Neurochemical Research (2019) 44:1781–1795
https://doi.org/10.1007/s11064-019-02833-1

REVIEW

Possible Existence of the Hypothalamic-Pituitary-Hippocampal (HPH) Axis: A Reciprocal Relationship Between Hippocampal Specific Neuroestradiol Synthesis and Neuroblastosis in Ageing Brains with Special Reference to Menopause and Neurocognitive Disorders

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Received: 6 February 2019 / Revised: 13 May 2019 / Accepted: 19 June 2019 / Published online: 28 June 2019

Abstract

The hippocampus-derived neuroestradiol plays a major role in neuroplasticity, independent of circulating estradiol that originates from gonads. The response of hypothalamus-pituitary regions towards the synthesis of neuroestradiol in the hippocampus is an emerging scientific concept in cognitive neuroscience. Hippocampal plasticity has been proposed to be regulated via neuroblasts, a major cellular determinant of functional neurogenesis in the adult brain. Defects in differentiation, integration and survival of neuroblasts in the hippocampus appear to be an underlying cause of neurocognitive disorders. Gonadotropin receptors and steroidogenic enzymes have been found to be expressed in neuroblasts in the hippocampus of the brain. However, the reciprocal relationship between hippocampal-specific neuroestradiol synthesis along neuroblastosis and response of pituitary based feedback regulation towards regulation of estradiol level in the hippocampus have not completely been ascertained. Therefore, this conceptual article revisits (1) the cellular basis of neuroestradiol synthesis (2) a potential relationship between neuroestradiol synthesis and neuroblastosis in the hippocampus (3) the possible involvement of aberrant neuroestradiol production with mitochondrial dysfunctions and dyslipidemia in menopause and adult-onset neurodegenerative disorders and (4) provides a hypothesis for the possible existence of the hypothalamic-pituitary-hippocampal (HPH) axis in the adult brain. Eventually, understanding the regulation of hippocampal neurogenesis by abnormal levels of neuroestradiol concentration in association with the feedback regulation of HPH axis might provide additional cues to establish a neuroregenerative therapeutic management for mood swings, depression and cognitive decline in menopause and neurocognitive disorders.

Keywords Estradiol · Neuroblastosis · Menopause · Hippocampus · Neurogenesis · Dementia · Neurocognitive disorders · Hypothalamic-pituitary-hippocampal axis

Abbreviations

3β-HSD	3-Beta-hydroxysteroid dehydrogenase
17β-HSD	17-Beta-hydroxysteroid dehydrogenase
AD	Alzheimer's disease
APOE	Apolipoprotein E
BDNF	Brain-derived neurotrophic factor
CaMKII	Ca^{2+}/Calmodulin-dependent protein kinase II
CREB	cAMP response element binding protein
ERK	Extracellular signal regulated kinase
ERα	Estrogen receptor-alpha
ERβ	Estrogen receptor-beta
FSH	Follicle stimulating hormone
GABA	Gamma-aminobutyric acid
GnRH	Gonadotropin releasing hormone
HD	Huntington's disease
HPG	Hypothalamic-pituitary–gonadal axis
HPH	Hypothalamic-pituitary-hippocampal axis
LDL	Low density lipoproteins
LH	Luteinizing hormone

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LTP	Long term potentiation
mTOR	Mechanistic/mammalian target of rapamycin
NSCs	Neural stem cells
P450scc	Cholesterol side chain cleavage enzyme
PD	Parkinson's disease
PI3K	Phosphoinositide 3-kinase
PKB	Protein kinase B
StAR	Steroidogenic acute regulatory protein

Introduction

Estrogen is the primary sex steroid hormone of females that play a central role in the development of secondary sexual characteristics and regulation of the menstrual cycle [1]. Estradiol is a major form of estrogen that exhibits key roles in a wide spectrum of biological functions ranging from embryogenesis to cognitive functions [2, 3]. While ovaries are the main source of estradiol production in women, menopause is the part of the ageing process in which menstrual cycle irreversibly ceases due to the depletion of ovarian follicles [4, 5], thereby leading to reduced levels of estradiol in the circulation [6]. As a result, menopause has been characterized by a chronic increase in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels in response to reduced level of estradiol [5–8]. The physiological levels of estradiol have been shown to play a crucial role in the regulation of hippocampus-based mood and cognitive functions, whereas the abnormal level of estradiol appears to disrupt hippocampal plasticity leading to depression and dementia-related problems [3, 9, 10]. Thus, the impulsive change in estradiol levels in women has been considered as a potential risk factor for the development of neurocognitive disorders upon the onset of menopause [11, 12]. Though estrogen replacement therapy (ERT) has been accepted to improve the mood disorders and provide defence against the occurrence of dementia, there have been some controversial reports that suggest ERT may not be beneficial in anti-ageing therapies [3, 10, 13]. In general, ERT is considered as an effective clinical strategy to manage the various symptoms like hot flashes, night sweats, insomnia, vaginal dryness, osteoporosis, coronary heart disease, depression and dementia that occur during menopause [4, 7, 14–16]. Notably, several observational studies have indicated that the female subjects undergoing ERT showed a significantly improved performance on the cognitive function tests [17–19]. It has been noticed that the prevalence of Alzheimer's disease (AD) appears to be less among females using ERT than that of non-ERT subjects [20–23]. Further, ERT has been suggested to improve the memory functions in elderly subjects with menopause and dementia [12, 18, 19, 24, 25]. While the underlying mechanisms for the beneficial effect of ERT on the cognitive functions have not been completely understood, ERT has been suggested to positively modulate the lipoprotein metabolisms, cerebrovascular function and neurotransmission in the brain [10, 26]. In contrast, there have been some confounding reports that suggest ERT can be a potential risk factor for the development of breast cancer, depression and neurocognitive disorders [27]. Unexpectedly, few case–control reports have indicated that long term use of ERT in menopausal subjects result in no effect on the cognitive functions [28, 29] whereas, some evidence suggests that ERT exacerbates the risk of developing cerebrovascular disorders and dementia including AD [21, 30]. The differential effects of ERT on the regulation of brain functions remain unclear. Therefore, the effect of estradiol levels on the regulation of neuroplasticity responsible for cognitive function has been an important subject of research focus in mental health and gerontology.

Adult neurogenesis is the process of producing new neurons from the neural stem cells (NSCs) through neuroblastosis, the generation of immature neurons in the brain [31–34]. Neuroblastosis has closely been linked to the regulation of sexual behaviour, mood and cognitive functions [31, 34]. The process of production of new neurons in the adult brain has been suggested to be regulated by various environmental and intrinsic factors including estradiol [32, 35]. Neuroestradiol production in the brain is crucial for the regulation of hippocampal neurogenesis responsible for the cognitive functions [35–37]. While the effect of circulating levels of estradiol on the regulation of hippocampal neurogenesis has widely been studied, the brain-specific synthesis of neuroestradiol and its role on the regulation of cognitive functions acting via hippocampal neurogenesis has been an intriguing subject of research focus. The estradiol synthesizing enzymes have been known to actively be expressed in neurons, glial cells and neuroblasts that are localized in the hippocampus of the brain [38–44]. While ageing has been recognized as a negative modulator of hippocampal plasticity, the age-related decline of estradiol synthesis and reduced neurogenesis has been proposed for the development of adult-onset neurocognitive disorders [45, 46]. Moreover, ageing women have been considered to be at a greater risk of developing dementia than men due to menopause-related physiological changes [11]. However, the impact of menopause and reduced level of estradiol seen in neurocognitive disorders on the mechanism underlying the abnormal hippocampal plasticity and cognitive deficits has not been clearly understood. Recently, the effect of neurosteroids appears to act on the regulation of the neuroplasticity independent of circulating estradiol [47, 48]. While feedback regulation of hypothalamus acting via pituitary towards the levels of circulating estradiol originating from gonads has been clearly recognized through hypothalamic-pituitary-gonadal (HPG) axis [49, 50], the hypothalamus-pituitary based response mechanism through GnRH, LH

and FSH towards the local synthesis of neuroestradiol in the hippocampus remains obscure. Though there have been some reports that indicated the response of the hippocampus towards the systemic circulation of estradiol [51, 52], the possible establishment of the brain-specific feedback loop towards the level of neuroestradiol in the hippocampus remains ambiguous in the existing literature. Notably, the complete removal of gonads did not have any major influence on the expression of aromatase, a major steroidogenic enzyme, in the hippocampus of the brain [53, 54] suggesting that production of neuroestradiol in the hippocampus can be regulated independent of the HPG axis [53]. Moreover, the expression of aromatase in the brain regions responsible for the cognitive functions is less likely to be associated with reproductive functions [55], thus the production of neuroestradiol might be regulated by a putative feedback mechanism. Besides, many neurocognitive disorders have been characterized by abnormal cholesterol metabolism, mitochondrial dysfunctions and oxidative stress [56, 57]. While cholesterol represents the primary source of estradiol synthesis, aberrant production of estradiol is found to be associated with dysregulation of lipid metabolism and mitochondrial dysfunctions in the brain of subjects with neurocognitive disorders [56–58]. Thus, the impact of defects in neuroestradiol synthesis resulting from mitochondrial dysfunctions on dysregulation of lipid metabolism might also be highly relevant to neurodegeneration and dementia in the abnormal ageing brains. Therefore, this conceptual article revisits (1) the cellular basis of neuroestradiol synthesis (2) a potential relationship between the neuroestradiol synthesis and neuroblastosis in the hippocampus (3) the possible involvement of mitochondrial dysfunctions and dyslipidemia in menopause and adult-onset neurodegenerative disorders with regards to abnormal estradiol production (4) attempted to link the neuroestradiol production in the hippocampus to the response of the hypothalamus-pituitary independent of its gonadal origin and foster a unifying hypothesis for the possible existence of the brain-specific hypothalamic-pituitary-hippocampal (HPH) axis.

Estradiol Synthesis in Ovaries and Hypothalamic-Pituitary-Gonadal Axis

Steroidogenesis is a key biochemical pathway accountable for the synthesis of sex hormones like testosterone and estrogen, primarily in gonads. Among them, estradiol has been known to exert a plethora of biological functions in many tissues throughout the body including the brain [3, 17, 26, 59, 60]. Leydig cells of testicles have been known to produce testosterone and a detectable amount of estradiol in men [61]. In women, estradiol has been known to mainly be produced by the ovarian follicles [8, 62]. Initially, the discharge of gonadotropin-releasing hormone (GnRH) from the hypothalamus has been known to stimulate the secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary [63, 64] (Fig. 1). While FSH has been known to primarily act on granulosa cells, LH has been known to influence theca cells [65], both leading to estradiol production from cholesterol by a sequential biochemical pathway in ovaries. Formation of pregnenolone from cholesterol by the catalytic activity of a mitochondrial enzyme, cytochrome P450(scc) appears to be the initial step for the synthesis of estradiol in ovaries [66]. Further, 3-β-hydroxysteroid dehydrogenase (3β-HSD) converts pregnenolone into progesterone in both theca and granulosa cells [67, 68]. Next, 17β-hydroxylase catalyses the conversion of progesterone into 17-hydroxyprogesterone, followed by the formation of androstenedione by the action of 17,20 lyase. Then, 17β- hydroxysteroid dehydrogenase (17β-HSD) appears to produce testosterone from androstenedione in theca cells during the luteal phase [69]. Finally, the conversion of testosterone into estradiol has been known to be catalysed by the aromatase enzyme in granulosa cells [70]. At the very beginning of the menstrual cycle, a decrease in the level of estradiol has been known to stimulate a transient surge of the gonadotrophins through the hypothalamic-pituitary-gonadal (HPG) axis [71]. The HPG feedback loop is very crucial for the regulation of estradiol production in the ovary and reproductive physiology [49, 50]. While FSH has been known to facilitate the growth of a dominant ovarian follicle through the production of estradiol, the release of a mature ovum appears to be triggered by the transient surge of LH[71–73]. As per the existing knowledge, the hypothalamus can sense the circulating level of estradiol; thus, the expression and pulsatilerelease of the GnRH in the hypothalamus are modulated in order to regulate the secretion of LH and FSH in the pituitary depending upon the factors that regulate sexual mood and the stage of menstrual cycle [49, 50, 74]. In addition, the extra-gonadal production of estradiol has also been detected in many tissues and organs including the brain [75]. However, the regulation of the hypothalamus-pituitary-mediated feedback loop in response to the level of non-gonadal estradiol originating from other tissues has not been clearly established [76]. Thus, it raises an extrapolation for the possible existence of additional feedback loops in the steroidogenic tissues independent of the HPG axis. While estradiol synthesis has been known to occur in the brain, understanding the feedback mechanism of hypothalamus acting via pituitary towards the brain-specific synthesis of neurosteroids might be highly relevant for the regulation of neuroplasticity with reference to mental health, ageing and disease [77, 78].

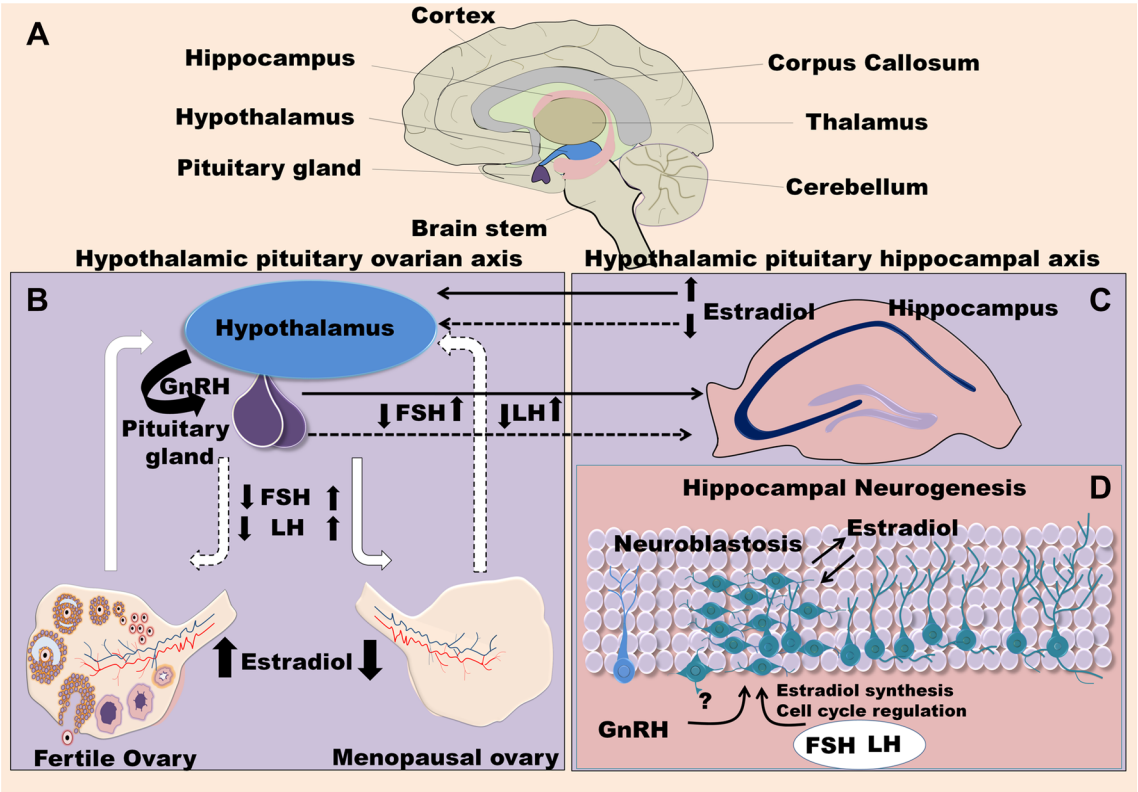

Fig. 1 Schematic representation of the HPG axis and the HPH axis: **a** An overview of different anatomical and functional regions of the adult brain. **b** Indication of oogenesis in the ovary of women during the reproductive period compared to the post-menopausal state. (Note: the arrow with solid lines represent the negative feedback loop of the HPG axis with reduced levels of FSH and LH upon increased level of estradiol production whereas the arrow with dashed lines denotes the constitutive positive feedback of HPG axis followed by increased circulation of FSH and LH levels due to the depletion of follicles and estradiol). **c** Graphical representation of the hippocampus and the HPH axis, in which the solid arrow represents the negative feedback loop of the proposed HPH axis with reduced levels of FSH and LH upon increased level of neuroestradiol production in the normal hippocampus. In contrast, the dashed arrow indicates the positive feedback response of the HPH axis resulting in increased secretion of FSH and LH upon reduced hippocampal estradiol. **d** A schematic summary of hippocampal neurogenesis and possible roles of FSH, LH and GnRH in association with neuroblastosis and estradiol synthesis

Production, Regulation and Neuromodulatory Effects of Estradiol in the Brain

The brain-specific neuroestradiol synthesis was initially indicated by Naftolin and co-workers in 1971 [79]. During the 1980s, the evidence for the occurrence of neurosteroidogenesis was validated in the brain [80]. In 1988, Leblanc P et al. demonstrated the presence of GnRH receptor in all over the Cornu Ammonis (CA) regions including the dentate gyrus (DG) of the hippocampus in the adult brain [81]. Further, Jennes L et al. in 1995, described that the regulation of expression of GnRH was found to be modulated by gonadal estradiol [82]. Further, Prange-Kiel and co-workers have reported that GnRH mediates estradiol synthesis in physiologically free slice culture of the hippocampus [77]. Further, it has been described that hippocampal neuroestradiol synthesis is important for neuroplasticity including synapse formation through the stereotaxic delivery of GnRH to the hippocampus of female rats [77, 83]. Recently, another report by Nelson et al. in 2016 have also indicated that the effect of the peripheral estradiol on the cognitive function can be modulated through GnRH mediated regulation of neuroestradiol production in the hippocampus [51]. In general, the release of GnRH from the hypothalamus to pituitary has been thought to occur via the hypophyseal portal system [84, 85]. Moreover, the neural pathway of GnRH neurons has been known to be distributed throughout the brain [86]. Besides, emerging evidence suggests that GnRH can also be circulated via cerebrospinal fluid (CSF) to all over the brain including the hippocampus [87, 88]. Recently, secretion of GnRH by neuroblast has also been reported in the brain [89, 90]. Therefore, GnRH might be locally synthesised by neuroblasts in the hippocampus, supplied via the CSF or from the neural pathway of hypothalamus neurons. On one hand, GnRH might play a crucial role in neuroestradiol synthesis

and the cell cycle regulation of neuroblasts through an autocrine mode [77], while on the other hand hippocampal derived GnRH might also induce the secretion of the FSH and LH in the pituitary through a paracrine manner which can further help in the regulation of neuroestradiol production in the hippocampus. Considering the fact, the existence of the expression of the LH and FSH receptors have also been confirmed in the hippocampus of the adult brain [91, 92]. Subsequently, the FSH and LH mediated synthesis of neuroestradiol has also been reported in the hippocampus in association with the regulation of neuroplasticity [91, 93]. Taken together, establishing the direct role of GnRH on the steroidogenesis independent of FSH and LH in gonads and other tissues requires a scientific attention.

The expressions of the steroidogenic enzymes such as StAR, 3β-HSD, 17β-HSD and aromatase have been localized throughout the mammalian brain [94–98]. In 1998, Furukawa et al. demonstrated the evidence for the presence of StAR in the brain of experimental rats [99]. Later on, neuronal-specific expressions of cytochrome P45017α and P450 aromatase were identified in the brain [42, 100]. Especially, the expression of aromatase has clearly been noticed in the various brain regions including the hippocampus [42, 97]. In the hippocampus, the localization of StAR and other steroidogenic enzymes are highly evident in the CA3, CA1 regions, and the DG[42, 97] in which the hippocampal neurogenesis happens to take place [31]. With regards to the subcellular localization, expressions of the StAR and aromatase have been reported to be high in the pre and post synaptic compartments of neurons [97, 101, 102]. The mossy fiber pathway of the hippocampus that originates from the DG projects at the CA3 layer [103]. Therefore, it is obvious that the terminal end of neurons and neuroblasts that are located in the granular cell layer (GCL) might contribute to an abundant expression of aromatase and StAR in the CA3 region of the hippocampus. Moreover, the aromatase expression in the limbic system of the brain is considered as an evolutionarily conserved process; thus, the higher level of cognitive function noticed in the mammalian brain along the evolutionary process is assumed to be overlapped with the production of neuroestradiol in the brain [76, 104]. Interestingly, the presence of neuroblasts has been described in most limbic areas of the adult brain. While the synthesis of neuroestradiol has experimentally been demonstrated in the primary neuronal and astrocytic cultures [1, 41, 105], the mitotically inactive fully matured neurons have been considered responsible for the basal de novo synthesis of neuroestradiol in the brain. However, neuroblasts have been known to exhibit electrophysiological properties including action potential [106] and neurotransmission[107] comparable to that of mature neurons in the brain. Neuroblasts are recognised to be the cellular entity for the functionality of neurogenesis that also contributes to the synaptic remodelling and cognitive functions in the brain. Moreover, the number of neuroblasts have been known to be regulated by numerous factors due to its multipotential capacity [56, 108–111]. While ongoing hippocampal neurogenesis in the brain has been linked to sexual behaviour [112], the contribution of the neurogenic cellular component that poses estrogenic capacity that synchronized with the regulation of sexual mood and cognitive functions has not been realized yet. Besides, neuroblasts have been known to be positive for the expression of gonadotropin receptors and steroidogenic pathway enzymes responsible for neuroestradiol production [97, 104, 113]. Considering the cell cycle dynamic, multipotent and neurogenic natures of neuroblasts, it can be speculated that neuroblasts can represent the regulatable cellular basis for neuroestradiol synthesis than mature neurons in the hippocampus of the brain. While the mitotic eventens of neuroblasts can be modulated by various factors, the regulation and variation of the neuroestradiol concentration can directly result from the absolute number of neuroblast population present in the hippocampus. Thus, neuroblasts may be one of the primary sources of neuroestradiol in the brain and the rate of neuroblastosis can be a determining factor for the level of neuroestradiol in the hippocampus. In contrast, the defect in the neuroestradiol synthesis might be attributed to impaired neuronal differentiation, integration and survival of the neuroblasts in the hippocampus, thereby leading to mood disorders and neurocognitive abnormalities including dementia [114].

During embryogenesis, neuroestradiol appears to play a crucial role in the development and migration of neuroblasts, leading to the establishment of the cytoarchitecture of the brain followed by commencement of synaptic plasticity [40, 115, 116]. In the adult brain, neuroestradiol has been shown to regulate the long-term potentiation (LTP) through the *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [117]. Thus, synthesis of neuroestradiol by aromatase in the brain appears to be essential for the neural connectivity, synaptic remodelling, neuroprotection and functional regulation of cognitive functions [35, 38, 75, 118]. In the brain, the hippocampus is the main target of neuroestradiol and its downstream signalling pathways responsible for various cellular functions [119, 120]. Estradiol has been known to act via estrogen receptor-α (ERα), estrogen receptor-β (ERβ) and G-protein coupled estrogen receptor (GPER), while a widespread expression of estrogen receptors has also been evident in the hippocampus [120, 121]. In the hippocampus, dendrites and axon of neurons have also been known to be positive for the expression of estrogen receptors [94, 122, 123]. Notably, the functional role of neuroestradiol has been known to be associated with GABAergic, cholinergic and serotonergic pathways of the brain [26]. Further, estradiol has been known to activate the expression of neuroplasticity

markers such as brain-derived neurotrophic factor (BDNF), cAMP response element binding (CREB) protein, $Ca2^{+}$/calmodulin-dependent protein kinase (CaMK)-II and mammalian target of rapamycin (mTOR) for the consolidation of memory process in the hippocampus [124–127]. Notably, the aforementioned estrogen-mediated signalling cascades have potently been implicated for the regulation of hippocampal neurogenesis and cognitive functions including learning and memory [128–130]. Thus, it suggests that the synthesis of neuroestradiol in the brain is essential for the process of hippocampal neurogenesis, whereas the defect in neuroestradiol synthesis in the hippocampus can be an underlying mechanism accountable for impaired neurogenesis and vice versa may contribute to the development of dementia-related problems.

Association of Abnormal Estradiol Levels with Neurocognitive Disorders and Dementia

Adult-onset neurodegenerative disorders have been characterized by the various neurocognitive deficits including dementia [131]. The incidence and risk of dementia-related neurocognitive disorders have exponentially been increasing in the ageing population as a reflection of rising human life expectancy worldwide [132]. Thus, the escalating incidence of dementia has become a major concern in medical practice and public health management. The aetiology and pathological manifestations of neurocognitive disorders are heterogeneous due to their comorbid nature. Neurocognitive deficits have been known to occur in response to progressive neurodegenerative, cerebrovascular, neurometabolic, neuroinflammatory, neuroendocrine and neuroregenerative disorders [56]. The clinical manifestations of dementia include gradual memory loss, abnormalities in language processing, deterioration of interpersonal skills, difficulty in coordination of motor tasks and behavioural disorders [31, 57, 133]. Moreover, abnormal levels of hippocampal volume, hippocampal atrophy, neurodegeneration, quiescence of NSCs and defect in neuronal differentiation in the hippocampus have been identified to be linked with the occurrence and progression of dementia. There has currently been no cure for dementia and thus, understanding the complex nature of abnormal ageing, identification of potential biomarker, shared molecular pathways and variants of dementia have been the long-standing scientific hound. Moreover, the commonalities among the different forms of dementia and the potential therapeutic target for the same remains largely unknown. Notably, several lines of scientific evidence suggest that the incidence of dementia has been higher in females than in male subjects [134]. Recently, menopause has also been recognised as a predominant risk factor for neurocognitive disorders including depression and dementia [21, 135]. Thus, understanding the regulation of hippocampal plasticity by abnormal neuroestradiol production in the brain may reveal a prominent therapeutic target to manage many neurocognitive disorders. Recently, failure in neuroregeneration, primarily in the hippocampus, has also been identified as a pathological hallmark of the major adult-onset progressive neurocognitive disorders like Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD) [31, 136]. Interestingly, the pathogenesis of neurocognitive disorders has been reported to be associated with gonadal dysfunctions, neuroinflammation, abnormal cholesterol metabolism, aberrant neurotransmission, oxidative stress, mitochondrial deformity and reactive neuroblastosis [31, 136–139]. It appears quite surprising that the neurocognitive disorders like AD have been characterized by high levels of circulating FSH and LH [93, 140, 141], but low levels of neuroestradiol in the hippocampus of the brain similar to menopausal subjects [142, 143]. Thus, it provides an assumption that disruption of an unknown endocrine pathway between the hypothalamus, pituitary and hippocampus may lead to a cascade of pathological events detrimental to the regulation of neuroestradiol production and to the hippocampal neurogenesis in the adult brain, thereby accounting for neurocognitive disorders. While cholesterol metabolism has been ascertained to be a key pathway of steroid production including estradiol, the feedback mechanisms resulting from abnormal production of estradiol may result in the dyslipidaemia. Considering the fact, elevated levels of FSH and LH have been linked to abnormal cholesterol metabolism in many neurocognitive disorders [144–146]. Therefore, a potential link between the levels of gonadotropins and dyslipidemia resulting from abnormal estradiol synthesis has been proposed as a risk factor for menopause and neurocognitive disorders.

A Potential Association Between the Increased Levels of Gonadotropins and Abnormal Lipid Metabolism in Neurocognitive Disorders and Menopause

Cholesterol is a primary precursor for the generation of steroid hormones including estradiol [147]. While circulating estradiol has been known to maintain the cholesterol homeostasis during the reproductive phase, dyslipidemia has been observed as a result of menopause, gonadal dysfunctions, diabetes, obesity and dementia-related neurodegenerative disorders [148, 149]. The epidemiological studies and experimental data have demonstrated that high levels of total cholesterol can predispose the risk of development of dementia in the ageing population [57, 150]. While aberrant cholesterol homeostasis has been known to be associated with the

pathogenesis of AD, HD and PD [56, 57, 151, 152], the polymorphism of apolipoprotein E (APOE) allele, especially the APOE-4 genotype, has been known to play a major role in abnormal cholesterol metabolism [57, 153]. It has been established that gonadotropins, especially FSH, play a major role in synthesis and storage of cholesterol in many tissues [145]. Initially, the monotropic surge in the circulation of FSH has been noticed in subjects of menopause [154]. The systemic administration of FSH and ovariectomy in experimental models has been shown to increase the synthesis and storage of cholesterol [154–156]. Strikingly, Short RA et al. in 2001 reported an increased concentration of FSH in serum samples from estrogen-free women with AD [140]. The menopausal women have also been characterised by increased levels of serum FSH in association with increased levels of total cholesterol [155, 157–159]. Recently, a gradual increase in the serum level of FSH has also been considered as a biomarker of ageing in women [160]. Similarly, the circulating levels of LH also appear to be higher in postmenopausal women [161]. It has been described that the LH signalling pathway increases the expression of StAR and P450scc-mediated cleavage of cholesterol in neuron [162]. In addition, an increased surge in the level of LH has also been linked with abnormal cholesterol deposition mediated cognitive decline in AD [163, 164]. As proof of the concept, the genetic knockdown of LH receptor has been shown to ameliorate the cognitive pathology in a transgenic mouse model of AD [165]. However, in line with the controversial reports on ERT, elevated expression of StAR and aromatase has been reported in the hippocampus of the human subjects with AD [83, 166]. In contrast the expression of aromatase appears to be lower in the hippocampus of the experimental mouse model of AD [167]. The reason for the aforementioned difference on the hippocampal specific expression of aromatase between the human AD brains and brains from animal models of AD is not clear. Notably, human AD brain has been characterized by the increased level of hippocampal neurogenesis [168]. However, hippocampal neurogenesis has been found to be reduced in the animal model of AD [169]. The difference in the grade of neuropathology might be the reason for the marked difference in hippocampal neurogenesis observed between the human and animal subjects of AD. Recently, reactive neuroblastosis has been proposed to contribute to the increased level of neurogenesis in human brains with neurodegenerative conditions [31]. Thus, it is obvious that the increased level of aromatase in the hippocampus of the human AD brain might be derived from the reactive neuroblasts.

Notably, the reason for the increased level of cholesterol in menopause appears to be derived from multifactorial origins. Though the abnormal intake of fat rich diet and decreased physical activity have been predicted for abnormal accumulation of cholesterol, dysregulation of the lipid metabolism in visceral adipose tissue has been proposed to be a potential risk factor for dyslipidaemia in menopause and neurocognitive disorders [170]. Women in menopausal transition state have been found to have an excess amount of visceral fat upon a decline in the level of estradiol production [171]. It has been reported that menopausal women tend to accumulate the visceral adipose tissue (VAT) leading to the increased risk of hyperlipidaemia, obesity, cerebrovascular and cardiovascular disorders [171, 172]. As a consequence, increasing evidence indicates that excess level of VAT has been known to mediate deleterious effects on neuroplasticity and cognitive function in menopause and ageing subjects [173]. There have been many correlative studies indicating that increased VAT has been tightly linked with loss of structural and functional plasticity of the brain leading to dementia [173, 174]. The mechanism behind the overall metabolic changes during the menopausal transition, in neurocognitive disorders, and their relation to the increase in visceral fat remain elusive. The decreased level of estrogen has been known to induce insulin resistance and alter glucose homeostasis and lipid metabolism in various organs including the brain [58]. Defects in the lipoprotein lipase activity in abdominal adipocytes resulting from reduced estradiol level have been proposed to induce dyslipidemia in menopause [175]. The effect induced level of gonadotropins towards the reduced estradiol level on the regulation of lipid metabolism in the adipose tissue and other organs including brain appears to play a major role in the increased deposition of VAT during menopause. Recently, Liu P et al. have demonstrated that inactivation of FSH mediated signalling through neutralizing antibody drastically reduced the cholesterol level in adipose tissues [176]. Another study by Zhao L et al. proposed that the altered LH/FSH ratio has been associated with the accumulation of VAT in elderly female subjects [177]. Taken together, reduced level of estrodiol, the increased levels of LH and FSH mutually or independent of each other can be responsible for abnormal levels of cholesterol metabolism in neurocognitive disorders and menopause.

Mitochondrial Dysfunction and Impaired Neurogenesis Mediated Defects in Neuroestradiol Synthesis in Neurocognitive Disorders

Metabolic imbalance and oxidative stress have been considered as part of early pathogenic events in various forms of neurocognitive disorders [56]. Mitochondria play the leading role in ATP production, calcium homeostasis, cellular metabolism, apoptosis and the synthesis of steroid hormones including estradiol [56, 178, 179]. Reciprocally, the physiological role of estradiol appears to maintain the energy

balance, cellular metabolic profile and reduce oxidative stress via its effects on mitochondria. The physiological levels of estradiol are known to effectively support the biogenesis and functions of mitochondria [178]. The expressions of estrogen receptors have been reported to be present in the mitochondria of various organs including the brain [178]. Estradiol has been known to regulate mitochondrial gene expression in physiological state, while the reduced level of neuroestradiol has been known to induce the mitochondrial dysfunction leading to the accumulation of oxidative stress, neuronal dysfunction and neurodegeneration accountable for cognitive vulnerability in ageing brain disorders [56, 180]. Conversely, the mitochondrial deformity may be a primary cause of impairment in estradiol production. Postmenopausal subjects often experience a depletion of energy due to mitochondrial dysfunction [180]. The reduced level of estradiol appears to induce mitochondrial dysfunction via the insulin signalling pathway in menopause. In general, neuroestradiol has been known to exert the neuroprotective mechanism acting via insulin- phosphoinositide 3-kinases (PI3Ks)/protein kinase B (PKB) signalling [58]. Reduced level of neuroestradiol and deficiency in its downstream signalling have been implicated for the defect in insulin signalling responsible for mitochondrial oxidative damage in the brain of menopause and neurocognitive disorders. The transport of cholesterol into mitochondria mediated by StAR has been a crucial step in the biosynthesis of steroid hormones [181]. StAR and cholesterol side-chain cleavage enzyme, P450scc, that converts cholesterol into pregnenolone have been known to be localized in the mitochondria [147, 181, 182]. Other steroidogenic enzymes, including 3β-HSD, 11β-hydroxylase and aldosterone synthase have also been known to be originating from the mitochondria [181]. It has been well documented that oxidative stress, reactive oxygen species and neuroinflammation-mediated defects in mitochondria can lead to neurodegeneration in the brain [111, 180, 183, 184]. Therefore, the defect in the expression of StAR and steroidogenic pathway enzymes resulting from mitochondrial dysfunction could be responsible for the decreased level of estradiol in brains of subjects with neurocognitive disorders.

Moreover, neuroestradiol is critical for the integrity of the structural and functional regulation of many cerebral regions including the hippocampus, amygdala and hypothalamus in which the occurrence of ongoing neurogenesis has convincingly been evident [185, 186]. Interestingly, adult neurogenesis in aforementioned limbic brain areas appears to be regulated by neuroestradiol [108, 109, 187]. Initially, Tanapat P et al. demonstrated the increased level of hippocampal neurogenesis in female rats during the proestrous stage compared to that of animals in the estrous and diestrous cycles [188]. Besides, neurodegenerative disorders have been characterized by the defects in neuroestradiol synthesis and impaired hippocampal neurogenesis in association with movement disorders and cognitive deficits [189]. Recently, the abnormal dyskinetic movements have been proposed to induce reactive neuroblastosis in the initial phase of neurodegenerative disorders [31]. However, in the late phase of the disease, the impaired differentiation and integration of neuroblasts have been noticed as an underlying mechanism of neuroregenerative failure, thereby leading to neurocognitive dysfunction. Increased levels of neuroinflammatory factors have been suggested to hinder the integration of neuroblasts into pre-existing neuronal circuits in the hippocampus [31, 32]. However, the molecular mechanisms responsible for this neuroregenerative failure in pathogenic brains have not clearly been established. Neuroestradiol has been known to influence the immune functions and inflammatory processes in the brain [190]. While levels of estradiol can be modulated by physical activity and immune functions, it can be assumed that abnormal movement disorder, elevated levels of neuroinflammatory factors resulting from activated immune cells could interfere with neuroestradiol synthesis and its downstream signalling pathways in the neuroblasts that are present in the hippocampus of the adult brain. Therefore, defects in hippocampal neurogenesis resulting from neuropathogenic events and menopause-related changes might be a potential underlying mechanism of reduction in the neuroestradiol production in the brain. Eventually, the drastic reduction in the neuroestradiol production might contribute to the neuroregenerative failure in the ageing brains. As a result, the defect in neuroblastosis might tend to disrupt the hypothalamus and pituitary based expressions of the gonadotrophins through reduced level of neuroestradiol, thereby leading to destructive cell cycle events in the hippocampus. Taken together, insight into the physiological basis for the homeostatic regulation between neuroblastosis and estradiol synthesis in the hippocampus towards a possible feedback loop acting via hypothalamus and pituitary may reveal a putative therapeutic target to manage age-related neurocognitive disorders and menopause.

Proposed Model for the Possible Existence of the of Hypothalamic-Pituitary-Hippocampal (HPH) Axis Towards Neuroestradiol Synthesis in Association with Neuroblastosis

Although some earlier studies have strongly indicated the integration of the hippocampus with HPG axis regulating via the neurosteroids [78, 83, 115], a potential feedback regulation from the hypothalamus-pituitary regions on the synthesis of neuroestradiol along neurogenic process in the hippocampus, independent of the circulating estradiol have not been clearly proposed yet. Based on the existing reports

for the evidence on the signalling of gonadotropin and estrogenic pathway in neuroblasts, it can be hypothesized that neuroblasts might be responsible for the production of neuroestradiol in the brain. The de novo synthesis of neuroestradiol in neuroblasts that originate in the hippocampus might be an important factor for the functional integration of new-born neurons responsible for cognitive functions in the intact adult brain. While a direct effect of GnRH on the production of estrogen in the gonads is unknown, the rationality for the GnRH mediated synthesis of neuroestradiol in the hippocampus of the brain require an extensive investigation. However, regulation of neuroestradiol production resulting from neuroblastosis may lead to the establishment of a brain-specific molecular feedback loop among the hypothalamus, pituitary and hippocampus through gonadotropins. While, estrogen synthesis, GnRH, FSH and LH have been identified to play a major role in cell cycle regulation in many cell types [76, 191], effects of hypothalamus-pituitary derived GnRH, LH and FSH, respectively on neuroblasts in association with neuroestradiol production in the hippocampus would facilitate the cell cycle aspects of the regulation of neurogenesis. Thus, the possibility for the existence of the *"hypothalamic-pituitary-hippocampal (HPH) axis"* can be proposed for the regulation of hippocampal plasticity in the adult brain (Fig. 1). The levels of neuroblastosis and estradiol production may synergistically complement each other for the integrity of the hippocampus through HPH axis in the normal adult brain. Moreover, pathogenic events observed in many neurocognitive disorders have been proposed to be associated with dysregulation of neuroestradiol synthesis and impaired hippocampal neurogenesis resulting in dementia. Considering the fact, dysregulation or imbalance between neuroestradiol synthesis and neuroblastosis in the hippocampus may result in the dysfunction of HPH loop leading to neuroregenerative failure in neurocognitive disorders. Therefore, understanding the biological significance of the direct feedback link between hippocampal neuroestradiol synthesis and gonadotropin levels in the brain will provide additional and valid cues to identify a neuroregenerative therapeutic target for menopause and neurocognitive disorders. Likewise, the role of neuroestrodiol and neurotestosterone synthesis along the neurogenic programme in the hippocampus may not be excluded for the HPH feedback loop involved cognitive functions in male subjects. The establishment and regulation of HPH axis might be the key factor for the neural development, synaptic plasticity and cognitive functions throughout the life. It can be expected that the onset and interference of the HPG axis with brain-specific HPH axis upon puberty might potentially be the underlying mechanism of reduction of neurogenesis and cognitive decline along ageing process. However, further studies are necessary to investigate effects of gonadal steroidogenesis, pregnancy-related hormonal changes, hormonal replacement therapy, contraceptive treatments, pharmacological modulators of the StAR protein, other forms of estrogen, carcinomas and toxins that interfere with the neuroestradiol levels and the regulation of neuroplasticity of the adult brain.

Conclusion

The abnormal regulation of the HPG axis has been linked to the decreased level of estradiol due to gonadal dysfunction or menopause. Thus far, the underlying mechanism for decreased ovarian steroid-induced neurocognitive disorders has been suggested for the abnormal hippocampal plasticity through the feedback loop of the HPG axis. While hippocampal neurogenic niche has been characterised by the expression of the neurosteroidogenic components, estradiol also appears to be synthesised by neuroblasts in the hippocampus. Thus, understanding the reciprocal relationship between neurosteroidogenesis and neuroblastosis in the hippocampus would provide an innovative outlook for the regulation of hippocampal neuroplasticity, for which the possible existence of a brain-specific feedback loop, namely, HPH axis might be highly relevant. The proposed HPH pathway in the brain could experimentally be tested and validated using advanced scientific tools. Thus, future experiments directed towards the regulation of HPH axis followed by understanding its biological significance may help in establishing a novel therapeutic target to manage neurocognitive disorders including dementia in the ageing population.

Acknowledgements MK has been supported by the Faculty Recharge Programme, University Grants Commission (UGC-FRP), New Delhi, India. MK would like to greatly acknowledge a start-up Grant from UGC-FRP, a research Grant (EEQ/2016/000639) and an Early Career Research Award (ECR/2016/000741) from DST-SERB, New Delhi, India. AY has been supported as JRF from DST SERB-EEQ/2016/000639. SAR has been supported as JRF from the DBT, India. CP thank DST-SERB, New Delhi, India for financial support (EMR/2017/003670). MME is highly acknowledging the support given by SQU in the form of an internal Grant (IG/AGR/FOOD/17/02). The authors acknowledge UGC-SAP, DST-FIST and PURSE for the infrastructure of the Department of Animal Science and Department of Biochemistry, Bharathidasan University.

Author Contributions MK conceived the present idea, hypothesis and generated the illustration. RKR, PAGP, MK and MA further developed the hypothesis and performed the literature search and made initial draft. MK, RKR, PAGP, SAR, AY, KB, CP, SS, AM, MME, MA contributed to the revision of article, made critical comments and suggestions. All authors discussed the content and contributed to the final manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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