

REVIEW

STEROID HORMONES AND BDNF

N. PLUCHINO,^a M. RUSSO,^{a,*} A. N. SANTORO,^a
P. LITTA,^b V. CELA^a AND A. R. GENAZZANI^a

^a Division of Obstetrics and Gynecology, University of Pisa, Pisa, Italy

^b Department of Gynecological Science and Human
Reproduction, University of Padova, Padova, Italy

Abstract—Brain-derived neurotrophic factor (BDNF) is a neurotrophin abundantly expressed in several areas of the central nervous system (CNS) and is known to induce a lasting potentiation of synaptic efficacy, to enhance specific learning and memory processes. BDNF is one of the key molecules modulating brain plasticity and it affects cognitive deficit associated with aging and neurodegenerative disease. Several studies have shown an altered BDNF production and secretion in a variety of neurodegenerative diseases like Alzheimer's and Parkinson's diseases but also in mood disorders like depression, eating disorders and schizophrenia. Plasma BDNF is also a biomarker of impaired memory and general cognitive function in aging women. Gonadal steroids are involved in the regulation of several CNS processes, specifically mood, affective and cognitive functions during fertile life and reproductive aging. These observations lead many scientists to investigate a putative co-regulation between BDNF and gonadal and/or adrenal steroids and their relationship with gender difference in the incidence of mental diseases. This overview aims to summarize the current knowledge on the correlation between BDNF expression/function and both gonadal (progesterone, estrogens, and testosterone) and adrenal hormones (mainly cortisol and dehydroepiandrosterone (DHEA)) with relevance in clinical application.

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*Corresponding author.

E-mail address: marval86@libero.it (M. Russo).

Abbreviations: BDNF, brain-derived neurotrophic factor; CDK5, cyclin-dependent kinase 5; CNS, central nervous system; DEX, dexamethasone; DG, dentate gyrus; DHEA, dehydroepiandrosterone; EP, estrogen and progesterone; GABA(A), gamma-aminobutyric acid receptor A; GnRH, gonadotropin-releasing hormone; GR, glucocorticoid receptors; HPA axis, hypothalamic–pituitary–adrenal axis; IVF, *in vitro* fertilization; PMS, premenstrual syndrome; PR, progesterone receptor; MPA, medroxyprogesterone acetate; MR, mineralocorticoid receptors; SNB, spinal nucleus of the bulbocavernosus; Trk, protein kinase receptors.

Contents

| | |
|--|-----|
| Introduction | 271 |
| Cortisol and BDNF | 272 |
| Estrogens and bdnf | 273 |
| In vitro studies | 273 |
| In vivo studies | 273 |
| Progesterone and BDNF | 274 |
| Testosterone and BDNF | 274 |
| Dehydroepiandrosterone (DHEA) and BDNF | 275 |
| Sex steroids and BDNF: findings from human studies | 275 |
| Female reproductive milestones and BDNF | 275 |
| Conclusion and prospective | 276 |
| References | 277 |

INTRODUCTION

Brain-derived neurotrophic factor (BDNF) is a 27-kDa polypeptide that belongs to the neurotrophin family binding with high-affinity protein kinase receptors (Trk) and the unselective p75NGFR receptor. The BDNF gene has a complex structure with multiple regulatory elements and four promoters that are differentially expressed in central or peripheral tissue (Tapia-Arancibia et al., 2004). It is well known to play an important role in the survival, differentiation, and outgrowth of select peripheral and central neurons during development and in adulthood (McAllister et al., 1999; Sohrabji and Lewis, 2006). BDNF has also been shown to play an important role in activity-dependent synaptic plasticity in the hippocampus (Kang and Schuman, 1995; Korte et al., 1995) where, as in the dentate gyrus (DG) (Messaoudi et al., 1998), it is known to produce a lasting potentiation of synaptic efficacy probably involving calcium-induced calcium release (CICR) (Balkowiec and Katz, 2002; Kramar et al., 2004). Moreover, BDNF enhances glutamatergic synaptic transmission in hippocampal cultures through a presynaptic mechanism (Li et al., 1998). It is possible that these effects may, in turn, enhance specific learning and memory processes and help reduce cognitive deficits associated with aging and neurodegenerative disease (Gibbs, 1999). In fact, recent findings show that cellular events involved in memory encoding initiate BDNF signaling through synaptic TrkB, thereby ensuring that learning will trigger neurotrophic support (Musumeci and Minichiello, 2011). BDNF expression in the central nervous system (CNS) is modified by various kinds of brain insult (stress, ischemia, seizure activity, hypoglycemia, etc.) (Lindvall et al., 1994) and alterations in its expression may contribute

to some pathologies such as depression, Alzheimer's, and Parkinson's disease (Connor et al., 1997; Parain et al., 1999; Karege et al., 2002).

Recent studies also suggest that BDNF is a biomarker of impaired memory and general cognitive function in aging women (Komulainen et al., 2008).

Several authors have attributed various problems in health and wellbeing to the impaired adaptation of individuals to their environment, as a consequence of a dysfunctional hypothalamic–pituitary–adrenal (HPA) axis (the major pathway for regulating stress responses) and its cortisol production (Corbett et al., 2009). On the other hand, it has been shown in some experimental studies that BDNF regulates the HPA response to stress (Angelucci et al., 2005; Duman and Monteggia, 2006). For instance, Franklin and Perrot-Sinal (2006) investigated the effects of stress and sex and gonadal hormones on BDNF protein levels in CA1, CA3, and DG subregions of the hippocampus showing that stress increased BDNF levels in EP (estrogen and progesterone)-treated rats but it decreased BDNF levels in vehicle-treated rats.

Estrogens, progestagens and androgens arriving from gonads through blood vessels are able to modulate several brain functions. Receptors for gonadal steroids have been identified in several brain areas: amygdala, hippocampus, cortex, basal forebrain, cerebellum, locus coeruleus, midbrain rafe nuclei, glial cells, pituitary gland, hypothalamus and central gray matter (Speroff et al., 1995; Alonso-Solis et al., 1996; Genazzani et al., 1996). The mechanism of action of sex steroids at this level is similar to the same observed in the peripheral target organs, including both genomic and non-genomic effects (Palumbo et al., 1995; Mong and McCarthy, 1999).

Experimental and clinical studies highlight interactions between estrogens and progestins in the neuroendocrine control of the brain functions and its clinical implications (Genazzani et al., 1997). Neurosteroids, such as allopregnanolone, are synthesized in the brain, either *de novo* from cholesterol also by astrocytes and oligodendrocytes or by the local metabolism of blood-borne precursors (Mellon, 1994). Neurosteroids exert non-classical rapid actions as allosteric agonists of gamma-aminobutyric acid receptor A (GABA(A)) and also modulate classic neurotransmitters in the brain (Palumbo et al., 1995). Physiological or pathological modifications of the synthesis and release of neurosteroids play a relevant role in the control of brain function (Wang et al., 1996; Sundström et al., 1999).

Estrogens, produced *de novo* from cholesterol in the brain (Genazzani et al., 1997), are crucial in determining central gender dimorphism, and an estrogen-induced synaptic plasticity is evident during puberty and seasonal changes as well as during the ovarian cycle (Mellon, 1994). Particularly, in the female hippocampus, density of spines and spine synapses varied with the estrus cycle. In addressing this *in vivo*–*in vitro* discrepancy, they showed how gonadotropin-releasing hormone (GnRH) regulated estradiol synthesis via an aromatase-mediated mechanism and consistently regulated spine synapse density and the expression of synaptic proteins. Along these lines, GnRH receptor

density was higher in the hippocampus than in the cortex and hypothalamus, and estrus cyclicity of spinogenesis was found in the hippocampus, but not in the cortex. Since GnRH receptor expression also varies with the estrus cycle, the sexual dimorphism in estrogen-regulated spine synapse density in the hippocampus very likely results from differences in the GnRH responsiveness of the male and the female hippocampus (Fester et al., 2012). Estrogens act on the CNS both through genomic mechanisms, modulating synthesis, release and metabolism of neurotransmitters, neuropeptides and neurosteroids, and through non-genomic mechanisms, influencing electrical excitability, synaptic function and morphological features (Wang et al., 1996). As a consequence, it has been demonstrated that estrogen's neuroactive effects protect against a wide range of neurotoxic insults (Sundström et al., 1999). Clinical evidence has revealed that, during the climacteric period, estrogen withdrawal leads to modifications in mood, behavior and cognition. Estrogen replacement therapy is able to improve mood and cognitive efficiency after menopause (Nelson and Bulun, 2001; Genazzani et al., 2007a,b).

Androgens play a pivotal neuroactive role during the “organizational/developmental” phase, mainly in the fetal–neonatal period, when they participate in the formation of neuronal circuits, as well as during the aging process when it has been proved to directly affect hippocampal spine synapse density, suggesting a physiopathological role for androgen in the modulation of cognitive function and the development of neurodegenerative disease (Genazzani et al., 2007a,b).

The fact that also ovarian steroids are involved in the regulation of the CNS processes, in particular mood, affective and cognitive functions, leads many scientists to study a possible correlation between BDNF and sex steroids, in both animals and humans.

CORTISOL AND BDNF

Cortisol is traditionally viewed as the most important stress hormone in humans (Sapolsky et al., 2000). In recent years cortisol has been shown to play a much broader role in human functioning (Erickson et al., 2003). Several authors have attributed various problems in health and wellbeing to impaired coping strategies of individuals to environment and/or to the consequence of a dysfunctional hypothalamic–pituitary–adrenal (HPA) axis—the major pathway for regulating stress responses—and its cortisol production (McEwen, 1998; Corbett et al., 2009). In animals, exposure to stress early in life (for example, repeated maternal separation) has been found to induce a relative decrease in the expression of BDNF and to subsequent neuronal atrophy and degeneration in the hippocampus and the cortex, which can persist into adulthood (Roceri et al., 2004; Murakami et al., 2005; Song et al., 2006).

Glucocorticoids are also involved in BDNF regulation (Barbany and Persson, 1992, 1993). A fairly recent study has shown that cortisol exerts a differential influence on BDNF regulation in the rat hippocampus as a function of

the specific receptor involved (glucocorticoid or mineralocorticoid receptors—GR or MR) (Hansson et al., 2000). Cyclin-dependent kinase 5 (CDK5) regulates GR- and MR-mediated transcriptional activity. Using cultured cortical neurons, Kino et al. (2010) showed that aldosterone, an MR agonist, increased BDNF mRNA, while DEX (dexamethasone), a GR agonist, reduced BDNF level. These authors found that both a CDK5 inhibitor and the knockdown of CDK5 suppressed the positive and negative effects of aldosterone and DEX, respectively, on BDNF expression, suggesting that CDK5 has a role in glucocorticoid-mediated BDNF expression in neurons (Hansson et al., 2000).

Additionally, *in vivo* analysis of phosphorylation alterations of GR after acute and/or chronic stress has been performed because the phosphorylation of GR affects the control of gene expression. Adzic et al. (2009) investigated hippocampal and cortical levels of GR phosphorylation using rats exposed to acute immobilization stress, chronic isolation stress, or a combination of these two stressors. Phosphorylated GR at serine 232 in hippocampal tissue was increased by acute and chronic stress, whereas cortical GR phosphorylation predominated in the case of chronic stress exposure. Furthermore, BDNF mRNA in hippocampal tissue was decreased after chronic stress, while cortical BDNF was upregulated by the same stress condition. Different regulatory systems may influence BDNF production in hippocampal or cortical regions under stressful conditions, although both brain regions are putatively correlated with depressive behavior (Adzic et al., 2009). In addition, exogenous stimuli, such as physical activity (Neeper et al., 1991) and light exposure (Castrén et al., 1992), can influence the expression of BDNF, particularly in the rat cortex and hippocampus (Bova et al., 1998) suggesting a pivotal role for this neurotrophin in homeostasis.

ESTROGENS AND BDNF

In vitro studies

As described above, estrogens have multiple functions in the brain. Some reports suggest the involvement of BDNF in modulating estrogen actions (Scharfman and MacLusky, 2006). Sohrabji et al. (1995), showed that estrogen could regulate the expression of BDNF *via* the estrogen response element on the *BDNF* gene. In dissociated hippocampal cultures, 17 β -E2 downregulates the expression of BDNF in GABAergic neurons to 40% of control within 24 h of exposure, and the downregulation returns to basal levels within 48 h (Murphy et al., 1998). Recently, it was reported that 17 β -E2 increases protein levels of BDNF in hippocampal slice cultures (Aguirre and Baudry, 2009). In contrast, another group reported that 17 β -E2 does not change the expression of BDNF in cultured hippocampal neurons (Sato et al., 2007). In hypothalamic slice cultures, levels of BDNF mRNA were not changed by either acute or chronic treatment of 17 β -E2 (Viant et al., 2000). In midbrain cultures, 17 β -E2 increased BDNF protein levels (Ivanova et al., 2001).

Remarkably, 17 β -E2 induces the release of BDNF in DG granule cells in hippocampal slice cultures, and 17 β -E2-dependent synaptogenesis was induced *via* the secreted BDNF (Sato et al., 2007). It has been demonstrated that sympathetic innervation of the rat uterus undergoes profound remodeling influenced by estrogen action (Zoubina et al., 2001). In particular terminal sympathetic axons degenerate when levels rise and regenerate when estrogen levels decline. Kriszan-Agbas and co-workers have examined the role of neurotrophins in estrogen-mediated uterine sympathetic nerve remodeling. For this purpose, they demonstrated how estrogen injection of ovariectomized female rats raised BDNF protein and mRNA in myometrium and endometrium. Myometrium from ovariectomized rats induced neuritogenesis in estrogen-free conditions, and this was abolished when BDNF was added to the medium. These findings suggest that neuritogenic properties of the rodent uterus are altered by regulating BDNF synthesis, which inhibits sympathetic neurite outgrowth (Kriszan-Agbas, 2003).

In vivo studies

It has been reported that 28 weeks after ovariectomy in rats, BDNF mRNA levels are significantly reduced in almost all hippocampal layers and the cortex (Singh et al., 1995). Estradiol replacement essentially reversed this effect in the hippocampus, suggesting a regional divergence in ovarian steroid requirements for BDNF expression. In addition, it has been reported that the levels of BDNF mRNA fluctuated significantly during the estrous cycle in CA1, CA3, and CA4 areas of the hippocampus. The highest levels were detected on the morning of diestrus 2, when progesterone levels are relatively low, and the lowest levels were detected on the afternoon of pro-estrus, when progesterone levels were highest (Gibbs, 1998). These authors also demonstrated that in ovariectomized rats, BDNF mRNA increased throughout the hippocampus in response to hormone replacement, particularly in response to the administration of estrogen plus progesterone. The increase in BDNF mRNA in the hippocampus occurred concomitantly to a decrease in BDNF protein in this region. In contrast, a similar combined treatment produces substantial increases in BDNF mRNA and protein in the piriform cortex (Lindvall et al., 1994). These data demonstrated how hormone replacement alters BDNF mRNA and protein levels in a region-specific manner. Estrogen treatment has also been reported to improve learning acquisition in a radial maze task and performance in a working memory task of ovariectomized rats (Daniel et al., 1997; O'Neal et al., 1996), suggesting that the protective effect of estrogens on cognitive functions linked to the hippocampus could be mediated by BDNF. In addition, it has been shown that the well-known stress-atrophy of apical dendrites of CA3 pyramidal neurons occurs in male but not female rats, thus highlighting the role of female sex hormones in the protection of brain against damage (Galea et al., 1997). Interestingly, prolonged (7 weeks) but not short-term estrogen deprivation prevented exercise induced

up-regulation of BDNF mRNA (Berchtold et al., 2001). Finally, it was recently reported that the estrogen receptor (ER) is colocalized with BDNF in pyramidal cells of the CA3 hippocampal layer, and to a lesser extent in CA1 (Solum and Handa, 2001). In addition, estrogen and neurotrophins share some signaling pathways (Singh et al., 1999), which could partially explain some of the trophic estrogen effects on neurite growth and differentiation.

PROGESTERONE AND BDNF

Several studies have shown the neuroprotective effect of progesterone in experimental models that mimic pathogenic aspects of brain dysfunction during the aging process. For instance, progesterone pre-treatment protected hippocampal neurons from toxicity associated with FeSO₄ and amyloid (Goodman et al., 1996). In addition, cerebral cortical explants and primary hippocampal neurons were protected from glutamate-induced cell death (Nilsen and Brinton, 2002; Kaur et al., 2007) although the clinically used progestin, medroxyprogesterone acetate (MPA), failed to protect hippocampal neurons against glutamate toxicity (Kaur et al., 2007). It is well known that progesterone also regulates BDNF expression. In fact recently, Aguirre and Baudry (2009), reported that, in hippocampal slice cultures, progesterone up-regulates BDNF proteins). In their research, long-term progesterone treatment following 17 β -E2 administration attenuates 17 β -E2-induced neuroprotection in hippocampal slice cultures. Moreover, Kaur et al. (2007) demonstrated that progesterone up-regulates both BDNF mRNA and protein levels in cerebral cortical explants. In contrast, two independent groups provided evidence that progesterone neuroprotection is not given through BDNF in rodents (Nilsen and Brinton, 2002; Jones et al., 2005). Jones et al. (2005) provides strong evidence that progesterone has neuroprotective properties in a mouse model of traumatic brain injury, but suggests that the steroid achieves this effect through mechanisms independent of the inflammatory response or growth factor up-regulation. On the other hand, recent findings suggest that progesterone enhancement of endogenous neuronal BDNF could provide a trophic environment within the lesioned spinal cord and might be part of the progesterone activated-pathways to provide neuroprotection (González et al., 2004).

However, in considering the neuroprotective effects of progesterone, one must also consider the possibility that the effects of progesterone may be mediated by its metabolite, allopregnanolone (3 α ,5 α -tetrahydroprogesterone or THP). Interestingly, allopregnanolone exerts complex acute actions in several corticolimbic structures following i.p. administration (Naert et al., 2007). In the hippocampus, the content of BDNF following an injection of allopregnanolone was first decreased after 30 min following the injection and significantly increased after 3 h. In the amygdala, BDNF content had increased after 15–60 min from allopregnanolone, returned to normal,

and increased again after 5 h. Finally, in the hypothalamus, BDNF levels had decreased (Naert et al., 2007). Collectively these studies suggest that part of the immediate or the long-term behavioral effects exerted by steroidogenic antidepressants may be explained by the effects of these drugs on allopregnanolone synthesis, which in turn may up-regulate BDNF content and expression in corticolimbic neurons.

Furthermore, because previously published data suggested that BDNF may be a relevant mediator of progesterone protective actions (González et al., 2004), Jodhka et al. (2009) determined whether progesterone and MPA, the most commonly used progestins in hormone therapy in the United States, differed in their ability to regulate BDNF. Their findings demonstrated that progesterone elicited an increase in both BDNF mRNA and protein levels, whereas MPA acetate did not. In addition, using both a pharmacological inhibitor of the progesterone receptor (PR) and PR knockout mice, they determined that effects of progesterone were mediated by the classical PR. Synthetic progestins used in clinical practice differ for receptor profile, metabolism and signal transduction. Thus, higher glucocorticoid activity of MPA with respect progesterone might explain the different effect on CNS BDNF level in comparison with natural progesterone, although this biological process has not been tested yet.

TESTOSTERONE AND BDNF

Androgens also exhibit a wide array of neuroprotective and neurotherapeutic effects in motoneurons, including supporting cell survival, axonal regeneration, and dendritic maintenance (Little et al., 2009). However, only few studies have evaluated the effect of testosterone on BDNF and its relation to gender difference. In motoneurons of the spinal nucleus of the bulbocavernosus (SNB), a sexually dimorphic and highly androgen-sensitive motor population in the lumbar spinal cord of rats, treatment with testosterone and BDNF has an interactive effect on the regulation of androgen receptor expression (Yang and Arnold, 2000) as well as dendritic length (Yang et al., 2004). Combined treatment with both testosterone and BDNF is more effective than treatment with either compound alone in the maintenance of androgen receptor immunoreactivity in axotomized SNB motoneurons (Yang and Arnold, 2000). On the other hand, testosterone administration was shown to increase BDNF protein levels in castrated male rats (Verhovshek et al., 2010). Another group also indicated that BDNF mediates the effects of testosterone on neuronal survival (Rasika et al., 1999). Gonadectomy in male rats induced a significant decrease in the protein levels of BDNF and PSD-95 in the CA1 area, which was prevented by testosterone replacement. Testosterone in adulthood prevented the differential response properties of spine maturation in sublayers of dendritic spines in the CA1 area via the actions of BDNF and PSD-95 (Brenowitz, 2012).

However, the degree of castration in female rats and the role of testosterone replacement on BDNF central modifications and the requirement of aromatase remain unexplored.

DEHYDROEPIANDROSTERONE (DHEA) AND BDNF

DHEA and its sulfate metabolite (DHEAS) are the major androgens secreted by the human adrenal gland. A decline in their production is the most characteristic age-related change in the adrenal cortex (Krysiak et al., 2008; Goel and Cappola, 2011). Recently a study was undertaken to know the possible neuroprotective role of DHEA against the development of Alzheimer's disease in an experimental rat model. Alzheimer's disease was produced in young female ovariectomized rats. Half of these animals also received oral DHEA (250 mg/kg body weight, three times weekly) for 18 weeks. Control groups of animals received either DHEA alone, or no DHEA, or were not ovariectomized. After such treatment the animals were analyzed for oxidative stress biomarkers such as hydrogen peroxide, nitric oxide and malondialdehyde, total antioxidant capacity, reduced glutathione, glutathione peroxidase, glutathione reductase, superoxide dismutase and catalase activities, antiapoptotic marker Bcl-2 and brain-derived neurotrophic factor. Significant depletion in brain Bcl-2 and brain-derived neurotrophic factor levels was also detected. Significant amelioration in all investigated parameters was detected as a result of treatment of Al-intoxicated ovariectomized rats with DHEA. These results clearly indicate a neuroprotective effect of DHEA against Alzheimer's disease (Aly et al., 2011).

DHEA administration causes a significant increase in serotonin levels (Svec and Porter, 1997) and there are findings showing the interactions between serotonin, BDNF, and DHEA (Martinowich and Lu, 2008). It seems that BDNF is a mediator of the DHEA activity in the brain tissue (Svec and Porter, 1997). BDNF promotes the survival and differentiation of serotonin neurons (Pinnock et al., 2009). On these bases several lines of evidence suggest that BDNF might be an important agent of therapeutic recovery from depression, and it might also provide protection against stress-induced neuronal damage (Nestler et al., 2002; Duman, 2002).

SEX STEROIDS AND BDNF: FINDINGS FROM HUMAN STUDIES

Although many studies have been undertaken to examine the presence of BDNF, it is also expressed and secreted from several tissues (e.g. endothelial cells, smooth muscle cells, the myometrium and the endometrium) (Donovan et al., 1995). BDNF is also present in the human plasma and, since platelets represent a major storage site of BDNF in peripheral blood, serum levels are higher than plasma levels (Lommatzsch et al., 2005). Therefore, platelets appear to be a unique BDNF transportation system in the human body (Fujimura et al., 2002). There is evidence that BDNF serum levels are closely related to BDNF concentrations in the

central nervous system (Karege et al., 2002). Intact BDNF in the peripheral circulation crosses the BBB by a high-capacity, saturable transport system (Pan et al., 1998; Karege et al., 2005). Irrespective of the yet unknown mechanism, there is also accumulating evidence that BDNF serum levels are affected by altered BDNF release or utilization in the central nervous system (Staats et al., 2005). As described above neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases, appear to be associated with decreased levels of BDNF in the brain (Connor et al., 1997; Parain et al., 1999), although low serum levels of BDNF are thought to characterize major depression (Karege et al., 2002), schizophrenia (Toyooka et al., 2002) and eating disorders, such as bulimia and anorexia nervosa (Nakazato et al., 2003; Monteleone et al., 2005). Decreased serum levels of BDNF in mothers before and after childbirth: this phenomenon might reflect an increased risk for the development of mood disorders in the perinatal period (Lommatzsch et al., 2006). It is well known that a number of affective disorders linked to impaired LHPA activity such as major depression, post-traumatic stress disorder (PTSD) and anorexia nervosa) are more commonly diagnosed in females than males (Kessler et al., 1993). There is an important gender difference in the rate of hormonal changes with aging: in menopausal women estradiol falls to nearly undetectable levels, whereas in healthy men testosterone production declines slowly (Janowsky, 2006). In addition, Komulainen et al. (2008) found that decreased plasma BDNF level is a biomarker of cognitive impairment in non-demented aging women, but not in men: this study is the first one describing the association between circulating BDNF level and cognitive function in the general population (The DR's EXTRA Study). It has been shown that plasma concentrations decrease significantly with age or weight gain, whereas platelet or serum levels do not seem to be altered (Lommatzsch et al., 2005). Growing evidence showed BDNF was essential for the oocyte maturation *in vitro* fertilization (IVF) (Seifer et al., 2002, 2006). Kawamura et al. (2005) had observed that BDNF enhanced the first polar body emission and promoted oocyte development into preimplantation embryos. Seifer et al. (2003) demonstrated the the presence of BDNF in human IVF, including normal cycle and IVF cycle, and found that BDNF played an important role in the progress of follicle formation and oocyte maturation. Modifications in platelet BDNF have been reported in women throughout the menstrual cycle (Lommatzsch, 2005): studies have shown higher levels during the luteal phase than in the follicular phase; moreover serum levels of BDNF are lower in women than in men, probably because count platelets are higher in men than in women (Lommatzsch, 2005).

Female reproductive milestones and BDNF

On this basis, Begliuomini et al. (2007) aimed to investigate if plasma BDNF varies according to women's hormonal status (menstrual cycle, amenorrhea and

menopause). Data show a close relationship between hormonal status and neurotrophic milieu. In fact, women with regular ovulatory cycles present higher BDNF levels when compared with amenorrheic or postmenopausal women suggesting a predominant role of sex steroid hormones in the regulation of neurotrophin expression. In addition a strong negative correlation was found between plasma BDNF levels and the number of years since menopause (Begliuomini et al., 2007). These findings could at least partially explain the increased incidence of neurodegenerative diseases (such as Alzheimer's and Parkinson's disease) after the menopause transition, supporting the hypothesis that BDNF may be considered a biomarker of general cognitive function in aging women (Komulainen et al., 2008). Furthermore, scientists observed that circulating changes in BDNF levels according to menstrual cycle phase demonstrate that the rate of fluctuations of BDNF and estradiol are similar: both are low at very first days of the cycle, then rise until day 14, reaching a peak just before ovulation, approximately just a few hours before the LH surge. These findings may confirm a role for BDNF in the complex mechanism that leads to ovulation, probably under the direct influence of E2. BDNF may be considered a valid marker of follicular maturation (Seifer et al., 2002, 2003, 2006). After this 'pre-ovulatory peak', both E2 and BDNF show a trend to decrease up to days 16–17 of the menstrual cycle. Concurrently, progesterone starts to increase, due to its secretion by the corpus luteum, under the influence of LH. During the mid-luteal phase, a new significant rise in plasma BDNF levels occurs (days 20–24). In postmenopausal women, hormonal replacement therapy is able to increase BDNF low menopausal levels nearly to those of the follicular phase (Begliuomini et al., 2007). High plasma BDNF levels observed in the luteal phase may be related, at least in part, to an ovarian synthesis. This source is likely the corpus luteum and, to a lesser extent, the secretive endometrium, since it has been reported that the rat endometrium expresses both BDNF protein and mRNA (Krizsan-Agbas et al., 2003). Indeed, the higher levels of BDNF observed in menstrual blood than in plasma and its identification in the human endometrium further support the role of this neurotrophin in female reproductive function evidencing that endometrium could be a possible source of this neurotrophin (Russo et al., 2012).

Furthermore, the close interplay between sex steroids, BDNF and mood has been detected in women with premenstrual syndrome (PMS) that showed lower luteal phase BDNF levels compared to normal women. (Cubeddu et al., 2011). PMS begins on corpus luteum formation and disappears with luteolysis. The role of a personal vulnerability to the brain effects of gonadal steroids is reinforced by the fact that symptoms are absent during non-ovulatory cycles, abolished by ovariectomy or treatment with ovulation inhibitors and reinstated by the administration of exogenous hormones. The lower luteal BDNF levels in PMS might be a consequence of an altered hormonal milieu and might play a role in the onset of mood symptoms.

Interestingly, paroxetine, a common SSRI used in PMS, increases BDNF (Cubeddu et al., 2010).

However, it is reasonable to suppose that changes in the plasma BDNF levels are not only endocrine based, but also influenced by other factors, such as neurotransmitters, sensorial stimuli. Indeed, recently it has been shown that plasma BDNF levels, as well as cortisol levels, are significantly higher in the morning when compared with the night, with a trend of constant decrease during the day. In addition, plasma BDNF and cortisol are positively correlated suggesting that these two factors may be physiologically co-regulated, in order to maintain the homeostasis of integrated cerebral activities (Begliuomini et al., 2008). It has been also demonstrated how BDNF plasma levels showed a diurnal rhythm in the follicular phase, although the diurnal rhythm was blunted in the luteal phase whereas in women undergoing oral contraceptives the trend was similar to that observed during the follicular phase of normal menstruating women. In postmenopausal women, BDNF and cortisol levels significantly decreased during the day. BDNF has a diurnal variation in women that is somewhat analogous to cortisol variation; however, the amplitude of the variation in BDNF levels appears to be influenced by ovarian function. Interactions between BDNF, the hypothalamus–pituitary–adrenal axis and sex steroids might play a critical role in the human homeostasis and adaptation. The fact that in women BDNF showed a diurnal rhythm in the follicular phase although the diurnal rhythm was blunted in the luteal phase confirming the hypothesis, also in this case, that high plasma BDNF levels observed during the luteal phase may be at least partly due to local production by the corpus luteum (Pluchino et al., 2009).

Although the function of BDNF in reproductive tissues remains largely unknown, the strict association between plasma level, endometrial level and gonadal steroids, supports additional roles of this neurotrophin on endometrial function and remodeling. Pregnancy is accompanied by a decrease in serum BDNF, and levels remain low after childbirth (Lommatzsch et al., 2006), although no data are available about its correlation with as post-partum depression.

CONCLUSION AND PROSPECTIVE

Sex steroid hormones and neurotrophic factors are involved in the development of the adolescent brain and have been implicated in the neuroendocrine control of reproduction as well as in brain adaptation during reproductive aging. Intriguing hypotheses have been also postulated for a BDNF role in the pathogenesis of reproductive depression disorders and neurodegenerative diseases. Relationship between sex hormones and cognitive function is complex and remains unclear. There is an important gender difference in the rate of hormonal changes with aging: in menopausal women estradiol falls to nearly undetectable levels, whereas in healthy men testosterone production declines slowly. Male and female brain BDNF changes in response to physiological or

pathological levels of circulating steroid hormones could help to explain some of the developmental sex differences in the pathogenesis of neurodevelopmental disorders.

The correlation between estrogens and BDNF levels, its identification in ovarian follicles and in the endometrium further supports additional functions of this neurotrophin outside the CNS while formulating a hypothesis for its role during embryo development and implantation. Knowledge of the interactions between BDNF, the hypothalamus–pituitary–adrenal axis and sex steroids is essential to improve the understanding of the biology of human homeostasis, adaptation and reproductive function.

REFERENCES

- Adzic M, Djordjevic J, Djordjevic A, Niciforovic A, Demonacos C, Radojic M, Krstic-Demonacos M (2009) Acute or chronic stress induce cell compartment-specific phosphorylation of glucocorticoid receptor and alter its transcriptional activity in Wistar rat brain. *J Endocrinol* 202:87–97.
- Aguirre CC, Baudry M (2009) Progesterone reverses 17beta-estradiol-mediated neuroprotection and BDNF induction in cultured hippocampal slices. *Eur J Neurosci* 29:447–454.
- Alonso-Solis R, Abreu P, López-Coviella I, Hernández G, Fajardo N, Hernández-Díaz F, Díaz-Cruz A, Hernández A (1996) Gonadal steroid modulation of neuroendocrine transduction: a transynaptic view. *Cell Mol Neurobiol* 3:357–382.
- Aly HF, Metwally FM, Ahmed HH (2011) Neuroprotective effects of dehydroepiandrosterone (DHEA) in rat model of Alzheimer's disease. *Acta Biochim Pol* 58:513–520.
- Angelucci F, Brene S, Mathe AA (2005) BDNF in schizophrenia, depression and corresponding animal models. *Mol Psychiatry* 10:345–352.
- Balkowiec A, Katz DM (2002) Cellular mechanisms regulating activity-dependent release of native brain-derived neurotrophic factor from hippocampal neurons. *J Neurosci* 22:10399–10407.
- Barbany G, Persson H (1993) Adrenalectomy attenuates kainic acid-elicited increases of messenger RNAs for neurotrophins and their receptors in the rat brain. *Neurosci* 54:909–922.
- Barbany G, Persson H (1992) Regulation of neurotrophin mRNA expression in rat brain by glucocorticoid. *Eur J Neurosci* 4:396–403.
- Begliomini S, Casarosa E, Pluchino N, Lenzi E, Centofanti M, Freschi L, Pieri M, Genazzani AD, Luisi S, Genazzani AR (2007) Influence of endogenous and exogenous sex hormones on plasma brain-derived neurotrophic factor. *Hum Reprod* 22:995–1002.
- Begliomini S, Lenzi E, Ninni F, Casarosa E, Merlini S, Pluchino N, Valentino V, Luisi S, Luisi M, Genazzani AR (2008) Plasma brain-derived neurotrophic factor daily variations in men: correlation with cortisol circadian rhythm. *J Endocrinol* 197:429–435.
- Berchtold NC, Kessler JP, Pike CJ, Adlard PA, Cotman CW (2001) Estrogen and exercise interact to regulate brain-derived neurotrophic factor mRNA and protein expression in the hippocampus. *Eur J Neurosci* 14:1992–2002.
- Bova R, Micheli MR, Quadralucci P, Zucconi GG (1998) BDNF and trkB mRNA oscillate in the rat brain during the light–dark cycle. *Mol Brain Res* 57:321–324.
- Brenowitz EA (2012) Testosterone has sublayer-specific effects on dendritic spine maturation mediated by BDNF and PSD-95 in pyramidal neurons in the hippocampus CA1 area. *Neuroscience*.
- Castrén E, Zafra H, Thoenen H, Lindholm D (1992) Light regulates expression of brain-derived neurotrophic factor mRNA in rat visual cortex. *PNAS* 89:9444–9448.
- Connor B, Young D, Yan Q, Faull RL, Synek B, Dragunow M (1997) Brain-derived neurotrophic factor is reduced in Alzheimer's disease. *Brain Res Mol Brain Res* 49:71–81.
- Corbett BA, Schupp CW, Levine S, Mendoza S (2009) Comparing cortisol, stress, and sensory sensitivity in children with autism. *Autism Res* 2:39–49.
- Cubeddu A, Bucci F, Giannini A, Russo M, Daino D, Russo N, Merlini S, Pluchino N, Valentino V, Casarosa E, Luisi S, Genazzani AR (2011) Brain-derived neurotrophic factor plasma variation during the different phases of the menstrual cycle in women with premenstrual syndrome. *Psychoneuroendocrinology* 36:523–530.
- Cubeddu A, Giannini A, Bucci F, Merlini S, Casarosa E, Pluchino N, Luisi S, Luisi M, Genazzani AR (2010) Paroxetine increases brain-derived neurotrophic factor in menopausal women. *Menopause* 17:338–343.
- Daniel JM, Fader AJ, Spencer AL, Dohanich GP (1997) Estrogen enhances performance of female rats during acquisition of a radial arm maze. *Horm Behav* 32:217–225.
- Donovan MJ, Miranda RC, Kraemer R, McCaffrey TA, Tessarollo L, Mahadeo D, Sharif S, Kaplan DR, Tsoulfas P, Parada L, et al (1995) Neurotrophin and neurotrophin receptors in vascular smooth muscle cells. Regulation of expression in response to injury. *Am J Pathol* 147:309–324.
- Duman RS (2002) Synaptic plasticity and mood disorders. *Mol Psychiatry* 7:29–34.
- Duman RS, Monteggia LM (2006) A neurotrophic model for stress related mood disorders. *Biol. Psychiatry* 59:1116–1127.
- Erickson K, Drevets W, Schulkin J (2003) Glucocorticoid regulation of diverse cognitive functions in normal and pathological emotional states. *Neurosci Biobehav Rev* 27:233–246.
- Fester L, Prange-Kiel J, Zhou L, Blittersdorf B, Bohm J, Jarry H, Schumacher M, Rune GM (2012) Estrogen-regulated synaptogenesis in the hippocampus: sexual dimorphism in vivo but not in vitro. *J Steroid Biochem Mol Biol* 131:24–29.
- Franklin TB, Perrot-Sinal TS (2006) Sex and ovarian steroids modulate brain-derived neurotrophic factor (BDNF) protein levels in rat hippocampus under stressful and non-stressful conditions. *Psychoneuroendocrinology* 31:38–48.
- Fujimura H, Altar CA, Chen R, Nakamura T, Nakahashi T, Kambayashi J, Sun B, Tandon NN (2002) Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation. *Thromb Haemost* 87:728–734.
- Galea LA, McEwen BS, Tanapat P, Deak T, Spencer RL, Dhabharv FS (1997) Sex differences in dendritic atrophy of CA3 pyramidal neurons in response to chronic restraint stress. *Neuroscience* 81:689–697.
- Genazzani AR, Lucchesi A, Stomati M, Catarsi S, Genazzani AD, Criscuolo M, Petraglia F (1997) Effects of sex steroid hormones on the neuroendocrine system. *Eur J Contracept Reprod Health Care* 2:63–69.
- Genazzani AR, Petraglia F, Purdy RH (1996) *The Brain: Source and Target for Sex Steroid Hormones*. Camforth, UK: Parthenon Publishing Group.
- Genazzani AR, Pluchino N, Freschi L, Ninni F, Luisi M (2007a) Androgens and the brain. *Maturitas* 57:27–30.
- Genazzani AR, Pluchino N, Luisi S, Luisi M (2007b) Estrogen, cognition and female ageing. *Hum Reprod Update* 2:175–187.
- Gibbs RB (1998) Levels of trkA and BDNF mRNA, but not NGF mRNA, fluctuate across the estrous cycle and increase in response to acute hormone replacement. *Brain Res* 787:259–268.
- Gibbs RB (1999) Treatment with estrogen and progesterone affects relative levels of brain-derived neurotrophic factor mRNA and protein in different regions of the adult rat brain. *Brain Res* 844:20–27.
- Goel RM, Cappola AR (2011) Dehydroepiandrosterone sulfate and postmenopausal women. *Curr Opin Endocrinol Diabetes* 18:171–176.
- González SL, Labombarda F, González Deniselle MC, Guennoun R, Schumacher M, De Nicola AF (2004) Progesterone up-regulates

- neuronal brain-derived neurotrophic factor expression in the injured spinal cord. *Neuroscience* 125:605–614.
- Goodman Y, Bruce AJ, Cheng B, Mattson MP (1996) Estrogens attenuate and corticosterone exacerbates excitotoxicity, oxidative injury, and amyloid-peptide toxicity in hippocampal neurons. *J Neurochem* 66:1836–1844.
- Hansson AC, Cintra A, Belluardo N, Sommer W, Bhatnagar M, Badre M, Ganten D, Fuxe K (2000) Gluco- and mineralcorticoid receptor-mediated regulation of neurotrophic factor gene expression in the dorsal hippocampus and the neocortex of the rat. *Eur J Neurosci* 12:2918–2934.
- Ivanova T, Küppers E, Engele J, Beyer C (2001) Estrogen stimulates brain-derived neurotrophic factor expression in embryonic mouse midbrain neurons through a membrane-mediated and calcium-dependent mechanism. *J Neurosci Res* 66:221–230.
- Janowsky JS (2006) The role of androgens in cognition and brain aging in men. *Neuroscience* 138:1015–1020.
- Jodhka PK, Kaur P, Underwood W, Lydon JP, Singh M (2009) The differences in neuroprotective efficacy of progesterone and medroxyprogesterone acetate correlate with their effects on brain-derived neurotrophic factor expression. *Endocrinology* 150:3162–3168.
- Jones NC, Constantin D, Prior MJ, Morris PG, Marsden CA, Murphy S (2005) The neuroprotective effect of progesterone after traumatic brain injury in male mice is independent of both the inflammatory response and growth factor expression. *Eur J Neurosci* 21:1547–1554.
- Kang H, Schuman EM (1995) Long-lasting neurotrophin-induced enhancement of synaptic transmission in the adult hippocampus. *Science* 267:1658–1662.
- Karege F, Bondolfi G, Gervasoni N, Schwald M, Aubry JM, Bertschy G (2005). *Biol Psychiatry* 57:1068–1072.
- Karege F, Perret G, Bondolfi G, Schwald M, Bertschy G, Aubry JM (2002) Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychiatry Res* 109:143–148.
- Kaur P, Jodhka PK, Underwood WA, Bowles CA, de Fiebre NC, de Fiebre CM, Singh M (2007) Progesterone increases brain-derived neurotrophic factor expression and protects against glutamate toxicity in a mitogen-activated protein kinase- and phosphoinositide-3 kinase-dependent manner in cerebral cortical explants. *J Neurosci Res* 85:2441–2449.
- Kawamura K, Kawamura N, Mulders SM, Sollewijn GMD, Hsueh AJ (2005) Ovarian brain-derived neurotrophic factor (BDNF) promotes the development of oocytes into preimplantation embryos. *Proc Natl Acad Sci U S A* 102:206–211.
- Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB (1993) Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. *J Affect Disord* 29:85–96.
- Kino T, Jaffe H, Amin ND, Chakrabarti H, Zheng Y, Chrousos GP, Pant HC (2010) Cyclin-dependent kinase 5 modulates the transcriptional activity of the mineralocorticoid receptor and regulates expression of brain-derived neurotrophic factor. *Mol Endocrinol* 24:941–952.
- Komulainen P, Pedersen M, Hänninen T, Bruunsgaard H, Lakka TA, Kivipelto M, Hassinen M, Rauramaa TH, Pedersen BK, Rauramaa R (2008) BDNF is a novel marker of cognitive function in ageing women: the DR's EXTRA Study. *Neurobiol Learn Mem* 90:596–603.
- Korte M, Carroll P, Wolf E, Brem G, Thoenen H, Bonhoeffer T (1995) Hippocampal long-term potentiation is impaired in mice lacking brain-derived neurotrophic factor. *Proc Natl Acad Sci U S A* 92:8856–8860.
- Kramer EA, Lin B, Lin CY, Arai AC, Gall CM, Lynch G (2004) A novel mechanism for the facilitation of theta-induced long-term potentiation by brain-derived neurotrophic factor. *J Neurosci* 24:5151–5161.
- Krizsan-Agbas D, Pedchenko T, Hasan W, Smith PG (2003) Oestrogen regulates sympathetic neurite outgrowth by modulating brain-derived neurotrophic factor synthesis and release by the rodent uterus. *Eur J Neurosci* 18:2760–2768.
- Krysiak R, Frysz-Naglak D, Okopie B (2008) Current views on the role of dehydroepiandrosterone in physiology, pathology and therapy. *Pol Merkur Lekarski* 24:66–71.
- Li YX, Zhang YO, Lester HA, Schuman EM, Davidson N (1998) Enhancement of neurotransmitter release induced by brain-derived neurotrophic factor in cultured hippocampal neurons. *J Neurosci* 18:10231–10240.
- Lindvall O, Kokaia Z, Bengzon J, Elmer E, Kokaia M (1994) Neurotrophins and brain insults. *Trends Neurosci* 17:490–496.
- Little CM, Coons KD, Sengelaub DR (2009) Neuroprotective effects of testosterone on the morphology and function of somatic motoneurons following the death of neighboring motoneurons. *J Comp Neurol* 20:359–372.
- Lommatzsch M, Hornych K, Zingler C, Schuff-Werner P, Hoppner J, Virchow JC (2006) Maternal serum concentrations of BDNF and depression in the perinatal period. *Psychoneuroendocrinology* 31:388–394.
- Lommatzsch M, Zingler D, Schuhbaeck K, Schloetcke K, Zingler C, Schuff-Werner P, Virchow JC (2005) The impact of age, weight and gender on BDNF levels in human platelets and plasma. *Neurobiol Aging* 26:115–123.
- Martinowich K, Lu B (2008) Interaction between BDNF and serotonin: role in mood disorders. *Neuropsychopharmacology* 33:73–83.
- McAllister AK, Katz LC, Lo DC (1999) Neurotrophins and synaptic plasticity. *Annu Rev Neurosci* 22:295–318.
- McEwen B (1998) Stress, adaptation, and disease: allostasis and allostatic load. *Ann N Y Acad Sci* 840:33–44.
- Mellon SH (1994) Neurosteroids: biochemistry, modes of action and clinical relevance. *J Clin Endocrinol Metab* 78:1003–1008.
- Messaoudi E, Baresen K, Srebo B, Bramham CR (1998) Acute intrahippocampal infusion of BDNF induces lasting potentiation of synaptic transmission in the rat dentate gyrus. *J Neurophysiol* 79:496–499.
- Mong JA, McCarthy MM (1999) Steroid-induced developmental plasticity in hypothalamic astrocytes: implications for synaptic patterning. *J Neurobiol* 40:602–619.
- Monteleone P, Fabrazzo M, Martiadis V, Serritella C, Pannuto M, Maj M (2005) Circulating brain-derived neurotrophic factor is decreased in women with anorexia and bulimia nervosa but not in women with binge-eating disorder: relationships to co-morbid depression, psychopathology and hormonal variables. *Psychol Med* 35:897–905.
- Murakami S, Imbe H, Morikawa Y, Kubo C, Senba E (2005) Chronic stress, as well as acute stress, reduces BDNF mRNA expression in the rat hippocampus but less robustly. *Neurosci Res* 53:129–139.
- Murphy DD, Cole NB, Segal M (1998) Brain-derived neurotrophic factor mediates estradiol-induced dendritic spine formation in hippocampal neurons. *Proc Natl Acad Sci U S A* 95:11412–11417.
- Musumeci G, Minichiello L (2011) BDNF Trk-B signalling in fear learning: from genetics to neural networks. *Rev Neurosci* 22:303–315.
- Naert G, Maurice T, Tapia-Arancibia L, Givalois L (2007) Neuroactive steroids modulate HPA axis activity and cerebral brain-derived neurotrophic factor (BDNF) protein levels in adult male rats. *Psychoneuroendocrinology* 32:1062–1078.
- Nakazato M, Hashimoto K, Shimizu E, Kumakiri C, Koizumi H, Okamura N, Mitsumori M, Komatsu N, Iyo M (2003) Decreased levels of serum brain-derived neurotrophic factor in female patients with eating disorders. *Biol Psychiatry* 54:485–490.
- Neeper SA, Gonez-Pinhilla F, Choi J, Cotman CW (1991) Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. *Mol Cell Biol* 11:143–153.
- Nelson LR, Bulun SE (2001) Estrogen production and action. *J Am Acad Dermatol* 45:116–124.
- Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM (2002) Neurobiology of depression. *Neuron* 34:13–25.
- Nilsen J, Brinton RD (2002) Impact of progestins on estrogen-induced neuroprotection: synergy by progesterone and 19-

- norprogesterone and antagonism by medroxyprogesterone acetate. *Endocrinology* 143:205–212.
- O'Neal MF, Means LW, Poole MC, Hamm RJ (1996) Estrogen affects performance of ovariectomized rats in a two-choice waterscape working memory task. *Psychoneuroendocrinology* 21:51–65.
- Palumbo MA, Salvestroni C, Gallo R, Guo AL, Genazzani AD, Artini PG, Petraglia F, Genazzani AR (1995) Allopregnanolone concentration in hippocampus of prepubertal rats and female rats throughout estrous cycle. *J Endocrinol Invest* 18:853–856.
- Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ (1998) Transport of brain-derived neurotrophic factor across the blood–brain barrier. *Neuropharmacology* 37:1553–1561.
- Parain K, Murer MG, Yan Q, Fauchoux B, Agid Y, Hirsch E, Raisman-Vozari R (1999) Reduced expression of brain-derived neurotrophic factor protein in Parkinson's disease substantia nigra. *Neuroreport* 10:557–561.
- Pinnock SB, Lazic SE, Wong HT, Wong IHW, Herbert J (2009) Synergistic effects of dehydroepiandrosterone and fluoxetine on proliferation of progenitor cells in the dentate gyrus of the adult male rat. *Neuroscience* 158:1644–1651.
- Pluchino N, Cubeddu A, Begliuomini S, Merlini S, Giannini A, Bucci F, Casarosa E, Luisi M, Cela V, Genazzani AR (2009) Daily variation of brain-derived neurotrophic factor and cortisol in women with normal menstrual cycles, undergoing oral contraception and in postmenopause. *Hum Reprod* 9:2303–2309.
- Rasika S, Alvarez-Buylla A, Nottebohm F (1999) BDNF mediates the effects of testosterone on the survival of new neurons in an adult brain. *Neuron* 22:53–62.
- Roceri M, Cirulli F, Pessina C, Peretto P, Racagni G, Riva MA (2004) Postnatal repeated maternal deprivation produces age-dependent changes of brain-derived neurotrophic factor expression in selected rat brain regions. *Biol Psychiatry* 55:708–714.
- Russo N, Russo M, Daino D, Freschi L, Fiore L, Merlini S, Bucci F, Santoro AN, Pluchino N, Luisi S, Genazzani AR (2012) Evaluation of brain-derived neurotrophic factor in menstrual blood and its identification in human endometrium. *Gynecol Endocrinol* 28:492–495.
- Sapolsky RM, Romero LM, Munck AU (2000) How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr Rev* 21:55–89.
- Sato K, Akaiishi T, Matsuki N, Ohno Y, Nakazawa K (2007) Beta-Estradiol induces synaptogenesis in the hippocampus by enhancing brain-derived neurotrophic factor release from dentate gyrus granule cells. *Brain Res* 1150:108–120.
- Scharfman HE, MacLusky NJ (2006) Estrogen and brain-derived neurotrophic factor (BDNF) in hippocampus: complexity of steroid hormone-growth factor interactions in the adult CNS. *Front Neuroendocrinol* 27:415–435.
- Seifer DB, Feng B, Shelden RM, Chen S, Dreyfus CF (2002) Brain-derived neurotrophic factor: a novel human ovarian follicular protein. *J Clin Endocrinol Metab* 87:655–659.
- Seifer DB, Feng B, Shelden RM (2006) Immunocytochemical evidence for the presence and location of the neurotrophin-Trk receptor family in adult human preovulatory ovarian follicles. *Am J Obstet Gynecol* 194:1129–1134.
- Seifer DB, Lambert-Messerlian G, Schneyer AL (2003) Ovarian brain derived neurotrophic factor is present in follicular fluid from normally cycling women. *Fertil Steril* 79:451–452.
- Singh M, Meyer EM, Simpkins JW (1995) The effect of ovariectomy and estradiol replacement on brain-derived neurotrophic factor messenger ribonucleic acid expression in cortical and hippocampal brain regions of female Sprague–Dawley rats. *Endocrinology* 136:2320–2324.
- Singh M, Setalo G, Guan XP, Warren M, Toran-Allerand CD (1999) Estrogen-induced activation of mitogen-activated protein kinase in cerebral cortical explants: convergence of estrogen and neurotrophin signaling pathways. *J Neurosci* 19:1179–1188.
- Sohrabji F, Lewis DK (2006) Estrogen–BDNF interactions: implications for neurodegenerative diseases. *Front Neuroendocrinol* 27:404–414.
- Sohrabji F, Miranda RC, Toran-Allerand CD (1995) Identification of a putative estrogen response element in the gene encoding brain-derived neurotrophic factor. *Proc Natl Acad Sci U S A* 92:11110–11114.
- Solum DT, Handa RJ (2001) Localization of estrogen receptor alpha (ER alpha) in pyramidal neurons of the developing rat hippocampus. *Dev Brain Res* 128:165–175.
- Song L, Che W, Min-Wei W, Murakami Y, Matsumoto K (2006) Impairment of the spatial learning and memory induced by learned helplessness and chronic mild stress. *Pharmacol Biochem Behav* 83:186–193.
- Speroff L, Glass RH, Kase NH (1995) *Clinical Gynecological Endocrinology and Infertility*. fifth ed. Baltimore, Maryland, USA: Williams and Wilkins.
- Staats R, Stoll P, Zingler D, Virchow JC, Lommatzsch M (2005) Regulation of brain-derived neurotrophic factor (BDNF) during sleep apnoea. *Thorax* 60:688–692.
- Sundström I, Bäckström T, Wang M, Olsson T, Seippel L, Bixo M (1999) Premenstrual syndrome, neuroactive steroids and brain. *Gynecol Endocrinol* 13:206–220.
- Svec F, Porter J (1997) The effect of dehydroepiandrosterone (DHEA) on Zucker rat food selection and hypothalamic neurotransmitters. *Psychoneuroendocrinology* 22:57–62.
- Tapia-Arancibia L, Rage F, Givalois L, Arancibia S (2004) Physiology of BDNF: focus on hypothalamic function. *Front Neuroendocrinol* 25:77–107.
- Toyooka K, Asama K, Watanabe Y, Muratake T, Takahashi M, Someya T, Nawa H (2002) Decreased levels of brain-derived neurotrophic factor in serum of chronic schizophrenic patients. *Psychiatry Res* 110:249–257.
- Verhovshek T, Cai Y, Osborne MC, Sengelaub DR (2010) Androgen regulates brain-derived neurotrophic factor in spinal motoneurons and their target musculature. *Endocrinology* 151:253–261.
- Viant MR, Millam JR, Delany ME, Fry DM (2000) Regulation of brain-derived neurotrophic factor messenger RNA levels in avian hypothalamic slice cultures. *Neuroscience* 99:373–380.
- Wang M, Seippel L, Purdy RH, Backstrom T (1996) Relationship between symptom severity and steroid variation in women with premenstrual syndrome: study on serum pregnenolone, pregnenolone sulfate, 5 alpha-pregnane-3,20-dione and 3 alpha-hydroxy-5 alpha-pregnan-20-one. *J Clin Endocrinol Metab* 81:1076–1082.
- Yang LY, Arnold AP (2000) BDNF regulation of androgen receptor expression in axotomized SNB motoneurons of adult male rats. *Brain Res* 3:127–139.
- Yang LY, Verhovshek T, Sengelaub DR (2004) Brain-derived neurotrophic factor and androgen interact in the maintenance of dendritic morphology in a sexually dimorphic rat spinal nucleus. *Endocrinology* 145:161–168.
- Zoubina EV, Mize AL, Alper RH, Smith PG (2001) Acute and chronic estrogen supplementation decreases uterine sympathetic innervation in ovariectomized adult virgin rats. *Histol Histopathol* 16:989–996.