CMLS, Cell. Mol. Life Sci. 62 (2005) 257–270
1420-682X/05/030257-14
DOI 10.1007/s00018-004-4381-3

CMLS Cellular and Molecular Life Sciences

The role of hypothalamic-pituitary-gonadal hormones in the normal structure and functioning of the brain

S. Vadakkadath Meethal[a] and C. S. Atwood[a, b,*]

[a] Section of Geriatrics and Gerontology, Department of Medicine, University of Wisconsin and Geriatric Research, Education and Clinical Center, Veterans Administration Hospital, Madison, Wisconsin 53705 (USA)
[b] Institute of Pathology, Case Western Reserve University, Cleveland, Ohio 44106 (USA)

Abstract. Receptors for hormones of the hypothalamic-pituitary-gonadal (HPG) axis that regulate reproductive function are expressed throughout the brain, and in particular the limbic system. The most studied of these hormones, the sex steroids, contain receptors throughout the brain, and numerous estrogenic, progestrogenic and androgenic effects have been reported in the brain related to development, maintenance and cognitive functions. Although less studied, receptors for gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH) and activins also are found throughout the limbic system on a number of cell types, and they too transduce signals from circulating hormones as demonstrated by their multiple effects on the growth, development, maintenance and function of the brain. This review highlights the point that because of the feedback loops within the HPG axis, it is difficult to ascribe structural and functional changes during development, adulthood and senescence to a single HPG hormone, since a change in the concentration of any hormone in the axis will modulate hormone concentrations and/or receptor expression patterns for all other members of the axis. The most studied of these situations is the change in serum and neuronal concentrations of HPG hormones associated with menopause/andropause. Dysregulation of the HPG axis at this time results in increases in the concentrations of serum GnRH, gonadotropins and activins, decreases in the serum concentrations of sex steroid and inhibin, and increases in GnRH and LH receptor expression. Such changes would result in significantly altered neuronal signaling, with the final result being that there is i.e. increased neuronal GnRH, LH and activin signaling, but decreased sex steroid signaling. Therefore, loss of cognitive function during senescence, typically ascribed to sex steroids, may also result from increased signaling via GnRH, LH or activin receptors. Future studies will be required to differentiate which hormones of the HPG axis regulate/maintain cognitive function. This introductory review highlights the importance of the identification of HPG hormone neuronal receptors and the potential of serum HPG hormones to transduce signals to regulate brain structure and function during development and adult life.

Key words. Hormone; hypothalamic-pituitary-gonadal axis; receptor; brain; neuron; activins; inhibins; gonadotropin-releasing hormone; luteinizng hormone; follicle-stimulating hormone; sex steroids.

Introduction

This first review in the series provides an overview of background information regarding the role of the hypothalamic-pituitary-gonadal (HPG) axis in the functioning of the brain, and will describe the hormones and feedback regulation of the HPG axis, hormone receptor localization throughout the brain, and how these hormones affect the normal structure (growth, development and maintenance) and functioning (cognition and behavior) of the brain. Finally, we review changes in HPG hormone signaling to the brain following the dysregulation of the HPG axis such as occurs following menopause, during andropause and after castration.

* Corresponding author.
Mailing address: University of Wisconsin-Madison Medical School, Wm S. Middleton Memorial VA Hospital (GRECC 11G), 2500 Overlook Terrace, Madison, Wisconsin 53705 (USA),
Fax: +1 608 280 7291, e-mail: csa@medicine.wisc.edu

HPG axis

The nature of the HPG axis was first proposed in the early 1930s by Moore and Price [1], who put forth the idea that the cyclical nature of ovarian changes (including ovulation and estrus) could be explained as a reciprocal interplay between the ovary and the anterior pituitary gland [2]. Shortly thereafter, work by Hohlweg and Junkmann [3] indicated that the hypothalamus was interposed as an intermediary between the feedback action of the ovarian hormones and pituitary gland (fig.1). The hormones of the HPG axis are the principal hormones responsible for regulating reproduction and include centrally and peripherally produced hormones. In the human and many mammals the centrally produced hormones include gonadotropin-releasing hormone (GnRH) from the hypothalamus and the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), from the pituitary. Peripherally produced hormones include estrogen, progesterone, testosterone and inhibins that are primarily of gonadal origin, while activins and follistatin are produced in all tissues, including the gonads [4].

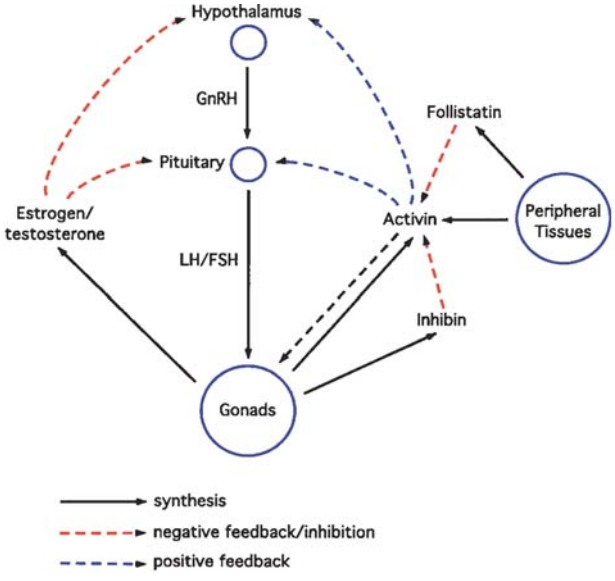

Figure 1. The HPG axis. The concentration of each of the HPG axis hormones is regulated by complex feedback loops. The loop is initiated in the periphery by activins which stimulate the hypothalamus to release gonadotropin releasing hormone (GnRH). This in turn stimulates the anterior pituitary to secrete the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These then bind to receptors on the gonads and stimulate oogenesis/spermatogenesis, as well as sex steroid and inhibin production. The sex steroids feed back to the hypothalamus and pituitary, resulting in a decrease in gonadotropin secretion. Inhibin, produced primarily in the gonads in association with oogenesis/spermatogenesis, is known to bind to and block activin receptors. Activins stimulate GnRH and gonadotropin secretion; however, the mechanism by which activin production is regulated has yet to be determined. Inhibin therefore indirectly controls gonadotropin synthesis. Follistatin, expressed in many different tissues, inhibits activin binding to its receptor.

The levels of each of these hormones are regulated by a complex feedback loop – activins from the periphery stimulate GnRH secretion from the hypothalamus, which stimulates the anterior pituitary to secrete the gonadotropins, LH and FSH into the bloodstream, which in turn bind to receptors in the gonads and stimulate oogenesis/spermatogenesis as well as sex steroid and inhibin production [5] (fig. 1). The sex steroids (and inhibin) then negatively feedback to the hypothalamus and pituitary, resulting in a decrease in gonadotropin secretion [6]. GnRH secretion, and hence gonadotropin secretion, is modulated by activins, which are produced in many tissues [7, 8]. Activin signaling is in turn modulated by two different mechanisms, one mediated via inhibins and the other mediated via follistatin (reviewed in [9]). Inhibin binds to and inactivates activin receptors in a competitive manner. This inhibitory action is significantly enhanced in tissues whose cell membranes express β-glycan [10]. Follistatin, expressed in a variety of different tissues, irreversibly binds to activins and prevents them from binding to their receptors [11, 12]. Since inhibins are primarily produced in the gonads and their production is dependent on folliculogenesis/spermatogenesis [13], they are intimately involved in the regulation of the HPG axis and are a direct indicator of fertility. Follistatin is expressed in many different tissues, and serum concentrations are known to change during pregnancy [14] and puberty [15], as well as with certain medical conditions, such as polycystic ovary syndrome [6, 16]. The levels of the HPG hormones vary depending on the reproductive state of the organism throughout life. Normal serum concentrations of HPG hormones in the human during childhood, adult reproductive life and post-reproductive life are shown in table 1.

Role of HPG axis hormones in the health of the brain

The influence of hormones of the HPG axis on brain structure (development and maintenance) and function has become well established over the last century. Although most attention has focused on sex steroids, it is perhaps not surprising that hormones involved in sex steroid synthesis also affect brain structure and function. The following section will detail the affects of all hormones of the HPG axis in order of their production (activins/inhibin/follistatin, GnRH, gonadotropins and sex steroids) on regulating brain structure (developmental and maintenance biochemistry) and function (physiology and cognition).

Activin, follistatin and inhibin

Neuronal Development and Maintenance: Activins (βA, βB, βC, βD, βE; ~28 kDa) are members of the trans-

Table 1. Representative concentrations of serum HPG hormones during childhood, adult reproductive life and post-reproductive life in the human. Taken from [154–164]. Data for activin, inhibins and follistatin represent all published data.

Hormone	Childhood (3-10 years)		Reproductive Adult		Post-menopause/andropause	
	Boys	Girls	Men	Women	Men	Women
Androstenedione	2 nM	0.5 nM	3.0–5.0 nM	3.5–7.0 nM	1.62 nM	2.3 nM
Dihydrotestosterone	1 nM	–	3.22 nM	0.17–1 nM	3.22 nM	0.5 nM
17β-Estradiol	44 pM	57 pM	<180 pM	70–>740 pM	85 pM	14 pM
Estrone	0.2 nM	–	1.3 nM	1.3 nM	1 nM	1.1 nM
Progesterone	1.8 nM	1.8 nM	0.49 nM	<6–64 nM	0.49 nM	–
Pregnanolone	–	–	5.6 nM	3.9 nM	1.3 nM	2.2 nM
Testosterone	1 nM	–	10–35 nM	< 3.5 nM	1–15 nM	0.66 nM
GnRH	–	–	–	20 pg/ml	–	–
LH	0.2–1 IU/ l	0.2–1 IU/ l	1.3–13 IU/ l	0.8–57 IU/ l	5–15 IU/ l	40–104 IU/l
FSH	0.8 IU/ l	0.8 IU/ l	0.9–15 IU/ l	1.4–21 IU/ l	12–25 IU/ l	34–96 IU/l
Activin A	–	–	1.38 µg/ l 0.7 µg/l 0.47 µg/l	1.16 µg/l 0.6 µg/l ~0.2 µg/l	1.48 µg/l 1.09 µg/l 0.58–0.74 µg/l	1.48 µg/l 0.67 µg/l 0.43–0.93 µg/l
Inhibin A	–	–	479–613 IU/l	1000 IU/l	415 IU/l	–
Inhibin B	–	–	70 ng/ l 200 ng/l	– –	80 ng/l 78–165 ng/l	– –
Follistatin	–	–	10 µg/l	10 µg/l	20 µg/l	17.2 µg/l

Red, decrease in concentration; blue, increase in concentration, compared to reproductive adult.

forming growth factor-β superfamily and signal via activin receptors that are enriched in neurons of the developing and adult brain (see below; [17, 18]). Like other members of the axis, activins also are involved in developmental as well as cognitive functions.

Activins and their corresponding messenger RNAs have a broad anatomical distribution that has been well-documented in the regulation of the growth and differentiation of a variety of tissues types, including the brain [18–20]. In rodents, endogenous activins and their cognate receptors (see below) regulate mesoderm induction, body axis formation and organogenisis in the developing embryo and are expressed in parallel during embryogenesis in the rapidly dividing cells of the basal forebrain ventricular zone. In 10.5- and 12.5-day embryos expression of the βA subunit message is abundant in mesenchymal tissue, including the developing face [21]. By 16 days post-coitum, βA-subunit message is localized in the striatum of the brain, at 18 days post-coitum it is detected in the cerebral cortex and in late fetal cortex it is enriched in post-mitotic neurons at the lower boundary of the dense cortical plate. In contrast, βB transcripts are strongly expressed in selected regions of the brain, in particular the fore- and hindbrain, and in the spinal cord in 10–12 day embryos [21]. Starting at 14 days post-coitum, βB-subunit message is found in the area of rapidly dividing cells surrounding the forebrain ventricle, and this message continues to be expressed in these areas throughout embryogenesis. The expression of activins follows the well-characterized radial gradient of cortical development. As development progresses, βA activin expression continues to be enriched in neurons at the boundary between the hypercellular cortical plate and the subjacent, more mature deep layers [22]. These changes in the expression of activins have been shown to regulate neurotransmitter phenotype expression in peripheral neurons [23, 24]. Activin co-operates with fibroblast growth factor 2 to induce a rapid expression of tyrosine hydroxylase, but not other neurotransmitter systems, in both proliferating ventricular zone progenitors and their post-mitotic progeny in vitro [25].

Follistatin and inhibins (A/B) likely modulate the effects of activins during post-implantation rat embryogenesis. Follistatin irreversibly binds to activins and prevents them from binding to their receptors [11, 12], while in-

hibins bind to and inactivate activin receptors in a competitive manner, and this inhibitory action is significantly enhanced in tissues whose cell membranes express β-glycan [10]. Although the interaction of these hormones (and β-glycan) in regulating activin signaling remains to be fully elucidated, follistatin message has been observed in all tissues of the developing rodent (except the heart and vessels), localizing with βA-subunit and/or ActRIIB, but interestingly it is not found in the same cell types within tissues [18].

Neuronal Function: Activins have a well-documented role in promoting neural plasticity in the developing and adult brain, with the expression of activin in response to synaptic and developmental activity modulating differentiative processes: activin expression increases in situations requiring decreased plasticity and decreases in situations requiring increased plasticity. βA activin appears to be regulated as a rapid response gene in the developing brain since βA activin messenger RNA (mRNA) expression is rapidly upregulated in early postnatal cortex and striatum by γ-aminobutyric acid (GABA) and glutamate antagonists [22]. βA activin mRNA also is rapidly and transiently induced in neurons of the adult rat brain by excitatory synaptic input [22], as its expression in neurons of layers II/III and V/VI rapidly decreases following sensory deafferentation of the visual cortex or systemic administration of dizocilpine. Activin also has been shown to significantly impair the formation of long-term potentiation (LTP) induced by low tetanic stimulation (60 Hz for 0.27 s), but not that by strong tetanic stimulation (60 Hz for 0.5 s), as might be expected during periods of increased synaptic plasticity [26]. Likewise, convulsive seizure caused by kainate significantly increased the expression of activin βA mRNA in the adult rat hippocampus [27]. This same group showed that high-frequency stimulation of the perforant pathway, which produced a persistent LTP (>10 h), caused a marked increase at 3 h in the level of activin βA mRNA at the dentate gyrus of urethane-anesthetized rats.

Another example of changes in neuronal plasticity during adult life being modulated by activin has been reported for rats in modulating behavior when fed lysine-deficient diets [28]. Activin βA-induced changes in neuronal plasticity appear to drive ingestive behavior (motivation) for a particular food constituent (i.e. lysine) to maintain amino acid homeostasis. The ratio of brain activin and inhibin has been shown to modulate motivation to work for a complete diet (versus a lysine-deficient diet), since continuous inhibin or follistatin, but not activin, infusion into the lateral hypothalamic area was found to inhibit bar pressing, which is normally quite strong in rats maintained on lysine-deficient diets [29]. Subsequent studies modulating activin βA activity using an antibody specific for activin βA injected into the lateral hypothalamic area confirmed the effects were due to activin βA levels, and not a direct affect of inhibin or follistatin [30]. These results illustrate the importance of activins in the formulation of memory.

Activin also possesses neurotrophic properties, being a potent survival factor for neurogenic clonal cell lines, retinal neurons, midbrain dopaminergic and primary rat hippocampal neurons [31]. This neurotrophic action appears to be mediated by activins' potentiation of the depolarization-induced elevation in intracellular Ca^{2+} concentration.

GnRH

GnRH is a 10-amino acid peptide that is cleaved from a larger precursor protein by enzymatic processing and packaged in storage granules that are transported down axons to the external zone of the median eminence. The peptide is released in synchronized pulses from nerve endings into the hypophyseal portal system every 30–120 min to stimulate the biosynthesis and secretion of LH and FSH from pituitary gonadotropes (see [32] and references therein). GnRH has not been reported to have any direct role in the developmentor maintenance of brain structures. However, GnRH may signal via the secretion of gonadotropins to promote development of the brain (see Gonadotropin section).

Neuronal Function: Although the concentration of circulating GnRH is very low due to its short half-life [33, 34], GnRH signaling via the GnRH receptor in extrapituitary tissues of the brain appears to play an important role in neurotransmission. The source of GnRH binding to these receptors is unknown, however experiments using the GnRH agonist leuprolide acetate have demonstrated that activation of GnRH receptors induces a long-lasting enhancement of synaptic transmission mediated by ionotropic glutamate receptors in CA1 pyramidal neurons of rat hippocampal slices [35, 36]. This suggests that GnRH can increase the intrinsic neuronal excitability of both CA1 and CA3 pyramidal neurons in the hippocampus, an important integrative region for reproductive processes, both endocrinologically and behaviorally. The high densities of GnRH receptor (see below) in the limbic system in areas concerned with the regulation of behavioral functions [37] help explain changes in sex behavior in rats and other species following peripheral or central injections of GnRH [38–40]. In this regard, it will be interesting to examine the newly identified members of the GnRH family (GnRH II and GnRH III) with respect to their role in modulating structure and function in the brain. Miller and colleagues (2001) have proposed that GnRH II has a neurotransmitter-neuromodulatory role based on the wide distribution of GnRH II in the central and peripheral nervous system [41], including human neuro-

blastoma cell lines [42], and the binding of GnRH-II in frog sympathetic ganglia to high-affinity receptors that potently inhibit M-type K^+ channels [43].

Gonadotropins

Neuronal development and maintenance: The gonadotropins LH, human chorionic gonadotropin (hCG) and FSH, together with thyroid stimulating hormone (TSH), form the family of glycoprotein hormones (see [43a] for a review). LH, FSH and TSH are produced by the pituitary gland, while the LH homolog hCG originates from the placenta. Each member of the glycoprotein hormones (molecular mass 30–40 kDa) consists of a common α-subunit and a hormone-specific β-subunit that are associated through non-covalent interactions. The β-subunits confer functional specificity of the hormones even though they share considerable homology.

Besides their well-known actions on gonadal tissues, hCG/LH (LH is 83% homologous to hCG and shares the same receptor). And FSH may play a critical role in brain development and neuronal differentiation. Gonadotropins belong to a growth factor family with a cystine knot structural motif, suggesting that LH/hCG, like nerve growth factor, may have neurotropic effects [44, 45]. Indeed, rat neurons cultured in the presence of highly purified hCG have been shown to respond in a dose-dependent manner by increasing the outgrowth of neurite processes and total cellular protein, and by decreasing apoptosis [46]. Therefore, the high concentrations of CG during pregnancy may promote the rapid development of the fetal brain. At birth, the concentration of gonadotropin (hCG) plummet following loss of the chorion. However, low levels of LH are still present in a non-pulsatile fashion during pre-puberty where brain development continues, albeit slowly.

Neuronal Function: As early as the 1950s, numerous reports began to indicate that gonadotropins elicit responses in neuronal cells as diverse as altered electrical activity of the brain, respiration, excitability and behavior in the rabbit [47–49]. The behavioral changes observed in the rabbit following gonadotropin treatment include decreased feeding [50], facilitation of extinction of the conditioned avoidance response and decreased exploratory behavior [51]. More recent studies performed by the group of Rao, Lei and colleagues [52] have demonstrated that the intraperitoneal (IP) or intracerebroventricular (ICV) injections of hCG on the morning of proestrus of cycling female rats induces changes in several hippocampus- and hypothalamus-associated behaviors. Specifically, hCG-treated animals were generally less active and showed less exploratory and stereotypic behavior than saline-injected control animals, while taste neophobia was dramatically decreased following IP or ICV injection of hCG [52]. In addition, it has been demonstrated that hCG administration to cycling female rats increases high- and low-amplitude sleep via modulation of sleep-inducing and sleep-awakening eicosanoids [53]. It has been suggested that hCG is therefore soporific during pregnancy, a time of markedly elevated hCG [54]. In humans, FSH levels have been shown to negatively correlate with visuospatial function in young adult men and women [55]. In women, FSH and LH both positively correlate with word fluency. Women are poorer than men on visuospatial tests and better on verbal fluency, which is consistent with women's generally higher FSH levels and the negative relationship between FSH and visuospatial skills and the positive relationship with fluency.

Sex steroids

Neuronal Development and Maintenance: Sex steroids are the most-studied HPG hormones that have neuronal receptors, and have widespread effects throughout the brain on a number of different pathways, including the serotonin system, catecholaminergic neurons, basal forebrain cholinergic system as well as the hippocampal formation (see [56] for a review). The sex steroids, although mainly produced in the gonads, also are generated in the adrenal glands, brain and other tissues.

As early as the 1960s, the sex steroids were described as having a duel function – an inductive or organizational role on the undifferentiated brain (as they also do in the undifferentiated genital tract), and an activational role on the differentiated brain with the expression of overt patterns of sexual behavior [2, 57]. With regards to the growth and development of the brain, the reader is directed toward a number of excellent reviews on this topic in this series (Simpkins et al., Bates et al. and Gleason et al.). Briefly, sex steroids have been reported to modulate neuronal growth [59] and differentiation, promoting neurite development and migration that lead to changes in synaptogenesis [59–62]. As part of these differentiative processes, estrogens, progestins and androgens are known to modulate dendritic spine density, with the loss of sex steroids generally resulting in decreased spine density [63, 64]. Sex steroid-induced morphological changes appear to underlie perhaps the most important of the physiological effects of gonadal steroids on the brain: the differentiation of sexually dimorphic brain regions during development [57, 65, 66]. These regions of the brain differ both structurally and functionally between males and females. Such sexually dimorphic structures are formed during mammalian CNS development in response to varying levels of gonadal steroids [67, 68]. It is thought that sex steroids impart long-lasting (differentiative) changes to the genome and organization of the cell nucleus such as altering the access of steroid-receptor complexes to DNA regulation

sites [66, 69]. This in turn alters cellular responsiveness to subsequent hormone challenges months or years later, such as is thought to occur with the changing hormonal milieu during puberty [70, 71]. Interestingly, sex differences in the pattern of connectivity between various limbic regions related to reproductive functions have also been described [62]. However, studies in transsexuals (see Bates et al., this series) and estrogen receptor knockout mice (see Simpkins et al., this series) have brought into question the role of sex steroids in the sexual differentiation of the brain.

Aside from these long-term changes, ovarian hormones also regulate synapse turnover in the CA1 region of the hippocampus during the 4- to 5-day estrous cycle of the female rat. Formation of new excitatory synapses is induced by estradiol and involves N-methyl-D-aspartate (NMDA) receptors, whereas downregulation of these synapses involves intracellular progestin receptors [72]. Although NMDA receptor activation is required for synapse formation, inhibitory interneurons may play a pivotal role, as they express nuclear estrogen receptor-alpha (ERα). It also is likely that estrogens may locally regulate events at the sites of synaptic contact in the excitatory pyramidal neurons where the synapses form [56].

Neuronal Function: The role of sex steroids in brain function was recognized much earlier than their structural role; in the first half of last century the loss of androgens and then their replacement in castrates was shown to clearly influence normal cognitive function related to reproduction (reviewed in [57] and [73]). Similar observational studies also were performed in women whereby changes in sex hormones led to clear psychological changes during the menstrual cycle. Since these early studies, it has become apparent that sex steroids modulate cognitive and motor abilities. For example, women score higher on certain cognitive tests during periods of raised plasma estrogen or both estrogen and progesterone [74]. Conversely, the sudden loss of estrogen following hysterectomy or 'chemical' castration (with anti-gonadotropin drugs) during adult reproductive life results in mild cognitive deficits [75–77]. These cognitive effects were demonstrated by Sherwin and Tulandi [77] to be due to estrogen loss, as the administration of estrogen together with leuprolide acetate ameliorated the effects of chemical castration on memory loss and depression. Interestingly, no similar declines in cognitive performance have been reported following chronic loss of estrogens after menopause, indicating at least a partial cognitive adaptive response to chronic low-level estrogen. At least in men don't appear to neurosteroids produced in the brain at this time compensate for the loss of gonadally produced sex steroids [165].

Progesterone also has been shown to influence reproductive behavior [78] and cognitive function [79] (see [80] for a review), and metabolites of progesterone have been correlated with measures of fatigue, confusion and immediate recall [81]. While estrogens increase brain excitability, progestins decrease brain excitability [80]. In addition, progesterone has been shown to have profound anesthetic properties and to increase the concentration of monoamine oxidase, the enzyme that catabolizes serotonin in the brain [80, 82, 83]. Progesterone also has been shown to have neuroprotective effects on both neurodegenerative and cognitive processes [84] as well as promyelinating effects [85].

More recently, over the last 40 years the role of sex steroids in the mediation of important neurotransmitters and hormones (neurotransmitter uptake and enzyme activity) during both the neonatal period and adulthood [86–88] has been described (see also reviews in this series by Bates et al. and Simpkins et al.). Other functional changes ascribed to the sex steroids include the increase in cerebral blood flow, protection against glutamate induced toxicity and apoptosis, anti-inflammatory actions and antioxidant properties [66, 89–92]. Despite this evidence that sex steroids impact neuronal function, the exact mechanism by which sex steroids modulate brain function remain to be elucidated.

HPG hormone receptors

The brain structural and functional changes induced by HPG hormones imply that their corresponding receptors also are expressed on neuronal cells. GnRH and gonadotropins signal via plasma membrane G-protein coupled receptors containing leucine-rich repeats, activins signal via type I and type II receptors that are serine/threonine kinases, and sex steroids signal via nuclear protein receptors. The following sections describe HPG hormone receptors identified in the brain.

Activin receptors

Activins regulate embryonic development by signaling through type I and type II receptor proteins (both of which are serine/threonine kinases). Activin receptors have been well-characterized throughout the brain [93] and are enriched in neurons of developing and adult brain [17, 18]. Receptor transcripts for ActR IIA and ActR IIB are observed in the neuroectoderm as it develops into spinal cord, brain and eyes of developing chicks [94, 95] and rats [18, 21]. In the rat, ActRIIA mRNA is found exclusively in neuronal tissue from 14 days post-coitum until birth. ActRIIB mRNA also is found in brain, spinal cord and ganglion, but usually appears earlier in development than the ActRII message, suggesting these two receptors serve different roles during activin-induced development. During the period of organogenesis in

mice, the sites of expression of activin receptors type IIA and IIB mRNA generally coincide with or are adjacent to the sites of activin β subunit expression [21]. Activin signaling through the Act RI and ActRII is mediated via Smad and forkhead signaling molecules [96, 97].

GnRH receptors

GnRH receptor is a G-protein-coupled receptor, which is 328 amino acids long, and is necessary for GnRH to initiate the release of gonadotropins from pituitary gonadotropes [32, 98]. Although species variation exists in the expression of GnRH receptor in extrapituitary tissues [99], GnRH receptor is present in rodent (see below) and human hippocampus [100]. GnRH receptor has been localized to extrapituitary areas of the rodent brain (using radiolabeled GnRH agonists and immunocytochemistry), including the hippocampus, amygdala, entorhinal cortex and subiculum, lower amounts in the septum and frontal cortex, but are not found in great numbers in the hypothalamus [36, 37, 101–114]. The density of GnRH receptor appears to be highest in the stratum oriens and stratum radiatum of the CA1–CA4 regions of Ammon's horn [37, 104]. The highest density of GnRH agonist binding sites (B_{max} = 11.6 ± 1.0 fmol/mg protein) is observed in the stratum radiatum of the CA3 region (cf pituitary tissues, B_{max} = 20.7 ± 2.8 fmol/mg protein) [37]. Studies using GnRH agonists have identified a high affinity binding site in the hippocampus within the low nanomolar range that compares closely with the pituitary GnRH receptor (see table 2), suggesting an important role for GnRH in modulating hippocampal function. Lower affinity binding sites in the high nanomolar/low micromolar range also have been reported in rat brain crude particulate preparations. Both native GnRH and GnRH antagonist have been shown to be potent competitors of GnRH agonist binding to the rodent receptor [37, 108]. Interestingly, GnRH binding in rat brain preparations has been localized to the mitochondrial fraction [115], as has an endopeptidase activity able to degrade GnRH [116]. This activity was metal ion and membrane structure dependent and detected in heavy and light mitochondrial fractions of the rat adenohypophysis with a distribution pattern similar to that of the mitochondrial and lysosomal reference enzymes cytochrome oxidase and beta-galactosidase [116]. In the human brain, we have found GnRH receptor immunoreactivity in the cell body as well as along the apical dendrites of hippocampal pyramidal neurons. GnRH receptor immunoreactivity is weaker in cortical tissue; however, immunoblot analyses of these tissues indicated GnRH receptor variants of ~30, 48 and 62 kDa [100].

GnRH receptor is detectable at day 6 post-partum in the rat [106] and continues to increase over time, reaching a maximum around puberty (35 and 45 days of age for male and female rats, respectively). Thereafter, the receptor concentration decreases to low levels during adult reproductive life before increasing in older rats (17 and 21 months of age). This increase in GnRH receptor concentration in post-reproductive animals appears to be due to decreased gonadal hormone production, since castrated male and female rats (high LH/FSH, low E/T) display increased GnRH receptor expression, while male and female rats treated with testosterone and estradiol/progesterone have decreased GnRH receptor expression [110, 117]. In this respect, receptor concentration is highest in proestrus (6.11 ± 0.90 fmol/mg) and significantly lower during estrus (2.4 ± 0.29 fmol/mg) [108]. In addition to steroid changes in GnRH receptor expression, the affinity of GnRH receptor for GnRH decreases 18-fold during diestrus I and estrus, compared with ovariectomized animals [108].

Although hippocampal GnRH receptors, like those in the pituitary, appear to be modulated by circulating steroid hormones, administration of the GnRH agonist (triptorelin) to rats (low LH/FSH and low E/T) has been shown to downregulate hippocampal GnRH receptors only transiently [107]. In contrast, triptorelin increased testicular GnRH receptor levels for 10 days before returning to baseline [107]. This differential regulation of GnRH receptors between the pituitary, brain and testis indicates that hormones other than the gonadotropins and sex steroids, perhaps together with β-glycan expression, may be involved in regulating hippocampal GnRH receptor expression. Since gonadectomy and GnRH agonist treatment [118] also lead to loss of inhibin, activins may differentially upregulate GnRH receptor levels in the testes (the site of inhibin production) [119]. Interestingly, administration of high doses of the antagonist BIM 21009 to rats also markedly decreased GnRH receptor levels in the pituitary, but only modestly reduced hippocampal GnRH receptor levels (after 1 day of treatment) [107]. Melatonin administration to old rats and mice also offset the increase in GnRH receptor expression in the hip-

Table 2. Affinity of GnRH and GnRH agonists within the rat hippocampus and pituitary.

	Hippocampus (K_d)	Pituitary (K_d)
High-affinity binding site (nM)	0.28 ± 0.03 [37]	0.29 ± 0.08 [37]
	1 [105]	
	0.5–0.6 [109]	
	0.12 ± 0.01 [108]	
Low-affinity binding sites (nM)	139 [115]	
	5800 [115]	

pocampus with aging [113]. These results suggest that circadian changes in melatonin may also modulate GnRH receptor number during reproductive life. Colchicine as well as kainic acid injections into the rat brain considerably reduce the number of hippocampal GnRH receptors [104]. Interestingly, in the electrolytically and kainic-acid-lesioned animals, there was the appearance of non-displaceable GnRH binding sites within a well-defined area corresponding to the lesioned, gliosis-rich area [104].

GnRH receptors signal via activation of mitogenic-activated protein kinase (MAPK) cascades, such as ERK and JNK [116] in pituitary cells. Although little is known about signaling cascades in the brain, binding of GnRH agonist to hippocampal GnRH receptor causes a dose-dependent increase in inositol phosphates as well as changes in intracellular Ca^{++} levels of the target neurons [110, 112].

Gonadotropin receptors

LH/hCG receptors are G-protein coupled receptors that until recently were thought to be present only in the gonads. Recent studies, however, have demonstrated that LH/hCG receptors (like sex steroid, GnRH and activin receptors) are present on many non-gonadal tissues, including neuronal cells (see [121] and references therein and [122]), indicating this as a target tissue for LH and hCG. Unlike the gonadotropin LH, receptors for FSH have not been detected in neuronal cell types. Therefore, the effects of FSH on word fluency described previously [55] are either non-receptor mediated, or are due to the indirect actions mediated by other hormones. This would also be the case with biological or cognitive changer seen with the FORKO mouse.

All human neuronal cell types (neurons, astrocytes, glia) studied to date possess LH/hCG receptors [122–124]. Mature glycosylated and phosphorylated LH/hCG receptor (~92 kDa), immature full-length LH/hCG receptor (59-kDa) and minor variants that migrate at 48 and 68 kDa have been detected by immunoblot analyses in the cortex of young and aged individuals [124]. Likewise, LH/hCG receptor expression (mRNA and protein) has been detected in the adult rat brain with the highest density of LH/hCG receptors being found within the hippocampus followed by the hypothalamus, cerebellum, choroid plexus, ependymal tanycytes of third, fourth, and lateral ventricles, cortex, brain stem and anterior pituitary [125]. No difference in the distribution of hCG/LH receptors between male and female rat brains was detected by this group [126]. The relevance of neuronal LH/hCG receptors is indicated by the finding that LH can cross the blood-brain barrier [52].

Immortalized mouse hypothalamic and hippocampal GT1-7 and HN33p cells, human M17 neuroblastoma cells as well as gonadotropes, contain LH/hCG receptor [123, 124]. M17 neuroblastoma cells contain a number of LH/hCG receptor variants [124], including the mature glycosylated and phosphorylated LH/hCG receptor protein (~92 kDa), the immature full-length LH/hCG receptor (59-kDa) and a number of minor variants migrating at 36, 40, 48, 68 and 110 kDa [127, 128]. The full-length immature LH/hCG receptor, which migrates as a 59-kDa band [129], is the major band detected in M17 neuroblastoma cells (as well as human brain). Therefore, neurons express immature, mature and truncated variants of the LH/hCG receptor by which LH might mediate signaling. The signal transduction pathways by which LH/hCG receptors transmit their neuronal signals have not been examined.

In addition to identifying that LH/hCG receptors are present on human neurons, we recently showed that the expression of neuronal LH/hCG receptors is modulated by 17β-estradiol [124]. At physiological concentrations of 17β-estradiol (0.1 nM), expression of the immature 59-kDa LH/hCG receptor is maximal (greater than 0 nM 17β-estradiol). However, treatment with increasing concentrations of 17β-estradiol, including physiologically relevant concentrations of 17β-estradiol (1 nM), decreases the expression of immature LH receptor in a dose, dependent manner. Interestingly, levels of the mature forms of the LH receptor (~68, 92 and 110 kDa) were increased at high concentrations of 17β-estradiol (10 nM and 100 nM). Thus, following menopause when 17β-estradiol levels are low (<0.1 nM), a moderate expression of LH/hCG receptor would still be expected. Interestingly, the levels of higher molecular weight (mature) LH/hCG receptor variants were increased at higher concentrations of 17β-estradiol (10–100 nM). Although the physiological relevance of this finding is unclear, high concentrations of 17β-estradiol might drive LH/hCG receptor maturation at such times when pituitary LH secretion is decreased in order to mediate lowered LH signaling. Treatment of M17 cells with LH (as little as 1 mIU/ml) resulted in a small dose-dependent increase in immature and mature LH receptor variants. Truncated forms of the LH receptor (<55 kDa) also increased in a dose-dependent manner, with higher LH concentrations (10 and 30 mIU/ml). Together, these results indicate that like reproductive tissues 17β-estradiol and LH can modulate LH receptor expression, and may therefore regulate signaling mediated via the LH receptor.

Sex steroid receptors

The sex steroid receptors, estrogen (ERα and ERβ), androgen and progesterone (PRA and PRB), aside from being found in the hypothalamus and pituitary, are widely distributed in the brain, with the highest concentrations being found in the limbic system (amygdala, cerebral cor-

tex, midbrain central grey) and structures of the telencephalon [80, 130–134]. ERs also have been reported in the spinal cord, brainstem, sensory ganglia and pelvic autonomic ganglia [135]. Ultrastructural data reveals extranuclear ERα immunoreactivity within select dendritic spines on hippocampal principal cells, axons, axon terminals and glial processes [56]. It has been suggested that the presence of ER in dendrites is responsible for synapse formation in which filopodia from dendrites grow out to find new synaptic contacts, and estrogens regulate local, post-transcriptional events via second messenger systems [56]. However, despite this widespread distribution of ERs throughout the CNS, no grossly observable phenotypic change in the brain has been observed in either ERα or ERβ knockout mice, suggesting that the effects of estrogens on these two known ERs have relatively little role in CNS development [136].

Estrogens appear to function via both receptor-mediated and non-receptor mediated pathways. Indeed, the actions of non-receptor binding estrogen analogues indicate that ERs are not required for the neuroprotective effects of estrogens. This is supported by the findings that different therapeutic windows exist for physiological and pharmacological doses of estrogens, again suggesting that different doses afford neuroprotective action through different mechanisms [56a]. Additionally, receptor-mediated mechanisms of action may involve genomic or non-genomic pathways. PRs also have been identified in peripheral and central glial cells [137]. Estrogens, but not progestins, have been shown to induce the expression of PRA, (but not PRB) in the hippocampus [138, 139], although there is no change in PR isoform content in the hippocampus during the estrous cycle [140]. Sex steroids signaling in neuronal cells is not well understood, but appears to involve both receptor-dependent and -independent mechanisms (see [141, 142] for reviews).

Changes in hormonal signaling to neurons following dysregulation of the HPG axis following menopause and during andropause

The loss of gonadal function with menopause and during andropause results in the complete dysregulation of the HPG hormonal axis as the organism attempts to maintain reproductive function. The decline in sex steroid production by the gonads following menopause and during andropause leads to a loss of hypothalamic feedback inhibition that stimulates GnRH and gonadotropin production [4] in a futile attempt to increase gonadal sex steroid production. In addition, the decrease in gonadal inhibin production at this time [5] results in decreased activin receptor inhibition, and together with the increase in bioavailable activin [12] leads to a further increase in the secretion of GnRH and gonadotropins [143–145]. The lack of negative feedback from the ovary (both estradiol and inhibin) is therefore responsible for the unopposed elevation of GnRH release and gonadotropin secretion following ovarian senescence leading to a 3- to 4-fold and a 4- to 18-fold increase in the concentrations of serum LH and FSH, respectively [146] (table 1). Men also experience a greater than 2-fold, and 3-fold, increase in LH and FSH, respectively, as their reproductive function deteriorates [147] during andropause. Follistatin levels increase at this time, perhaps as a response, albeit insufficient, to limit activin signaling.

How these changes in peripheral circulating hormones affect signaling for brain structure and function will be dependent not only on hormone concentration but also upon changes induced by these altered serum hormone concentrations on tissue receptor expression. As mentioned above, hippocampal GnRH receptor expression is increased in old rats [106] and following castration [117]. Similarly, we have shown that low concentrations of gonadal steroids and high concentrations of LH such as is seen with menopause/andropause promotes LH receptor expression in human neuroblastoma cells [124]. Although it is not known how the dysregulation of the HPG axis affects hypothalamic/pituitary activin receptor expression, ovariectomy induces a rapid increase in pituitary ActRII mRNAs in rats [148]. Ovariectomy and aging also leads to a reduction in hippocampal ER in mice [149, 150] and hippocampal AR in rats [151, 152]. Therefore, in summary, the dysregulation of the HPG axis following menopause/andropause leads to increased GnRH, activin and LH signaling and decreased sex steroid signaling, in the aging brain.

Conclusions

The presence of HPG hormone receptors (LH/hCG, GnRH, activins and sex steroid) throughout the adult brain strongly suggests that their cognate hormones signal via these receptors to elicit structural and functional instructions during development, adult reproductive life and senescence. Indeed, these receptors have been shown to elicit signals central to the growth and development, maintenance and normal functioning, as well as the degeneration of the brain. At the present time, it is difficult to determine whether the effects ascribed to a particular HPG hormone with regard to neuronal structure and function are mediated via its own receptor signaling, or via feedback regulation on other HPG hormone receptors; such is the case for estrogen modulation of GnRH, gonadotropin and progesterone receptor expression in neuronal cells [124, 139, 153]. Likewise, it is not clear to what extent the above cognitive and functional observations are due to one hormone per se (e.g. sex steroids), or to their regulation of the production of another (e.g. gonadotro-

pins), or to the combined signaling of HPG hormones. In the case of the gonadotropins, we recently demonstrated that LH, not estrogens, appears to be responsible for modulating amyloid-β precursor protein processing, driving it towards the amyloidogenic pathway [123]. Exceptions to this logic include the short-term behavioral changes elicited by many HPG hormones and the signaling of activins via activin receptors during early development prior to the expression of other HPG hormone receptors. Otherwise, caution is required in the interpretation of results obtained from hormonal modulation studies such as following castration, administration of hormones and even the blocking of receptor signaling.

Following reproductive life, changes in serum and neuronal concentrations of HPG hormones (increased gonadotropins, increased activins, increased GnRH and decreased sex steroids which lead to increased GnRH and LH receptor expression) associated with menopause/andropause will significantly alter signaling to neurons. The affects of this altered neuronal signaling on the structure and function of the brain as it relates to neurodegeneration will be the topics of the following five reviews.

1 Moore C. R. and Price D. (1932) Gonad hormone functions, and the recigrocal infuence between gonads and hypopluysis with its bearing on the problem of sex hrmone antagonism. Am. J. of Anat. **50:** 13–67
2 Harris G. W. (1964) Sex hormones, brain development and brain function. Endocrinology **75:** 627–648
3 Hohlweg W. and Junkmann K. (1932) Klin. Wschr. **11:** 321
4 Carr B. R. (1998) Disorders of the ovary and female reprodctive tract. In:Williams Textbook of Endocrinology, pp. 751–817, Wilson J. D., Kronenberg H. M. and Larsen P. R. (eds), W. B. Saunders, Philadelphia, PA
5 Reichlin S. (1998) Neuroendocrinology. In: Williams Textbook of Endocrinology, 10th edn, Nelson J. D., Kronenberg H. M. and Larson P. P. (eds), pp. 165–248, N. B. Saunders, Philadelphia, PA
6 Thorner M., Vance M., Laws E. Jr, Horvath E. and Kovacs K. (1998) The anterio pituitary. In: Williams Textbook of Endocrinology, pp. 249–340, Wilson J. D., Kronenberg H. M. and Larsen P. R. (eds), W. B. Saunders, Philadelphia, PA
7 Ling N., Ying S. Y., Ueno N., Shimasaki S., Esch F., Hotta M. et al. (1986) Pituitary FSH is released by a heterodimer of the beta-subunits from the two forms of inhibin. Nature **321:** 779–782
8 Vale W., Rivier J., Vaughn J., McClintock R., Corrigan A., Woo W. et al. (1986) Purification and characterization of an FSH releasing protein from porcine ovarian follicular fluid. Nature **321:** 776–779
9 Atwood C. S., Barzilai N., Bowen R. L., Brown-Borg H. M., Jarrard D. F., Fu V. X. et al. (2003) Pennington scientific symposium on mechanisms and retardation of aging. Exp Gerontol. **38:** 1217–1226
10 Lewis K. A., Gray P. C., Blount A. L., MacConell L. A., Wiater E., Bilezikjian L. M. et al. (2000) Betaglycan binds inhibin and can mediate functional antagonism of activin signalling. Nature **404:** 411–414
11 DeKretser D. M., Hedger M. P., Loveland K. L. and Phillips D. J. (2002) Inhibins, activins and follistatin in reproduction. Hum. Reprod. Update **8:** 529–541
12 Gray P. C., Bilizikjian L. M. and Vale W. (2002) Antagonism of activin by inhibin and inhibin receptors: a functional role for betaglycan. Mol. Cell. Endocrinol. **188:** 254–260
13 Knight P. G. and Glister C. (2001) Potential local regulatory functions of inhibins, activins and follistatin in the ovary. Reproduction **121:** 503–512
14 Shang T., Zhao L., Li H. and Liu Z. H. (2003) [Concentration of follistatin in maternal serum at term and its expression in placenta]. Zhonghua Fu Chan Ke Za Zhi **38:** 390–393
15 Foster C. M., Phillips D. J., Wyman T., Evans L. W., Groome N. P. and Padmanabhan V. (2000) Changes in serum inhibin, activin and follistatin concentrations during puberty in girls. Hum. Reprod. **15:** 1052–1057
16 Eldar-Geva T., Spitz I. M., Groome N. P., Margalioth E. J. and Homburg R. (2001) Follistatin and activin A serum concentrations in obese and non-obese patients with polycystic ovary syndrome. Hum Reprod **16:** 2552-2556
17 Cameron H. A. and Gould E. (1994) Adult neurogenesis is regulated by adrenal steroids in the dentate gyrus. Neuroscience **61:** 203–209
18 Roberts V. J., Barth S., el-Roeiy A. and Yen S. S. (1994) Expression of inhibin/activin system messenger ribonucleic acids and proteins in ovarian follicles from women with polycystic ovarian syndrome. J. Clin. Endocrinol. Metab. **79:** 1434–1439
19 Roberts V. J., Sawchenko P. E. and Vale W. (1991) Expression of inhibin/activin subunit messenger ribonucleic acids during rat embryogenesis. Endocrinology **128:** 3122–3129
20 Roberts V. J., Barth S. L., Meunier H. and Vale W. (1996) Hybridization histochemical and immunohistochemical localization of inhibin/activin subunits and messenger ribonucleic acids in the rat brain. J. Comp. Neurol. **364:** 473–493
21 Feijen A., Goumans M. J. and van den Eijnden-van Raaij A. J. (1994) Expression of activin subunits, activin receptors and follistatin in postimplantation mouse embryos suggests specific developmental functions for different activins. Development **120:** 3621–3637
22 Andreasson K. and Worley P. F. (1995) Induction of beta-A activin expression by synaptic activity and during neocortical devel opment. Neuroscience **69:** 781–796
23 Coulombe J. N., Schwall R., Parent A. S., Eckenstein F. P. and Nishi R. (1993) Induction of somatostatin immunoreactivity in cultured ciliary ganglion neurons by activin in choroid cell-conditioned medium. Neuron **10:** 899–906
24 Fann M. J. and Patterson P. H. (1994) Neuropoietic cytokines and activin A differentially regulate the phenotype of cultured sympathetic neurons. Proc. Natl. Acad. Sci. USA **91:** 43–47
25 Daadi M., Arcellana-Panlilio M. Y. and Weiss S. (1998) Activin co-operates with fibroblast growth factor 2 to regulate tyrosine hydroxylase expression in the basal forebrain ventricular zone progenitors. Neuroscience **86:** 867–880
26 Ikegaya Y., Saito H., Torii K. and Nishiyama N. (1997) Activin selectively abolishes hippocampal long-term potentiation induced by weak tetanic stimulation in vivo. Jpn J Pharmacol **75:** 87–89
27 Inokuchi. K., Kato A., Hiraia K., Hishinuma F., Inoue M. and Ozawa F. (1996) Increase in activin beta A mRNA in rat hippocampus during long-term potentiation. FEBS Lett. **382:** 48–52
28 Torii K., Hanai K., Oosawa K., Funaba M., Okiyama A., Mori M. et al. (1993) Activin A: serum levels and immunohistochemical brain localization in rats given diets deficient in L-lysine or protein. Physiol. Behav. **54:** 459–466
29 Hawkins R. L., Inoue M., Mori M. and Torii K. (1995) Effect of inhibin, follistatin, or activin infusion into the lateral hypothalamus on operant behavior of rats fed lysine deficient diet. Brain Res. **704:** 1–9
30 Hawkins R. L., Murata T., Inoue M., Mori M. and Torii K. (1998) Activin antiserum infused into the lateral hypothalamic area affects operant behavior of rats fed lysine-deficient diet. Proc. Soc. Exp. Biol. Med. **219:** 149–153
31 Iwahori Y., Saito H., Torii K. and Nishiyama N. (1997) Activin exerts a neurotrophic effect on cultured hippocampal neurons. Brain Res. **760:** 52–58

32 Millar R. P., Lu Z. L., Pawson A. J., Flanagan C. A., Morgan K. and Maudsley S. R. (2004) Gonadotropin-releasing hormone receptors. Endocr. Rev. **25:** 235–275

33 Redding T. W., Kastin A. J., Gonzales-Barcena D., Coy D. H., Coy E. J., Schalch D. S. et al. (1973) The half-life, metabolism and excretion of tritiated luteinizing hormone-releasing hormone (LH-RH) in man. J. Clin. Endocrinol. Metab. **37:** 626–631

34 Fauconnier J. P., Teuwissen B. and Thomas K. (1978) Rate of disappearance in plasma of synthetic LH-RH intravenously injected in man. Gynecol. Obstet. Invest. **9:** 229–237

35 He D., Funabashi T., Sano A., Uemura T., Minaguchi H. and Kimura F. (1999) Effects of glucose and related substrates on the recovery of the electrical activity of gonadotropin-releasing hormone pulse generator which is decreased by insulin-induced hypoglycemia in the estrogen-primed ovariectomized rat. Brain Res. **820:** 71–76

36 Lu F., Yang J. M., Wu J. N., Chen Y. C., Kao Y. H., Tung C. S. et al. (1999) Activation of gonadotropin-releasing hormone receptors produces neuronal excitation in the rat hippocampus. Chin. J. Physiol. **42**: 67–71

37 Leblanc P., Crumeyrolle M., Latouche J., Jordan D., Fillion G., L'Heritier A. et al. (1988) Characterization and distribution of receptors for gonadotropin-releasing hormone in the rat hippocampus. Neuroendocrinology **48:** 482–488

38 Moss R. L. (1979) Actions of hypothalamic-hypophysiotropic hormones on the brain. Annu. Rev. Physiol. **41:** 617–631

39 Riskind P. and Moss R. L. (1979) Midbrain central gray: LHRH infusion enhances lordotic behavior in estrogen-primed ovariectomized rats. Brain. Res. Bull. **4:** 203–205

40 Sakuma Y. and Pfaff D. W. (1980) Excitability of female rat central gray cells with medullary projections: changes produced by hypothalamic stimulation and estrogen treatment. J. Neurophysiol. **44:** 1012–1023

41 Troskie B., King J. A., Millar R. P., Peng Y. Y., Kim J., Figueras H. et al. (1997) Chicken GnRH II-like peptides and a GnRH receptor selective for chicken GnRH II in amphibian sympathetic ganglia. Neuroendocrinology **65:** 396–402

42 Chen A., Yahalom D., Laskar-Levy O., Rahimipour S., Ben-Aroya N. and Koch Y. (2001) Two isoforms of gonadotropin-releasing hormone are coexpressed in neuronal cell lines. Endocrinology **142:** 830–837

43 Bosma M. M., Bernheim L., Leibowitz M. D., Pfaffinger P. J. and Hille B. (1990) Modulation of M current in frog sympathetic ganglion cells. Soc. Gen. Physiol. Ser. **45:** 43–59

43a Themmen A. P. N. and Huhtaniemi I. T. (2000) Mutations of gonadotropins and gonadotropin receptors: elucidating the physiology and pathophysiology of pituitary-gonadal function. Endocr. Rev. **21:** 551–583.

44 Lapthorn A. J., Harris D. C., Littlejohn A., Lustbader J. W., Canfield R. E., Machin K. J. et al. (1994) Crystal structure of human chorionic gonadotropin. Nature **369:** 455–461

45 Sato A., Perlas E., Ben-Menahem D., Kudo M., Pixley M. R., Furuhashi M. et al. (1997) Cystine knot of the gonadotropin alpha subunit is critical for intracellular behavior but not for in vitro biological activity. J. Biol. Chem. **272:** 18098–18103

46 al-Hader A. A., Tao Y. X., Lei Z. M. and Rao C. V. (1997) Fetal rat brains contain luteinizing hormone/human chorionic gonadotropin receptors. Early Pregnancy **3:** 323–329

47 Faure J. and Loiseau P. (1954) [Effect of hormones on the electrical activity of the brain, respiration, excitability and behavior of the rabbit.]. Rev. Neurol. **91:** 460–468

48 Faure J. (1956) [Changes in bioelectric activity of the rhinencephalon and in behavior after administration of pituitary gonadotropins in rabbits]. Rev. Neurol. **95:** 490–497

49 Kawakami M. and Sawyer C. H. (1959) Neuroendocrine correlates of changes in brain activity thresholds by sex steroids and pituitary hormones. Endocrinology **65:** 652–668

50 Emanuele M. A., Tentler J., Emanuele N. V. and Kelley M. R. (1991) In vivo effects of acute EtOH on rat alpha and beta luteinizing hormone gene expression. Alcohol **8:** 345–348

51 Telegdy G., Rozsahegyi G. and Lissak K. (1971) Further data on the effect of human chorionic gonadotrophin on avoidance and exploratory behaviour in the rat. Acta Physiol. Acad. Sci. Hung. **40**: 215–220

52 Lukacs H., Hiatt E. S., Lei Z. M. and Rao C. V. (1995) Peripheral and intracerebroventricular administration of human chorionic gonadotropin alters several hippocampus-associated behaviors in cycling female rats. Horm. Behav. **29:** 42–58

53 Toth P., Lukacs H., Hiatt E. S., Reid K. H., Iyer V. and Rao C. V. (1994) Administration of human chorionic gonadotropin affects sleep-wake phases and other associated behaviors in cycling female rats. Brain Res. **654:** 181–190

54 Lei Z. M. and Rao C. V. (2001) Neural actions of luteinizing hormone and human chorionic gonadotropin. Semin. Reprod. Med. **19:** 103–109

55 Gordon H. W. and Lee P. A. (1986) A relationship between gonadotropins and visuospatial function. Neuropsychologia **24:** 563–576

56 McEwen B. (2002) Estrogen actions throughout the brain. Recent Prog. Horm. Res. **57:** 357–384

56a Falkenstein E., Tillmann H. C., Christ M., Feuring M. and Wehling M. (2000) Multiple actions of steroid hormones–a focus on rapid, nongenomic effects. Pharmacol. Rev. **52:** 513–556.

57 Young W. C., Goy R. W. and Phoenix C. H. (1964) Hormones and sexual behavior. Science **143:** 212–218

58 Gould E., Tanapat P., Rydel T. and Hastings N. (2000) Regulation of hippocampal neurogenesis in adulthood. Biol. Psychiatry 48: 715–720

59 McEwan P. E., Lindop G. B. and Kenyon C. J. (1996) Control of cell proliferation in the rat adrenal gland in vivo by the renin-angiotensin system. Am. J. Physiol. **271:** E192–198

60 Masumoto A., Natori S., Iwamoto H., Uchida E., Ohashi M., Sakamoto S. et al. (1991) Effect of insulin, glucagon or dexamethasone on the production of insulin-like growth factor I in cultured rat hepatocytes. Fukuoka Igaku Zasshi **82:** 136–141

61 Leranth C., Shanabrough M. and Redmond D. E. Jr (2002) Gonadal hormones are responsible for maintaining the integrity of spine synapses in the CA1 hippocampal subfield of female nonhuman primates. J. Comp. Neurol. **447:** 34–42

62 Simerly R. B. (2002) Wired for reproduction: organization and development of sexually dimorphic circuits in the mammalian forebrain. Annu. Rev. Neurosci. **25:** 507–536

63 Woolley C. S. and McEwen B. S. (1993) Roles of estradiol and progesterone in regulation of hippocampal dendritic spine density during the estrous cycle in the rat. J. Comp. Neurol. **336:** 293–306

64 Leranth C., Petnehazy O. and MacLusky N. J. (2003) Gonadal hormones affect spine synaptic density in the CA1 hippocampal subfield of male rats. J. Neurosci. **23:** 1588–1592

65 Arnold A. P. and Gorski R. A. (1984) Gonadal steroid induction of structural sex differences in the central nervous system. Annu. Rev. Neurosci. **7:** 413–442

66 McEwan B. S. (2001) Invited review: estrogens effects on the brain: multiple sites and molecular mechanisms. J. Appl. Physiol. **91:** 2785–2801

67 Peterson B. S., Leckman J. F., Scahill L., Naftolin F., Keefe D., Charest N. J. et al. (1992) Steroid hormones and CNS sexual dimorphisms modulate symptom expression in Tourette's syndrome. Psychoneuroendocrinology **17:** 553–563

68 Beyer C. (1999) Estrogen and the developing mammalian brain. Anat. Embryol. **199:** 379–390

69 Simerly C., Dominko T., Navara C., Payne C., Capuano S., Gosman G. et al. (2003) Molecular correlates of primate nuclear transfer failures. Science 300: 297

70 Beyer C. and Feder H. H. (1987) Sex steroids and afferent input: their roles in brain sexual differentiation. Annu. Rev. Physiol. **49:** 349–364

71 Grumbach M. M. (2002) The neuroendocrinology of human puberty revisited. Horm. Res. **57 Suppl. 2:** 2–14

72 McEwen B. S. and Woolley C. S. (1994) Estradiol and progesterone regulate neuronal structure and synaptic connectiv-

ity in adult as well as developing brain. Exp. Gerontol. **29:** 431–436
73 Daniels G. E. (1971) Approaches to a biological basis of human behavior. Dis. Nerv. Syst. **32:** 227–240
74 Kugaya A., Epperson C. N., Zoghbi S., van Dyck C. H., Hou Y., Fujita M. et al. (2003) Increase in prefrontal cortex serotonin 2A receptors following estrogen treatment in postmenopausal women. Am. J. Psychiatry 160: 1522–1524
75 Phillips S. M. and Sherwin B. B. (1992) Effects of estrogen on memory function in surgically menopausal women. Psychoneuroendocrinology **17:** 485–495
76 Varney N. R., Syrop C., Kubu C. S., Struchen M., Hahn S. and Franzen K. (1993) Neuropsychologic dysfunction in women following leuprolide acetate induction of hypoestrogenism. J. Assist. Reprod. Genet. **10:** 53–57
77 Sherwin B. B. and Tulandi T. (1996) 'Add-back' estrogen reverses cognitive deficits induced by a gonadotropin-releasing hormone agonist in women with leiomyomata uteri. J. Clin. Endocrinol. Metab. **81:** 2545–2549
78 Pinta E. R. (1978) Treatment of obsessive homosexual pedophilic fantasies with medroxyprogesterone acetate. Biol. Psychiatry **13:** 369–373
79 Graham E. A. and Glasser M. (1985) Relationship of pregnanediol level to cognitive behavior and mood. Psychosom. Med. **47:** 26–34
80 Sherwin B. B. (1999) Progestogens used in menopause. Side effects, mood and quality of life. J. Reprod. Med. **44:** 227–232
81 Freeman E. W., Purdy R. H., Coutifaris C., Rickels K. and Paul S. M. (1993) Anxiolytic metabolites of progesterone: correlation with mood and performance measures following oral progesterone administration to healthy female volunteers. Neuroendocrinology **58:** 478–484
82 Izquierdo J. A., Savini C., Borghi E., Rabiller G., Costas S. and Justel E. (1978) Role of ACTH on the effect of medroxyprogesterone in brain stem serotonin. Pharmacol. Res. Commun. **10:** 643–656
83 Luine V. N. and Paden C. M. (1982) Effects of monoamine oxidase inhibition on female sexual behavior, serotonin levels and type A and B monoamine oxidase activity. Neuroendocrinology **34:** 245–251
84 Roof R. L., Duvdevani R., Braswell L. and Stein D. G. (1994) Progesterone facilitates cognitive recovery and reduces secondary neuronal loss caused by cortical contusion injury in male rats. Exp. Neurol. **129:** 64–69
85 Schumacher M., Guennoun R., Robert F., Carelli C., Gago N., Ghoumari A. et al. (2004) Local synthesis and dual actions of progesterone in the nervous system: neuroprotection and myelination. Growth Horm. IGF Res. **14 Suppl. A:** 18–33
86. Hutchinson H. G., Trindade P. T., Cunanan D. B., Wu C. F. and Pratt R.E. (1997) Mechanisms of natriuretic-peptide-induced growth inhibition of vascular smooth muscle cells. Cardiovasc. Res. **35:** 158–167
87 Tobet S. A. and Hanna I. K. (1997) Ontogeny of sex differences in the mammalian hypothalamus and preoptic area. Cell. Mol. Neurobiol. **17:** 565–601
88 Torres J. M. and Ortega E. (2003) Precise quantitation of 5alpha-reductase type 1 mRNA by RT-PCR in rat liver and its positive regulation by testosterone and dihydrotestosterone. Biochem. Biophys. Res. Commun. **308:** 469–473
89 Arai A. and Lynch G. (1996) Response to repetitive stimulation of AMPA receptors in patches excised from fields CA1 and CA3 of the hippocampus. Brain Res. **716:** 202–206
90 Nilson L. N., Backman L., Sallsten G., Hagberg S. and Barregard L. (2003) Dose-related cognitive deficits among floor layers with previous heavy exposure to solvents. Arch. Environ. Health **58:** 208–217
91 Stein D. G. and Hoffman S. W. (2003) Estrogen and progesterone as neuroprotective agents in the treatment of acute brain injuries. Pediatr. Rehabil. **6:** 13–22
92 Zhao W., Goswami P. C. and Robbins M. E. (2004) Radiation-induced up-regulation of Mmp2 involves increased mRNA stability, redox modulation and MAPK activation. Radiat. Res. **161:** 418–429
93 Trudeau V. L., Theodosis D. T. and Poulain D. A. (1997) Activin facilitates neuronal development in the rat amygdala. Neurosci. Lett. **237:** 33–36
94 Ohuchi H., Noji S., Koyama E., Myokai F., Nishikawa K., Nohno T. et al. (1992) Expression pattern of the activin receptor type IIA gene during differentiation of chick neural tissues, muscle and skin. FEBS Lett. **303:** 185–189
95 Nohno T., Noji S., Koyama E., Myokai F., Ohuchi H., Nishikawa K. et al. (1993) Expression patterns of the activin receptor IIA and IIB genes during chick limb development. Prog. Clin. Biol. Res. **383B:** 705–714
96 Satoh M., Sugino H. and Yoshida T. (2000) Activin promotes astrocytic differentiation of a multipotent neural stem cell line and an astrocyte progenitor cell line from murine central nervous system. Neurosci. Lett. **284:** 143–146
97 Chen Y. G., Lui H. M., Lin S. L., Lee J. M. and Ying S. Y. (2002) Regulation of cell proliferation, apoptosis and carcinogenesis by activin. Exp. Biol. Med. (Maywood) **227:** 75–87
98 Miller G. M. and Gibson M. J. (1994) Opioidergic modulation of N-methyl-D,L-aspartic-acid-stimulated LH release in young adult but not older male mice. Neuroendocrinology **59:** 277–284
99 Kakar S. S., Rahe C. H. and Neill J. D. (1993) Molecular cloning, sequencing and characterizing the bovine receptor for gonadotropin releasing hormone (GnRH). Domest. Anim. Endocrinol. **10:** 335–342
100 Wilson A. C., Roche K. M., Vadakkadath Meethal S. and Atwood C. S. (2004) Localization of gonadotropin releasing hormone receptor on pyramidal neurons of the human hippocampus. Soc. Neurosci., Program Number 902.13
101 Reubi J. C. and Maurer R. (1984) Visualization of LHRH receptors in the rat brain. Eur. J. Pharmacol. **106:** 453–454
102 Badr M. and Pelletier G. (1987) Characterization and autoradiographic localization of LHRH receptors in the rat brain. Synapse **1:** 567–571
103 Haour F., Dussaillant M., Leblanc P. and Rostene W. (1987) [Demonstration and topographical distribution of LHRH receptors in the central nervous system in the normal and castrated male rat]. C. R. Acad. Sci. III **305:** 41–44
104 Reubi J. C., Palacios J. M. and Maurer R. (1987) Specific luteinizing-hormone-releasing hormone receptor binding sites in hippocampus and pituitary: an autoradiographical study. Neuroscience **21:** 847–856
105 Jennes L., Dalati B. and Conn P. M. (1988) Distribution of gonadrotropin releasing hormone agonist binding sites in the rat central nervous system. Brain Res. **452:** 156–164
106 Badr M., Marchetti B. and Pelletier G. (1989) Changes in hippocampal LH-RH receptor density during maturation and aging in the rat. Brain Res. Dev. Brain Res. **45:** 179–184
107 Ban E., Crumeyrolle-Arias M., Latouche J., Leblanc P., Heurtier J. F., Drieu K. et al. (1990) GnRH receptors in rat brain, pituitary and testis; modulation following surgical and gonadotropin-releasing hormone agonist-induced castration. Mol. Cell. Endocrinol. **70:** 99–107
108 Thompson T. L. and Moss R. L. (1992) Specific binding of 125I-LHRH agonist to hippocampal membranes: fluctuations during the estrous cycle. Peptides **13:** 891–896
109 Crumeyrolle-Arias M., Latouche J., Laniece P., Charon Y., Tricoire H., Valentin L. et al. (1994) 'In situ' characterization of GnRH receptors: use of two radioimagers and comparison with quantitative autoradiography. J. Recept. Res. **14:** 251–265
110 Jennes L., Brame B., Centers A., Janovick J. A. and Conn P. M. (1995) Regulation of hippocampal gonadotropin releasing hormone (GnRH) receptor mRNA and GnRH-stimulated inositol phosphate production by gonadal steroid hormones. Brain Res. Mol. Brain Res. **33:** 104–110

111 Jennes L., McShane T., Brame B. and Centers A. (1996) Dynamic changes in gonadotropin releasing hormone receptor mRNA content in the mediobasal hypothalamus during the rat estrous cycle. J. Neuroendocrinol. **8:** 275–281

112 Jennes L., Eyigor O., Janovick J. A. and Conn P.M. (1997) Brain gonadotropin releasing hormone receptors: localization and regulation. Recent Prog. Horm. Res. **52:** 475–490; discussion 490–471

113 Pierpaoli W. and Lesnikov V. (1997) Theoretical considerations on the nature of the pineal 'ageing clock'. Gerontology **43:** 20–25

114 Granger A., Ngo-Muller V., Bleux C., Guigon C., Pincas H., Magre S. et al. (2004) The promoter of the rat gonadotropin-releasing hormone receptor gene directs the expression of the human placental alkaline phosphatase reporter gene in gonadotrope cells in the anterior pituitary gland as well as in multiple extrapituitary tissues. Endocrinology **145:** 983–993

115 Liscovitch M. and Koch Y. (1982) Characterization and subcellular localization of GnRH analog binding in rat brain. Peptides **3:** 55–60

116 Leblanc P., L'Heritier A., Kordon C., Horsthemke B., Bauer K., Wattiaux-de Coninck S. et al. (1984) Characterization of a neutral endopeptidase localized in the mitochondrial matrix of rat anterior pituitary tissue with GnRH as a substrate. Neuroendocrinology **38:** 476–483

117 Badr M., Marchetti B. and Pelletier G. (1988) Modulation of hippocampal LHRH receptors by sex steroids in the rat. Peptides **9:** 441–442

118 Suzuki T., Miyamoto K., Hasegawa Y., Abe Y., Ui M., Ibuki Y. et al. (1987) Regulation of inhibin production by rat granulosa cells. Mol. Cell. Endocrinol. **54:** 185–195

119 Braden T. D. and Conn P. M. (1992) Activin-A stimulates the synthesis of gonadotropin-releasing hormone receptors. Endocrinology **130:** 2101–2105

120 Kostrouchova M., Krause M., Kostrouch Z. and Rall J. E. (2001) Nuclear hormone receptor CHR3 is a critical regulator of all four larval molts of the nematode *Caenorhabditis elegans.* Proc. Natl. Acad. Sci. USA **98:** 7360–7365

121 Bowen R. L., Smith M. A., Harris P. L., Kubat Z., Martins R. N., Castellani R. J. et al. (2002) Elevated luteinizing hormone expression colocalizes with neurons vulnerable to Alzheimer's disease pathology. J. Neurosci. Res. **70:** 514–518

122 Bukovsky A., Indrapichate K., Fujiwara H., Cekanova M., Ayala M. E., Dominguez R. et al. (2003) Multiple luteinizing hormone receptor (LHR) protein variants, interspecies reactivity of anti-LHR mAb clone 3B5, subcellular localization of LHR in human placenta, pelvic floor and brain, and possible role for LHR in the development of abnormal pregnancy, pelvic floor disorders and Alzheimer's disease. Reprod. Biol. Endocrinol. **1:** 46

123 Zhang F. P., Hamalainen T., Kaipia A., Pakarinen P. and Huhtaniemi I. (1994) Ontogeny of luteinizing hormone receptor gene expression in the rat testis. Endocrinology **134:** 2206–2213

124 Bowen R. L., Verdile G., Liu T., Parlow A. F., Perry G., Smith M.A. et al. (2004) Luteinizing hormone, a reproductive regulator that modulates the processing of amyloid-beta precursor protein and amyloid-beta deposition. J. Biol. Chem. **279:** 20539–20545

125 Lei Z. M. and Rao C. V. (1994) Novel presence of luteinizing hormone/human chorionic gonadotropin (hCG) receptors and the down-regulating action of hCG on gonadotropin-releasing hormone gene expression in immortalized hypothalamic GT1-7 neurons. Mol. Endocrinol. **8:** 1111–1121

126 Lei Z. M., Rao C. V., Kornyei J. L., Licht P. and Hiatt E. S. (1993) Novel expression of human chorionic gonadotropin/luteinizing hormone receptor gene in brain. Endocrinology **132:** 2262–2270

127 Indrapichate K., Meehan D., Lane T. A., Chu S. Y., Rao C. V., Johnson D. et al. (1992) Biological actions of monoclonal luteinizing hormone/human chorionic gonadotropin receptor antibodies. Biol. Reprod. **46:** 265–278

128 Bukovsky A., Chen T. T., Wimalasena J. and Caudle M. R. (1993) Cellular localization of luteinizing hormone receptor immunoreactivity in the ovaries of immature, gonadotropin-primed and normal cycling rats. Biol. Reprod. **48:** 1367–1382

129 Minegishi T., Delgado C. and Dufau M. L. (1989) Phosphorylation and glycosylation of the luteinizing hormone receptor. Proc. Natl. Acad. Sci. USA **86:** 1470–1474

130 McEwen B. S. (1988) Genomic regulation of sexual behavior. J. Steroid Biochem. **30:** 179–183

131 Guerra-Araiza C., Reyna-Neyra A., Salazar A. M., Cerbon M. A., Morimoto S. and Camacho-Arroyo I. (2001) Progesterone receptor isoforms expression in the prepuberal and adult male rat brain. Brain Res. Bull. **54:** 13–17

132 Gao W. J. and Goldman-Rakic P. S. (2003) Selective modulation of excitatory and inhibitory microcircuits by dopamine. Proc. Natl. Acad. Sci. USA **100:** 2836–2841

133 Nunez J. L., Huppenbauer C. B., McAbee M. D., Juraska J. M. and DonCarlos L. L. (2003) Androgen receptor expression in the developing male and female rat visual and prefrontal cortex. J. Neurobiol. **56:** 293–302

134 Shima H., Fujisawa H., Suehiro E., Uetsuka S., Maekawa T. and Suzuki M. (2003) Mild hypothermia inhibits exogenous glutamate-induced increases in nitric oxide synthesis. J. Neurotrauma **20:** 1179–1187

135 Papka R. E. and Mowa C. N. (2003) Estrogen receptors in the spinal cord, sensory ganglia and pelvic autonomic ganglia. Int. Rev. Cytol. **231:** 91–127

136 Couse J. F. and Korach K. S. (1999) Estrogen receptor null mice: what have we learned and where will they lead us? Endocr. Rev. **20:** 358–417

137 Baulieu E. E. (1997) Neurosteroids: of the nervous system, by the nervous system, for the nervous system. Recent Prog. Horm. Res. **52:** 1–32

138 Camacho-Arroyo I., Guerra-Araiza C. and Cerbon M. A. (1998) Progesterone receptor isoforms are differentially regulated by sex steroids in the rat forebrain. Neuroreport **9:** 3993–3996

139 Alves S. E., McEwen B. S., Hayashi S., Korach K. S., Pfaff D. W. and Ogawa S. (2000) Estrogen-regulated progestin receptors are found in the midbrain raphe but not hippocampus of estrogen receptor alpha (ER alpha) gene-disrupted mice. J. Comp. Neurol. **427:** 185–195

140 Guerra-Araiza C., Villamar-Cruz O., Gonzalez-Arenas A., Chavira R. and Camacho-Arroyo I. (2003) Changes in progesterone receptor isoforms content in the rat brain during the oestrous cycle and after oestradiol and progesterone treatments. J. Neuroendocrinol. **15:** 984–990

141 Behl C. (2002) Estrogen can protect neurons: modes of action. J. Steroid Biochem. Mol. Biol. **83:** 195–197

142 Blaustein J.D. (2003) Progestin receptors: neuronal integrators of hormonal and environmental stimulation. Ann. N. Y. Acad. Sci. **1007:** 238–250

143 Schwall R. H., Szonyi E., Mason A. J. and Nikolics K. (1988) Activin stimulates secretion of follicle-stimulating hormone from pituitary cells desensitized to gonadotropin-releasing hormone. Biochem. Biophys. Res. Commun. **151:** 1099–1104

144 Weiss J., Crowley W. F. Jr, Halvorson L. M. and Jameson J. L. (1993) Perifusion of rat pituitary cells with gonadotropin-releasing hormone, activin and inhibin reveals distinct effects on gonadotropin gene expression and secretion. Endocrinology **132:** 2307–2311

145 MacConell L. A., Lawson M. A., Mellon P. L. and Roberts V. J. (1999) Activin A regulation of gonadotropin-releasing hormone synthesis and release in vitro. Neuroendocrinology **70:** 246–254

146 Chakravarti S., Collins W. P., Forecast J. D., Newton J. R., Oram D. H. and Studd J. W. (1976) Hormonal profiles after the menopause. Br. Med. J. **2:** 784–787

147 Neaves W. B., Johnson L., Porter J. C., Parker C. R. Jr and Petty C. S. (1984) Leydig cell numbers, daily sperm production and serum gonadotropin levels in aging men. J. Clin. Endocrinol. Metab. **59:** 756–763

148 Dalkin A. C., Gilrain J. T. and Marshall J. C. (1994) Ovarian regulation of pituitary inhibin subunit and activin receptor type II gene expression: evidence for a nonsteroidal inhibitory substance. Endocrinology **135:** 944–949
149 Ehret G. and Buckenmaier J. (1994) Estrogen-receptor occurrence in the female mouse brain: effects of maternal experience, ovariectomy, estrogen and anosmia. J. Physiol. Paris **88:** 315–329
150 Adams M. M., Fink S. E., Shah R. A., Janssen W. G., Hayashi S., Milner T. A. et al. (2002) Estrogen and aging affect the subcellular distribution of estrogen receptor-alpha in the hippocampus of female rats. J. Neurosci **22:** 3608–3614
151 Ingraham H. A., Flynn S. E., Voss J. W., Albert V. R., Kapiloff M. S., Wilson L. et al. (1990) The POU-specific domain of Pit-1 is essential for sequence-specific, high affinity DNA binding and DNA-dependent Pit-1-Pit-1 interactions. Cell **61:** 1021–1033
152 Xiao L. and Jordan C. L. (2002) Sex differences, laterality and hormonal regulation of androgen receptor immunoreactivity in rat hippocampus. Horm. Behav. **42:** 327–336
153 Jegou B., Brekke I., Naess O., Torjesen P. and Hansson V. (1985) Properties and regulation of GnRH receptors in the anterior pituitary and the testis of the rat: different response of Leydig cell LH and GnRH receptors to hormonal treatments. Arch. Androl. **14:** 161–170
154 Lee P. A. and Migeon C. J. (1975) Puberty in boys: correlation of plasma levels of gonadotropins (LH, FSH), androgens (testosterone, androstenedione, dehydroepiandrosterone and its sulfate), estrogens (estrone and estradiol) and progestins (progesterone and 17-hydroxyprogesterone). J. Clin. Endocrinol. Metab. **41:** 556–562
155 Svensson J., Eneroth P., Gustafsson J. A., Ritzen M. and Stenberg A. (1978) Metabolism of androstenedione in skin and serum levels of gonadotrophins and androgens in prepubertal boys with hypospadias. J. Endocrinol. **76:** 399–409
156 Hummer L., Nielsen M. D. and Christiansen C. (1983) An easy and reliable radioimmunoassay of serum androstenedione: age-related normal values in 252 females aged 2 to 70 years. Scand. J. Clin. Lab. Invest. **43:** 301–306
157 Belanger A., Candas B., Dupont A., Cusan L., Diamond P., Gomez J. L. et al. (1994) Changes in serum concentrations of conjugated and unconjugated steroids in 40- to 80-year-old men. J. Clin. Endocrinol. Metab. **79:** 1086–1090
158 Labrie F., Belanger A., Cusan L. and Candas B. (1997) Physiological changes in dehydroepiandrosterone are not reflected by serum levels of active androgens and estrogens but of their metabolites: intracrinology. J. Clin. Endocrinol. Metab. **82:** 2403–2409
159 Labrie F., Belanger A., Cusan L., Gomez J. L. and Candas B. (1997) Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. J. Clin. Endocrinol. Metab. **82:** 2396–2402
160 Veldhuis J. D., Iranmanesh A., Demers L. M. and Mulligan T. (1999) Joint basal and pulsatile hypersecretory mechanisms drive the monotropic follicle-stimulating hormone (FSH) elevation in healthy older men: concurrent preservation of the orderliness of the FSH release process: a general clinical research center study. J Clin Endocrinol Metab **84:** 3506–3514
161 Baccarelli A., Morpurgo P. S., Corsi A., Vaghi I., Fanelli M., Cremonesi G. et al. (2001) Activin A serum levels and aging of the pituitary-goandal axis: a cross-sectional study in middle-aged and elderly healthy subjects. Exp. Gerontol. **36:** 1403–1412
162 Cunningham C. J., Sinnott M., Denihan A., Rowan M., Walsh J. B., O'Moore R. et al. (2001) Endogenous sex hormone levels in postmenopausal women with Alzheimer's disease. J. Clin. Endocrinol. Metab. **86:** 1099–1103
163 Elmlinger M. W., Kuhnel W. and Ranke M. B. (2002) Reference ranges for serum concentrations of lutropin (LH), follitropin (FSH), estradiol (E2), prolactin, progesterone, sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), cortisol and ferritin in neonates, children and young adults. Clin. Chem. Lab. Med. **40:** 1151–1160
164 Rasmuson S., Nasman B., Carlstrom K. and Olsson T. (2002) Increased levels of adrenocortical and gonadal hormones in mild to moderate Alzheimer's disease. Dement. Geriatr. Cogn. Disord. **13:** 74–79
165 Rosario E. R., Chang L., Stanczyk F. Z. and Pike C. J. (2004) Age-related testosterone depletion and the development of Alzheimer disease. JAMA **292:** 1431–1432