SE, Gonzalez Deniselle MC, Lara HE. Developmental and functional effects of steroid hormones on the neuroendocrine axis and spinal cord. J Neuroendocrinol 2016;28:10.
23. McEwen BS. Gonadal steroid action on brain sexual differentiation and sexual behavior. In: Bradford HF, editor. Neurotransmitter Interaction and Compartmentation. Boston, MA: Springer; 1982. p. 651-63.
24. Oshima M, Oshima H, Taketo MM. TGF-β receptor Type II deficiency results in defects of yolk sac hematopoiesis and vasculogenesis. Dev Biol 1996;179:297-302.
25. Sanford LP, Ormsby I, Gittenberger-de Groot AC, Sariola H, Friedman R, Boivin GP, *et al*. TGF beta2 knockout mice have multiple developmental defects that are non-overlapping with other TGF beta knockout phenotypes. Development 1997;124:2659-70.
26. Chegini NA, Flanders KC. Presence of transforming growth factor-beta and their selective cellular localization in human ovarian tissue of various reproductive stages. Endocrinology 1992;130:1707-15.
27. Zhao B, Chen YG. Regulation of TGF-β signal transduction. Scientifica 2014;23;2014.
28. Calp MK, Matsumoto JA, Van Der Kraak G. Activin and transforming growth factor-β as local regulators of ovarian steroidogenesis in the goldfish. Gen Comp Endocrinol 2003;132:142-50.
29. Oliveira MA, Martinez ER, Butzge AJ, Doretto LB, Ricci JM, Rodrigues MS, *et al*. Molecular characterization and expression analysis of anti-Müllerian hormone in common carp (*Cyprinus carpio*) adult testes. Gene Expr Patterns 2021;40:119169.
30. Krieglstein K, Henheik P, Farkas L, Jaszai J, Galter D, Krohn K, *et al*. Glial cell line-derived neurotrophic factor requires transforming growth factor-β for exerting its full neurotrophic potential on peripheral and CNS neurons. J Neurosci Res 1998;18:9822-34.
31. Airaksinen MS, Holm L, Hätinen T. Evolution of the GDNF family ligands and receptors. Brain Behav Evol 2006;68:181-90.
32. Naughton CK, Jain S, Strickland AM, Gupta A, Milbrandt J. Glial cell-line-derived neurotrophic factor-mediated RET signaling regulates spermatogonial stem cell fate. Biol Rep 2006;74:314-21.
33. Durbec P, Marcos-Gutierrez CV, Kilkenny C, Grigoriou M, Wartiowaara K, Suvanto P, *et al*. GDNF signalling through the Ret receptor tyrosine kinase. Nature 1996;381:789-93.
34. Tenenbaum L, Humbert-Claude M. Glial cell line-derived neurotrophic factor gene delivery in Parkinson's disease: A delicate balance between neuroprotection, trophic effects, and unwanted compensatory mechanisms. Front Neuroanat 2017;11:29.
35. Barry DS, Pakan JM, McDermott KW. Radial glial cells: Key organisers in CNS development. Int J Biochem Cell Biol 2014;46:76-9.
36. Xing L, Goswami M, Trudeau VL. Radial glial cell: Critical functions and new perspective as a steroid synthetic cell. Gen Comp Endocrinol 2014;203:181-5.
37. Pellegrini E, Mouriec K, Anglade I, Menuet A, Le Page Y, Gueguen MM, *et al*. Identification of aromatase-positive radial glial cells as progenitor cells in the ventricular layer of the forebrain in zebrafish. J Comp Neurol 2007;501:150-67.
38. Xing L, Venables MJ, Trudeau VL. Role of aromatase and radial glial cells in neurotoxin-induced dopamine neuron degeneration and regeneration. Gen Comp Endocrinol 2017;241:69-79.
39. Henderson CE, Phillips HS, Pollock RA, Davies AM, Lemeulle C, Armanini M, *et al*. GDNF: A potent survival factor for motoneurons present in peripheral nerve and muscle. Science 1994;266:1062-64.
40. Arenas E, Trupp M, Åkerud P, Ibáñez CF. GDNF prevents degeneration and promotes the phenotype of brain

noradrenergic neurons *in vivo*. Neuron 1995;15:1465-73.
41. Marks WJ Jr., Bartus RT, Siffert J, Davis CS, Lozano A, Boulis N, *et al*. Gene delivery of AAV2-neurturin for Parkinson's disease: A double-blind, randomised, controlled trial. Lancet Neurol 2010;9:1164-72.
42. Bartus RT, Weinberg MS, Samulski RJ. Parkinson's disease gene therapy: Success by design meets failure by efficacy. Mol Ther 2014;22:487-97.
43. Oppenheim RW, Houenou LJ, Parsadanian AS, Prevette D, Snider WD, Shen L. Glial cell line-derived neurotrophic factor and developing mammalian motoneurons: Regulation of programmed cell death among motoneuron subtypes. J Neurosci 2000;20:5001-11.
44. Viglietto GI, Dolci SU, Bruni PA, Baldassarre GU, Chiariotti LO, Melillo RM, *et al*. Glial cell line-derived neurotrophic factor and neurturin can act as paracrine growth factors stimulating DNA synthesis of Ret-expressing spermatogonia. Int J Oncol 2000;16:689-783.
45. Meng X, Lindahl M, Hyvonen ME, Parvinen M, de Rooij DG, Hess MW, *et al*. Regulation of cell fate decision of undifferentiated spermatogonia by GDNF. Science 2000;287:1489-93.
46. Howard MJ, Gershon MD. Role of growth factors in catecholaminergic expression by neural crest cells: *In vitro* effects of transforming growth factor beta1. Dev Dyn 1993;196:1.
47. Mamta SK, Raghuveer K, Sudhakumari CC, Rajakumar A, Basavaraju Y, Senthilkumaran B. Cloning and expression analysis of tyrosine hydroxylase and changes in catecholamine levels in brain during ontogeny and after sex steroid analogues exposure in the catfish, *Clarias batrachus*. Gen Comp Endocrinol 2014;197:18-25.
48. Sudhakumari CC, Senthilkumaran B, Raghuveer K, Wang DS, Kobayashi T, Kagawa H, *et al*. Dimorphic expression of tryptophan hydroxylase in the brain of XX and XY Nile tilapia during early development. Gen Comp Endocrinol 2010;166:320-9.
49. Raghuveer K, Sudhakumari CC, Senthilkumaran B, Kagawa H, Dutta-Gupta A, Nagahama Y. Gender differences in tryptophan hydroxylase-2 mRNA, serotonin, and 5-hydroxytryptophan levels in the brain of catfish, *Clarias gariepinus*, during sex differentiation. Gen Comp Endocrinol 2011;171:94-104.
50. Senthilkumaran B, Sudhakumari CC, Mamta SK, Raghuveer K, Swapna I, Murugananthkumar R. "Brain sex differentiation" in teleosts: Emerging concepts with potential biomarkers. Gen Comp Endocrinol 2015;220:33-40.
51. Xiao C, Wang Y, Liu H, Wang H, Cao J, Gao D. Intrastriatal glial cell line-derived neurotrophic factors for protecting dopaminergic neurons in the substantia nigra of mice with Parkinson disease. Neural Regen Res 2007;2:207-10.
52. Kobayashi T, Kajiura-Kobayashi H, Nagahama Y. Induction of XY sex reversal by estrogen involves altered gene expression in a teleost, tilapia. Cytogenet Genome Res 2003;101:289-94.
53. Gennotte V, Mélard C, D'Cotta H, Baroiller JF, Rougeot C. The sensitive period for male-to-female sex reversal begins at the embryonic stage in the Nile tilapia and is associated with the sexual genotype. Mol Rep Dev 2014;81:1146-58.
54. Larson TA. Sex steroids, adult neurogenesis, and inflammation in CNS homeostasis, degeneration, and repair. Front Endocrinol 2018;9:205.
55. Hatanaka Y, Hojo Y, Mukai H, Murakami G, Komatsuzaki Y, Kim J, *et al.* Rapid increase of spines by dihydrotestosterone and testosterone in hippocampal neurons: Dependence on synaptic androgen receptor and kinase networks. Brain Res 2015;1621:121-32.
56. Mannella P, Brinton RD. Estrogen receptor protein interaction with phosphatidylinositol 3-kinase leads to activation of phosphorylated Akt and extracellular signal-regulated kinase 1/2 in the same population of cortical neurons: A unified mechanism of estrogen action. J Neurosci 2006;26:9439-47.
57. Karaismailoğlu S, Erdem A. The effects of prenatal sex steroid hormones on sexual differentiation of the brain. J Turk Ger Gynecol Assoc 2013;14:163.
58. Miranda A, Sousa N. Maternal hormonal milieu influence on fetal brain development. Brain Behav 2018;8:e00920.
59. Lund TD, Salyer DL, Fleming DE, Lephart ED. Pre-or postnatal testosterone and flutamide effects on sexually dimorphic nuclei of the rat hypothalamus. Dev Brain Res 2000;120:261-6.
60. Yu L, Peter RE. Dopaminergic regulation of brain gonadotropin-releasing hormone in male goldfish during spawning behavior. Neuroendocrinology 1990;52:276-83.
61. Senthilkumaran B, Joy KP. Changes in hypothalamic catecholamines, dopamine-β-hydroxylase, and phenylethanolamine-N-methyltransferase in the catfish *Heteropneustes fossilis* in relation to season, raised photoperiod and temperature, ovariectomy, and estradiol-17β replacement. Gen Comp Endocrinol 1995;97:121-34.

How to cite this article: Mamta SK. Implicating transforming growth factor-β and sex steroids in the regulation of brain-gonadal functions. J Reprod Healthc Med 2022;3:9.