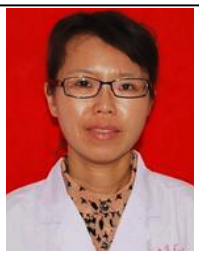
Send Orders for Reprints to reprints@benthamscience.ae

524 *Current Neuropharmacology,* **2015**, *13*, **524-535**

The Antidepressant-like Effects of Estrogen-mediated Ghrelin

Pu Wang[a], Changhong Liu[a], Lei Liu[a], Xingyi Zhang[b], Bingzhong Ren[a,*] and Bingjin Li[a,b,*]

[a]*Life Sciences institute, Northeast Normal University, Changchun, China 130024;* [b]*Jilin provincial key laboratory on molecular and chemical genetic, Second hospital of Jilin University, Changchun 130024, China*



B. Li

Abstract: Ghrelin, one of the brain-gut peptides, stimulates food-intake. Recently, ghrelin has also shown to play an important role in depression treatment. However, the mechanism of ghrelin's antidepressant-like actions is unknown. On the other hand, sex differences in depression, and the fluctuation of estrogens secretion have been proved to play a key role in depression. It has been reported that women have higher level of ghrelin expression, and ghrelin can stimulate estrogen secretion while estrogen acts as a positive feedback mechanism to up-regulate ghrelin level. Ghrelin may be a potential regulator of reproductive function, and estrogen may have additional effect in ghrelin's antidepressant-like actions. In this review, we summarize antidepressant-like effects of ghrelin and estrogen in basic and clinical studies, and provide new insight on ghrelin's effect in depression.

Keyword: Depression, estrogen, ghrelin, mechanism.

1. INTRODUCTION

Depression is a commonly-occurring, life-threatening, and debilitating psychiatric disorder, with the main symptom being feeling low incessantly. The patients suffering from depression will feel sad, anxious, hopeless or restless, and may lose interest in activities which were pleasurable before; develop anorexia or overeat and have problems to concentrate or remember details. Following such negative mood and behaviours, some people with severe depression often choose suicide or other extreme behaviours [1-5]. Depression has been reported to be associated with severe medical disorders, such as cardiovascular disorders, Alzheimer's Disease and cancer [2].

Although antidepressant drug development has made huge progress, due to the various pathogenic factors involved in depression, many of the drugs fail to get remarkable effects and many patients are resistant to the treatment. Therefore, it is necessary to find new antidepressants. It has been reported that there are sex differences in depression. Women are more vulnerable to depressive disorders, compared with men, showing approximately a 2:1 ratio [7, 8]. The gender differences in depression may relate to the differences in facing pressure, but most convincingly, the frequent occurrence of depression in women is affected by hormonal changes, e.g. estrogens and progestogens [6]. "Estrogens" are a group of sex steroid hormones, mainly produced by the ovaries and the placenta; adrenal cortex also produces a handful of estrogens. They are produced naturally in women's bodies in three shapes, estrone (e1), 17b-estradiol (e2), estriol (e3) [9], of which estradiol has more bioactivity under normal conditions [10]. Estrogens are known as important hormonal signals, but their effects are not limited. Clinical and rodent studies have shown that estrogens have profound and diverse effects on the brain, including modulation of neuronal proliferation, survival and plasticity and have effects on CNS through the neurotrophic and neuroprotective actions on central parts of the brain such as hippocampus, cortex, amygdala, and basal forebrain [11-13]. The effects are related to mood and cognition, so that the change of estrogen levels may be implicated with depressive behaviours and the treatment of estrogen may be a target for depression.

Ghrelin, which was identified for the first time in the rat stomach in 1999, is a novel peptide of 28 amino acids. It can be mainly synthesized in stomach and other places like small intestine, pancreas, lung, kidney, and ovaries. Some reports proved that ghrelin can be expressed in the hypothalamus or some other places in the brain [14-19]. Ghrelin is the endogenous ligand of the growth hormone secretagogue receptor 1a (GHS-R1a), which is expressed in agouti-related peptide/neuropeptide Y (AgRP/NPY) neurons in the arcuate nucleus of the hypothalamus [1]. The main known function of ghrelin is to increase pituitary release of growth hormone (GH), from anterior pituitary cells [17]. And several studies have indicated that the effect of ghrelin is *via* both direct and indirect pathways, including the vagal afferent nerve. In addition, the administration of ghrelin stimulates food intake, carbohydrate utilisation and an increase in the body weight, suggesting a role for ghrelin in energy balance. Nowadays, many references have been reported that ghrelin also has regulatory functions such as learning, memory, reward, motivation and neuroprotection, which have different levels of destruction when suffering from depression [18, 19]. So, it is not difficult to speculate that ghrelin may play a key role in depression.

What is the curative effect of estrogen or ghrelin treatment in depression, and what are the mechanisms of

*Address correspondence to these authors at the Life Sciences institute, Northeast Normal University, Changchun, China 130024; Tel: 0086-431-88796493; Fax: 0086-431-88796493; E-mails: bingjinli@hotmail.com or renbz279@nenu.edu.cn

1570-159X/15 $58.00+.00

their antidepressant-like actions? In this review, we will provide a summary of recent reports and try to find the link between ghrelin and estrogen for depression.

2. GHRELIN

2.1. The Link between Central Ghrelin, Food Intake and Depression?

Ghrelin is bound with ghrelin receptor named by GH secretagogue receptor (GHS-R), and produces physiological function. GHS-R has two isoformes, Ia and Ib [16]. GHS-R Ia has more pharmacological function compared with Ib. GHS-R1a is highly concentrated in hypothalamus, for the regulation of eating behaviors. However, hypothalamus is not the only place to express ghrelin receptors [20, 21], many studies have showed that GHSR1a is significantly expressed within the other regions of CNS [22], such as hippocampus, amygdala and dorsal raphe nucleus (DRN) [23]. The abundant expression shows that ghrelin receptors are involved in the numerous biological functions, which are extra-hypothalamic [18, 19]. The distribution of ghrelin and its receptors agrees with the surveys for depression and eating disorders.

Ghrelin is linked with the behaviours of food intake. It has been reported that microinjection of ghrelin in the hippocampus and DRN increased rat feeding behaviors in a dose-dependent manner [24] and intracerebral administration of ghrelin also increased food intake both in mice and rats [25, 26]. Nakazato *et al*., 2001 [26] reported that ICV administration of ghrelin increased food intake in GH deficient mice, suggesting that ghrelin increased food intake in GH independent manner. These results indicated that ghrelin plays an important role in central regulation of the feeding.

In clinical studies, two eating disorders are characterised by abnormal patterns of weight regulation and eating behaviors [27], named anorexia nervosa (AN) and bulimia nervosa (BN) [27]. AN leads to more deaths than any other psychiatric disorders, which is characterised by loss of body weight, obsessive thoughts of food, self-starvation, and disturbed body image [28]. AN patients have shown a high level of ghrelin [29], which is paradoxical to the characters of AN, some researchers suggested that ghrelin's high levels in AN patients may be an organism trying to stimulate appetite during calorie restriction [30]. On the contrary, patients with BN eat too much food. Patients with BN have been reported to have decreased levels of ghrelin [31, 32]. These evidences have proven that ghrelin plays a key role in the pathopoiesia and treatment of eating disorders.

There is a correlation between food intake behaviors and depression. Different types of stresses have different response to food intake; melancholic is associated with hypercortisolism, anorexia and weight loss, while atypical depression is associated with high anxiety, carbohydrate craving and weight gain [18, 33]. Therefore, it is reasonable to assume that ghrelin may play a role in depression.

2.2. Antidepressant-like effect of Ghrelin

To prove the antidepressant-like effects of ghrelin, strong evidences have been found in both rodents and humans. Ghrelin plasma levels were obviously increased 4 fold after restricting food intake of mice [23], the increase in ghrelin levels were also observed after fasting [36]. We can use calorie-restricted mice as the models to simulate the increase of ghrelin. It has been reported that calorie-restricted mice spent less immobile time in forced swimming test (FST), and showed more time in the open arm of the elevated plus maze test (EPM) [18]. However, these antidepressant-like effects did not occur in the genetic blockade of ghrelin signalling in GHSR 1a knockout (Ghsr1a-/-) mice with the same calorie restriction. The antidepressant-like effects were also produced by subcutaneous ghrelin injection. C57BL6/J mice with subcutaneous ghrelin injection showed significantly less depression-like behaviors in the EPM and FST [37], and GHSR knockout mice had more depressive-like behaviors. In addition, acute ghrelin reverses depression-like behaviors induced by bilateral olfactory bulbectomy in mice [38] and serotonin transporter (SRET), delta opioid receptor, and interleukin 1 beta *et al*., could be involved in the antidepressant-like effects of ghrelin.

In clinical studies, patients with major depression (MDD) have lower plasma ghrelin levels, and the antidepressant effects have been reported following ghrelin administration [31]. The evidence both in rodents and humans showed that when ghrelin levels upgrade, symptoms of depression can be alleviated, and because ghrelin levels can be increased both in endogenous and injection, it is more meaningful to study ghrelin's antidepressant-like effects.

2.3. The mechanisms of Ghrelin's Antidepressant-like Action

Ghrelin, as a new endogenous antidepressant, must have its benefits, the mechanisms of ghrelin's antidepressant-like action have become the most interested topics for researchers. Basic and clinical studies have provided evidence that the serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine (NE) neurotransmitter systems [39] are involved in the pathology and/or behavioral manifestations associated with depression, which are called the monoamine hypothesis. Moreover, depression has been associated with alterations of growth factors, particularly brain-derived neurotrophic factor (BDNF), and the related signalling factors associated with the BDNF signalling molecules, for instance cAMP, CREB [40]. Recently, studies demonstrated that ghrelin may play a major role in hippocampal neurogenesis in the treatment of depression [41]. In this review, we will discuss the mechanisms of ghrelin's antidepressant-like action through the hypotheses which are related to depression.

2.3.1. Ghrelin and Monoamine Hypothesis

The abnormal function of central serotonergic system is an important hypothesis for the mechanisms of depression [36]. There are strong evidences to prove that the dysfunction of 5-HT ergic system is related to depression and other mood disorders.

DRN neurons, especially neurons which utilize 5-HT as their major neurotransmitter, might be involved in the neuropathogenesis of ghrelin. Acute central administration of ghrelin, increased 5-HT and 5-HT receptors mRNA in mice DRN [45, 47]. Studies in Ghsr1a knock-out mice

showed a decreased mRNA expression of 5-HT receptors in DRN relative to their wild-type littermates [45]. The 5-HIAA levels and 5-HT receptors mRNA also increased with acute central ghrelin administration in amygdala [45]. From the above information, we conclude that the central serotonin system is a target for ghrelin.

Ghrelin receptors positively interact with not only 5-HT receptors but also dopamine (DA) receptors [42]. The action of ghrelin in the ventral tegmental area (VTA) is involved in dopaminergic neuronal firing and DA turnover, which is dependent on GHSR1a receptors, *via* glutamatergic inputs [29, 48]. Besides, the signal activated by ghrelin can reach the ARH where mainly the release of naradrenaline (NA) increases [51]. Because of the importance of monoamine hypothesis, the link between ghrelin and other receptors will be well studied in the future.

2.3.2. BDNF and Related Signal Transduction Pathways in Ghrelin's Antidepressant-like Effects

Most of the works on neurotrophic factors' hypothesis were focused on BDNF [40, 49-51]. Several strong evidence have proven that BDNF, a 27-kDa protein, acts as a key factor in the development of brain, such as neural plasticity, memory and learning [50, 52-54]. Stress leads to the decrease of BDNF levels, resulting in the abnormal activity of neurons and the administration of BDNF produces an antidepressant-like effect [49-52].

Ghrelin has been proved to improve cognitive ability in diabetic rats by improving the expression of BDNF and CREB. BDNF (F) knock-out mice had abnormal eating behaviors, and antidepressants treatment alleviated abnormal behaviors and increased BDNF levels. From the finding, we make an assumption that ghrelin has effects on the levels of BDNF. Evidences have proved that ghrelin stimulated the expression of CREB and pCREB [53]. However, whether other receptors like TrkB that activate BDNF expression are influenced by ghrelin is still unknown, and the works on other neurotrophic factors are still lacking.

2.3.3. Ghrelin's Treatment Increases Hippocampal Neurogenesis

Neurogenesis, a process of generating functionally integrated neurons from progenitor cells [54-63], has been proved to persist in adulthood in several mammals, including birds, rodents, monkeys, and humans. The subventricular zone (SVZ) and the subgranular zone (SGZ) are two major neurogenic zones where progenitor cells are found and continue to produce new neurons [55]. There has been much attention focused on neurogenesis in the hippocampus, because this structure is important in the process of learning, memory, and emotional responses.

The neurogenesis can be regulated by many factors, including environmental changes and pharmacological treatments [55]. Many kinds of stress can decrease neurogenesis of adults, including predator odor [64], social stress [65] and acute and chronic restraint stress [66]. The decrease of hippocampal neurogenesis by stress might be an important mechanism related to depressive disorders. Since many conventional antidepressant treatments increase neurogenesis in the adult hippocampus [68], we can conclude that neurogenesis may be linked to their antidepressant-like behavioral effects.

Several studies have reported that ghrelin enhances neurogenesis. Firstly, ghrelin was known to increase neurogenesis in the fetal spinal cord of rats and the nucleus of solitary tract and the dorsal motor nucleus of vagus in adult rats [69]. Recently, ghrelin was proved to directly increase hippocampal neurogenesis [71, 72]. Systemic administration of ghrelin to the ghrelin receptor knockout mice (Ghsr1a-/-) showed lower number of progenitor cells in the DG compared with those of the wild-type controls [69, 71]. In both *in vitro* and *in vivo* studies, ghrelin treatment stimulates neurogenesis, and the synthetic GHS-R agonist hexarelin has the same effect [51]. One of the ways for testing neurogenesis is *via* bromodeoxyuridine(BrdU). The number of BrdU- labeled cells shows the concentration in cell proliferation, reports have demonstrated that stress can reduce the BrdU-labeled cells in hippocampus [69], and the ghrelin treatment can enhance the BrdU- labeled cells in many part of the brain, including hippocampus. Although the role of ghrelin in stimulating neurogenesis is still unknown, it has been proved that ghrelin may act as an effective factor for neurons by controlling apoptotic pathways [72].

3. ESTROGEN

3.1. The Sex Differences in Depression and Reproductive Depression

The sex differences may lead to a different response to stress. From the introduction, women are 2 times more sensitive to stress 2 times than men. Rodent behaviour experiments revealed that female rats showed more mobility in open field test (OFT), greater open arm time in the EPM and lesser immobile time in the FST [73].

But sex differences in depression do not manifest throughout life. Before adolescence, the chance to suffer from depression for girls and boys are 1:1 [74]. From the onset of puberty, women have 2 to 3 times greater risk of depression than men [76]. But the sex ratios become equal again after menopause [75]. Women have high risk of depressive disorders during menstruation, pregnancy, post-partum and menopausal periods [73]. Recent US guidelines advised that all midlife women should be screened for depression, as midlife women (45-55 years old) [82] are more likely to suffer from depression than at other ages [78-80].

This result suggests that the change of sex hormones during the perimenopause and menopausal may play a key role in the manifestation of depression. And other researchers have found that women during perimenopause are more likely to suffer from depression than during postmenopause [85, 86].

3.2. The Link between Estrogen and Depression

Since sex hormones are related to the depression in women, estrogens - one kind of major sex hormones secreted by ovaries, may play an important role in the treatment of depression.

3.2.1. Estrogen and Depression

Reproductive aging in women is associated with the decrease of sex hormones (estradiol and estrone) [89]. Researchers have found that women during menopause were more likely to suffer from depression, when estrogen levels were decreased [76]. And women with depression showed lower levels of estradiol than control subjects [90]. Based on the reports, we conclude that the low levels of estrogens may be associated with depressed mood.

Ovariectomy (OVX), is a menopausal animal model, based on resection of ovaries, resulting in a depressive state. OVX animals are used to mimic the circulation levels of estrogen of women during menopause. Growing literatures suggested that OVX induced estrogen insufficiency [91]. Long-term ovariectomised mice displayed a significant lesser open arm activity in the EPM [82] and lesser struggling time in the FST [91, 92] than control animals. When given 4-months chronic stress to the OVX mice, results showed a significantly less struggling time in the FST compared to 2-weeks stress mice [91], which showed that long-term OVX may have greater danger to suffer from depression.

Estrogens have multiple functions in the brain [93]. There are two major subtypes of estrogen receptors, ER alpha and ER beta [94]. ERα is particularly expressed in the hypothalamus, preoptic area and amygdala, which are responsible for affective, motivational and cognitive responses [77, 94]. ERβ is particularly expressed in the hypothalamus, hippocampus, cerebral cortex, which may be related to the mechanisms of the antidepressant-like effects [95, 96]. When women were treated with the mixed estrogen receptor antagonist, tamoxifen, the patients were more likely to suffer from depression [76, 97]. The same evidence was observed in the experiments of animals [96, 97], so as to say that the abnormal ER expressions may lead to the fluctuation of estrogen levels, and cause mood disorders.

3.2.2. Antidepressant-like effects of Estrogen

Ovarian hormones exert anti-depressive actions in perimenopausal depression [82]. Also, Hormone replacement therapy (HRT) is a well-used therapy for this purpose. Estrogens, because of the functions in promoting neuronal growth, enhancing monoaminergic activity, and regulating the hypothalamic-pituitary-adrenal (HPA) axis [98], are considered to produce antidepressant-like effects.

Most studies on animal models are focussed on ovariectomised rats and mice [99], given that both acute and chronic treatment with 17-estradiol (the most well-known kind of estrogens) decreased the immobility time in the FST and tail suspension test (TST) [100], and increased the time spent in open arms in the EPM [101-103], such behaviour tests are well used in the screening of novel antidepressants, and the behaviours after estrogen proved the antidepressant-like effects of estradiol in OVX females. E2's antidepressant-like effects may relate to many factors, including the intra-cellular estrogen receptors (ERs), ERα and ERβ. For example, the ERs agonists ethynyl-estradiol (EE2) and diarylpropionitrile (DPN), induced antidepressant-like effects after an acute treatment [104]. After the chronic administration (7 or 14 days) of the agonist to ERs, E2 benzoate, also showed the decreasing immobility time in the FST [105]. And antagonists of ERs can block the antidepressant-like effects of Estrogen replacement therapy (ERT) [104].

In clinical studies, ERT was proved to have significant effects on improving mood disorders after menopause [77]. Six women were treated with estradiol, the ERT-group showed a decrease of depressive symptoms compared to control group [96, 106, 107]. Therefore, estrogen may be helpful for the depressive treatments, ERT may be a special and effective way to cure reproductive depression.

3.3. The Mechanisms of Estrogen's Antidepressant-like Actions

From the above description, we already simply understand the three hypotheses for antidepressant-like actions. They are monoamine hypothesis, neurotrophic factor hypothesis and neurogenesis hypothesis. In this part, we will list the reports and explore estrogens' mechanisms based on the hypotheses which are related to depression.

3.3.1. Estrogen and 5-HT

Wealth of data demonstrated that sex hormones are related to the regulation of serotonergic system [108-138]. The decrease in estrogens results in a reduction in 5-HT production [109], and the antidepressant treatment of estrogen has been proved to result in the up-regulation of 5-HT transporters and receptor expression [111] and increase the 5-HT levels. Although estrogens still have not demonstrated the effects on all 5-HT receptors, many reports have proven that manipulation of estrogen levels has effects on 5-HT1A receptors [112] and 5-HT2A receptors [113], which are related to mood disorders [114]. Table **1**. shows the previous studies related with estrogen and 5-HT [123-138].

According to the studies, both acute and chronic treatments of estradiol on both postmenopausal women and OVX animal models showed that estrogen can increase 5-HT2A receptor mRNA in the DRN and 5-HT2A receptor binding in the frontal cortex, anterior cingulated and other pieces [115, 116]. The 5-HT agonist meta-chlorophenylpiperazine (m-CPP) showed a better response to cortisol following estrogen, and the effects on 5-HT levels were blocked by the antagonists of 5-HT receptors. Estrogen receptors are expressed in 5-HT nucleus in DRN, and ERβ seem to be more effective to 5-HT system than ERα. In animal studies, after estrogen treatment for ovariectomised rats, the models showed increased 5-HT transporter (SERT) and 5-HT receptors mRNA in the dorsal raphe, while the estrogen receptor ERβ antagonist tamoxifen blocked these effects [109, 115], suggesting that ERβ mediated the process between estrogen and 5-HT. Not only 5-HT, estrogen also have positively modulation on NE network by increasing α1B NE receptors [119-121] and DA synthesis [122, 123].

3.3.2. Estrogen and BDNF

It has been known that stress decreases BDNF expression in several parts of brain, and the abnormal BDNF signalling is related to depression. Women have higher mean plasma BDNF levels than men [139], and women during

Table 1. Estrogen and 5-HT: animal studies [118].

Founder	Parameter	Effect	Brain region
1.Di Paolo, Diagle, Picard, and Barden (1983) [123]; 2.Johnson and Crowley (1983) [124]; 3.Morissette, Levesque, Belanger, and Di Paolo (1990) [125]; 4.Munaro (1978) [126].	5-HT turnover	↑	Dorsal raphe, amygdale
1.Cone, Davis, and Goy (1981) [127]; 2.Pecins-Thompson, Brown, Kohama, and Bethea (1996) [128]; 3.Cohen and Wise (1988) [129]; 4.McQueen *et al*. (1996) [130]; 5.Thomas *et al*. (1997) [131].	5-HT synthesis/release SERT/mRNA	↑	Dorsal raphe, SCN, median eminence VMH, LS, VN basolateral amygdala Dorsal raphe
1.Thomas *et al*. (1997) [131]	5-HT_{1A} binding/mRNA	↑	Midbrain
1. Biegon *et al*. (1983) [132]; 2. Osterlund, Halldin, and Hurd (2000) [133]; 3. Osterlund and Hurd (1998) [134]; 4. Pecins-Thompson and Bethea (1999) [135].	5-HT_{1A} binding/mRNA	↓	Cortex, limbic areas dorsal raphe
1.Cyr, Bosse, and Di Paolo (1998) [114]; 2. Fink and Sumner (1996) [116]; 3. Sumner and Fink (1995) [137]; 4. Sumner *et al*. (1999) [138].	5-HT_{2A} binding/mRNA	↑	Frontal CTX anterior cingulate olfactory CTX, NA piriform CTX dorsal raphe

adulthood have higher BDNF levels than amenorrheic or postmenopausal women [140], the sex difference and age-dependence of BDNF levels were explained by estrogens. There has been a wealth of data proving that low estrogen and BDNF levels were found in ovariectomised animals [14]. Estrogen may act as one of factors influencing the levels of BDNF mRNA and protein expression in female patients, and BDNF signalling could be related to the mechanism.

Results demonstrated that estrogen replacement no matter long-term (5 to 25 weeks) or short-term (72h to 5 days) increased BDNF mRNA levels in hippocampus, cortex and spinal cord [141, 142], and recently, 17b-E2 has been found to increase protein levels of BDNF [143]. Not only the levels of BDNF, estrogen were also reported to influence the levels of proteins which are in relation to BDNF. Evidences have proven that E2 increased CREB protein expression, as well as CREB phosphorylation (P-CREB) in the medial and basomedial subdivisions of amyadala, while on the other hand, E2 increased P-CREB immunolabeling but did not increase CREB protein levels in the CA1 and CA3 regions of hippocampus. And exogenous estradiol administration to OVX rats has been proved to increase BDNF through TrkB [144-146]. From the above information, we can conclude that the CREB signalling pathway and BDNF' s receptor TrkB are likely to activate BDNF expression following estrogen treatment.

3.3.3. Estrogen and Neurogenesis

As ovariectomised rodents suffered from depression, following an increasing cell death [150], and estrogen treatment reversed stress induced cell death. Therefore, we have hypothesis that estrogen enhances hippocampal neurogenesis to protect females from stress. The effects of estrogen in hippocampal neurogenesis have recently been reviewed in both *in vivo* and *in vitro*. *In vivo*, acute estradiol treatment within 4 hours significantly increased the proliferation of neurons and the survival of new neurons in female rats and voles [150, 151], while chronic (60 days) estrogen increased cell proliferation in middle-aged C57B1/6 mice [152, 153]. And *in vitro*, estrogen could increase the proliferation and survival of new neurons in rats [154-156]. The effects were abolished by ICI 182, 780, an estrogen receptor antagonist [148], which showed that effects of estradiol on the enhancement of hippocampal neurogenesis were mediated by estrogen receptors. And some evidence suggests that ERβ may be more involved in neurogenesis than ERα [149].

4. GHRELIN AND ESTROGEN

The plasma levels of ghrelin have sex differences and can be age-dependent [157-159]. In young women, ghrelin levels were 3 times higher than in young men [158] and ghrelin levels were significantly lower in middle-aged women while had no difference between young and elderly men [159]. In this part, we will pay attention to link ghrelin with estrogen, and try to find the common effects on depression.

4.1. Ghrelin and Estrogen have Mutual Promoting Effects

As ghrelin expressions were higher in females and showed age-related changes, estrogen may play a key role in

ghrelin expression. Numerous studies reported that estrogen up-regulates ghrelin level act as a positive feedback mechanism to ghrelin. 6-month or 24-month long term treatment with estrogen, increased ghrelin levels [160, 161], and oral treatment had a better effect than the transdermal treatment [159-162]. Some data suggested that estradiol supplementation increased total ghrelin concentration in postmenopausal women [163], while others suggested increased active ghrelin concentrations by 14%, without affecting total ghrelin concentrations [164]. These evidences suggested that estrogen may regulate ghrelin expression by increasing ghrelin secretion or enhancing hypothalamo-pituitary sensitivity to ghrelin. Further animal studies proved that estrogen may have a direct effect on ghrelin expression. Treating the rats estrogen for 8h significantly increased the level of ghrelin production and ghrelin mRNA expression [167], and ICI-182 780 (a pure ER antagonist) completely removed the effect of estrogen, suggesting that estrogen may influence ghrelin through ER, and ERα is more effective.

On the other hand, ghrelin also stimulates estrogen secretion. In past studies, the basal estradiol secretion during 24 h was 10.22 ± 0.39 pg/ml, while after the addition of 250 and 500 pg/ml of ghrelin, the estradiol secretion significantly increased to 12.14 pg/ml and 14.93 pg/ml [169]. The result suggested that ghrelin may have a modulatory effect in the ovary and may play a key role in the reproductive function.

4.2. Ghrelin Suppresses LH Pulse Frequency

E2 shows a negative feedback inhibition of luteinizing hormone (LH) [170,171], the highest level of estradiol decreases LH level [172], and after postmenopausal, women's plasma LH has a remarkable increase and LH mRNA expression increases [173-175], the same results have been shown in the OVX animals [176]. Estradiol treatment can decrease LH concentration, at the low dose [176]. As ghrelin may play a role in regulating the hypothalamic-pituitary-ovarian axis, recent studies reported that ghrelin modulated LH secretion [177]. Both 36-h fasting and intracerebroventricular injection of 20 mg/kg ghrelin in mice and ovariectomised mice decreased LH levels [168, 178]. The same results were also shown in adult ovariectomised rhesus monkeys [179-181], when treating them with a 5-h ghrelin (100-150 ug/h), the levels of plasma ghrelin increased 2.9 fold of baseline and the group with ghrelin significantly showed a decreased LH pulse frequency, while the group with saline remained unchanged [181].

In clinical studies, reports showed that ghrelin reduced plasma levels of LH in patients with major depression [182]. CNS may be a key region for ghrelin to work on the LH regulation [183]. As NPY and AGRP have been shown to suppress pulsatile LH release in the OVX mammals [184,185], and ghrelin increased the synthesis of both NPY and AGRP [186], it can be supposed that ghrelin may exert its effect by promoting the secretion of NPY and AGRP [187], the hypothesis was proved in an experiment that the action of ghrelin on LH was abolished in double knockout mice [181, 187]. Others think that ghrelin inhibits the action of LH secretion by corticotropin releasing hormone (CRH) release [188], because when pre-processed with astressin B (a nonspecific CRH receptor antagonist) [189], it abolished the decrease of LH [188]. Although the mechanism is still not clear, but it seems reasonable to assume that ghrelin can be a potential regulator of reproductive function.

4.3. Estrogens as Facilitators of Antidepressant Drugs

Estrogen not only be used as an individual antidepressant medication, but also be combined with other traditional antidepressant drugs, since the antidepressant-like effects of several kinds of drugs can be improved by the addition of estrogen [109, 190-193]. Men and women have difference in the response of antidepressants and these differences may be largely due to the presence of estrogen [109]. The serotonin re-uptake inhibitors (SSRIs), which increase 5-HT levels in the CNS [195], may have a similar mechanism with ghrelin. Animal studies have proven that SSRIs combined with estradiol produce enhanced antidepressant-like effect in females in the FST [86, 194-196]. And in clinical studies, SSRIs combined with estradiol treatment decreases the severity of depressive symptoms in perimenopausal women more effectively than SSRI therapy alone [197].

From the earlier discussion, we have already observed that ghrelin could be used as a new candidate of the antidepressant, and the mechanism of ghrelin's antidepressant-like action may be related to monoamime hypothesis especially 5-HT. Therefore, estrogen treatment (ET) could produce additional antidepressant-like effect with ghrelin.

5. CONCLUSIONS

Ghrelin is not only linked to the feeding behaviour and energy balance, but also has antidepressant-like effects. Evidence both on animal behaviour studies using FST, EPM and human studies in MDD have shown that the increase of ghrelin levels reduced depression-like behaviours, and the antagonism of ghrelin receptor Ghsr1a blocked the effects. The mechanisms of ghrelin's antidepressant-like actions may be explained in three hypotheses, 1) ghrelin enhances the levels of monoamines and their receptors in some regions of brain, such as increases the levels of 5-HT and the receptors 5-HT1A in dorsal raphe and amygdale; 2) ghrelin improves expression of BDNF and CREB/pCREB; 3) ghrelin enhances neurogenesis.

The link between ghrelin and estrogen has been discussed in this review. As ghrelin levels were age-dependent and higher in women than men. Evidence proved that estrogen enhanced the levels of ghrelin mRNA expression and ghrelin production, and ghrelin also had positive feedback regulation in estrogen secretion. Furthermore, studies showed that ghrelin regulated HPO axis. In addition, estrogen combined with other traditional antidepressant drugs showed better effects than antidepressant drugs alone. Ghrelin and estrogen may have an additional effect for the treatment of depression. However, further study is needed to confirm whether or not combined treatment with ghrelin and estrogen produce antidepressant-like effects.

In this review, we demonstrated the antidepressant-like effects of ghrelin and estrogen. Also, we propose the viewpoint that the combination of estrogen and ghrelin produces antidepressant-like effects. This review provides more useful information to clarify mechanisms of

antidepressant effects of ghrelin and ghrelin's effects on depression.

ROLE OF FUNDING SOURCE

This work was supported by Natural Science Foundation of China (31171123; 31300850; 81328011; 31471120); Jilin Provincial Department of Human Resources and Social Security Project ([2012] 39); Jilin Science and Technology Agency funding (20110726).

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Lang, U. E.; Borgwardt, S. Molecular Mechanisms of Depression: Perspectives on New Treatment Strategies. *Cell Physiol. Biochem.*, **2013**, *31*, 761-777. http://dx.doi.org/10.1159/000350094

[2] Penninx, B.W.; Guralnik, J. M.; Pahor, M.; Ferrucci, L.; Cerhan, J.R.; Wallace, R.B.; Havlik, RJ. Chronically depressed mood and cancer risk in older persons. *J. Natl. Cancer Inst*., **1998**, *90*, 1888-1893. http://dx.doi.org/10.1093/jnci/90.24.1888

[3] Bouvier, N. Trenque, T., Millart, H. Development of antidepressant drugs. *Exp. Prospects, Press*, **2003**, *32*, 519-522.

[4] Eric, J. N.; Michel, B.; Ralph, J. DiLeone; *et al*. Neurobiology of Depression. *Neuron*, **2002**, *28*, 13-25. http://dx.doi.org/10.1016/S0896-6273(02)00653-0

[5] Qing-Qiu, M.; Zhen, H.; Siu-Po; Yan-Fang, X.; Chun-Tao, C. Role of 5-HT1A and 5-HT1B receptors in the antidepressant-like effect of piperine in the forced swim test. *Neurosci. Lett.*, **2011**, *504*, 181-184. http://dx.doi.org/10.1016/j.neulet.2011.09.038

[6] Plácido, L.; García-Portilla, M. P. Llaneza-Suáreza, D., Armott, B.; Pérez-López, F. R. Depressive disorders and the menopause transition. *Maturitas*, **2012**, *71*, 120-130. http://dx.doi.org/10.1016/j.maturitas.2011.11.017

[7] Susan, Nolen-Hoeksema. Gender Differences in Depression. *Curr. Direct. Psychol. Sci.*, **2001**, *10*, 173-186. http://dx.doi.org/10.1111/1467-8721.00142

[8] Kessler, R. C.; McGonagle, K. A.; Swartz, M.; Blazer, D. G.; Nelson, C. B. Sex and depression in the National Comorbidity Survey I: Lifetime prevalence, chronicity, and recurrence. *J. Affect. Disord.*, **1993**, *29*, 85-96. http://dx.doi.org/10.1016/0165-0327(93)90026-G

[9] WU. Y. C.; Hill. R. A.; Gogos. A.; Van Den, B. M. Sex differences and the role of Estrogen in animal models of schizophrenia: interaction with BDNF. *Neuroscience*, **2013**, *239*, 67-83. http://dx.doi.org/10.1016/j.neuroscience.2012.10.024

[10] Heldring, N.; Pike, A.; Andersson, S.; Matthews, J.; Cheng, G.; Hartman, J.; Tujague, M.; Strom, A.; Treuter, E.; Warner, M.; Gustafsson, J. A. Estrogen receptors: how do they signal and what are their targets. *Physiol. Rev.*, **2007**, *87*, 905-931. http://dx.doi.org/10.1152/physrev.00026.2006

[11] Idil, C.; Ronald, S. D. Influence of Estradiol, Stress, and 5-HT2A Agonist Treatment on Brain-Derived Neurotrophic Factor Expression in Female Rats. *Soc. Biol. Psychiatry*, **2003**, *54*, 59-69. http://dx.doi.org/10.1016/S0006-3223(03)00236-1

[12] Behl, C. Oestrogen as a neuroprotective hormone. *Nat. Rev. Neurosci.*, **2002**, *3*, 433-442.

[13] Artigas, F. Limitations to enhancing the speed of onset of antidepressants-are rapid action antidepressants possible? *Hum. Psychopharmacol.*, **2001**, *16*, 29-36. http://dx.doi.org/10.1002/hup.180

[14] Dezheng, Z. Protein kinase Cd-mediated CREB Activation Regulates Ghrelin-induced Cyclooxygenase-2 Expression and Prostaglandin E2 Production in Human Colonic Epithelial Cells. *J. Cell. Biochem.*, **2007**, *102*, 1245-1255. http://dx.doi.org/10.1002/jcb.21355

[15] Kojima, M.; Hosoda, H.; Date, Y.; Nakazato, M.; Matsuo, H.; Kangawa, K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature*, **1999**, *402*, 656-660. http://dx.doi.org/10.1038/45230

[16] Howard, A. D.; Feighner, S. D.; Cully, D. F.; Arena, J.P., Liberator, P.A., Rosenblum, C.I., Hamelin, M., Hreniuk, D.L., Palyha, O.C., Anderson, J., Paress, P.S., Diaz, C., Chou, M., Liu, K.K., McKee, K.K., Pong, S.S., Chaung, L.Y., Elbrecht, A., Dashkevicz, M., Heavens, R., Rigby, M., Sirinathsinghji, D.J., Dean, D.C., Melillo, D.G., Patchett, A.A., Nargund, R., Griffin, P.R., DeMartino, J.A., Gupta, S.K., Schaeffer, J.M., Smith, R.G., Van der Ploeg, L.H. A receptor in pituitary and hypothalamus that functions in growth hormone release. *Science*, **1996**, *273*, 974-977. http://dx.doi.org/10.1126/science.273.5277.974

[17] Nakazato, M.; Murakami,N.; Date, Y.; Kojima, M.; Matsuo, H.; Kangawa, K.; Matsukura, S. A role for ghrelin in the central regulation of feeding. *Nature*, **2001**, *409*, 194-198. http://dx.doi.org/10.1038/35051587

[18] Schellekens, H.; Finger, B. C.; Dinan, T.G.; Cryan, J. F. Ghrelin signalling and obesity: At the interface of stress, mood and food reward. *Pharmacol. Ther.*, **2012**, *35*, 316-326. http://dx.doi.org/10.1016/j.pharmthera.2012.06.004

[19] Axel, S.; Martin, D.; Petra, S.; Michael, K. Ghrelin in mental health, sleep, memory. *Mol. Cell. Endocrinol.* , **2011**, *340*, 88-96. http://dx.doi.org/10.1016/j.mce.2011.02.013

[20] Cuellar, J. N.; Isokawa, M. Ghrelin-induced activation of cAMP signal transduction and its negative regulation by endocannabinoids in the hippocampus. *Neuropharmacology*, **2011**, *60*, 842-851. http://dx.doi.org/10.1016/j.neuropharm.2010.12.024

[21] Zigman, J. M.; Jones, J. E.; Lee, C. E.; Saper, C. B.; Elmquist, J. K. Expression of ghrelin receptor mRNA in the rat and the mouse brain. *J. Comp. Neurol.*, **2006**, *494*, 528-548. http://dx.doi.org/10.1002/cne.20823

[22] Andrews, Z. B. The extra-hypothalamic actions of ghrelin on neuronal function. *Trends Neurosci.* , **2011**, *34*, 131-37.

[23] Lutter, M.; Sakata, I.; Osborne-Lawrence, S.; Rovinsky, S.A., Anderson, J.G., Jung, S., Birnbaum, S., Yanagisawa, M., Elmquist, J.K., Nestler, E.J., Zigman, J.M. The orexigenic hormone ghrelin defends against depressive symptoms of chronic stress. *Nat. Neurosci.*, **2008**, *11*, 752-3. http://dx.doi.org/10.1038/nn.2139

[24] Carlini, V. P.; Varas, M. M.; Cragnolini, A. B.; Schiöth, H.B., Scimonelli, T.N., de Barioglio, S.R. Differential role of the hippoeampus, amygdale, and dorsal raphe nucleus in regulating feeding, memory, and anxiety-like behavioral responses to ghrelin. *Biochem. Biophys. Res. Commun.*, **2004**, *313*, 635-641. http://dx.doi.org/10.1016/j.bbrc.2003.11.150

[25] Tschop, M.; Smiley, D.L.; Heiman, M.L. Ghrelin induces adiposity in rodents. *Nature*, **2000**, *407*, 908-913. http://dx.doi.org/10.1038/35038090

[26] Nakazato, M.; Murakami, N.; Date, Y.; Kojima, M.; Matsuo, H.; Kangawa, K.; Matsukura, S. A role for ghrelin in the central regulation of feeding. *Nature*, **2001**, *409*, 194-198. http://dx.doi.org/10.1038/35051587

[27] Kenji, H.; Hiroki, K.; Michiko, N.; Eiji, S.; Masaomi, I. Role of brain-derived neurotrophic factor in eating disorders: Recent findings and its pathophysiological implications. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry*, **2005**, *29*, 499-504. http://dx.doi.org/10.1016/j.pnpbp.2005.01.007

[28] René, K. S.; Alin, A.; Kim, B.; Allan, F.; Kirsten, H.; Jan, F. Leptin, ghrelin, and endocannabinoids: Potential therapeutictargets in anorexia nervosa. *J. Psychiatric Res.*, **2009**, *43*, 671-679. http://dx.doi.org/10.1016/j.jpsychires.2008.09.007

[29] Usdan, L. S.; Khaodhiar, L.; Apovian, C. M. The endocrinopathies of anorexia nervosa. *Endocr. Pract.*, **2008**, *14*, 1055-1063. http://dx.doi.org/10.4158/EP.14.8.1055

[30] Rask-Andersen M.; Olszewski, P. K.; Levine, A.S.; Schiöth, H. B. Molecular mechanisms underlying anorexia nervosa: Focus on human gene association studies and systems controlling food intake. *Brain Res. Rev.*, **2010**, *62*, 147-164. http://dx.doi.org/10.1016/j.brainresrev.2009.10.007

[31] Monteleone, P.; Martiadis, V.; Fabrazzo, M.; Serritella, C.; Maj, M. Ghrelin and leptin responses to food ingestion in bulimia nervosa: implications for binge-eating and compensatory behaviours. *Psychol. Med.,* **2003**, *33*, 1387-1394. http://dx.doi.org/10.1017/S0033291703008316

[32] Philipp, H.; Simona, G.; Gabriella, M.; Ulrich, S.; Gregor, H. Reduction in total plasma ghrelin levels following catecholamine depletion: Relation to bulimic and depressive symptoms. *Psychoneuroendocrinology*, **2013**, *38*, 1545-1552. http://dx.doi.org/10.1016/j.psyneuen.2012.12.024

[33] Juruena, M. F.; Cleare, A. J. Overlap between atypical depression, seasonal affective disorder and chronic fatigue syndrome. *Rev. Bras. Psiquiatr.*, **2007**, *29*(Suppl. 1), S19-26. http://dx.doi.org/10.1590/S1516-44462007000500005

[34] Simon, G. E.; Von Korff, M.; Saunders, K.; Miglioretti, D. L.; Crane, P. K.; Belle, G.; Kessler, R.C. Association between obesity and psychiatric disorders in the US adult population. *Arch. Gen. Psychiatry*, **2006**, *63*, 824-830. http://dx.doi.org/10.1001/archpsyc.63.7.824

[35] Saliha, O.; Aslı, B.; Ummuhan, A.; Mustafa, B. Serum Ghrelin and Leptin Levels in Patients with Depression and the Effects of Treatment. *Psychiatry Investig*., **2014**, *11*(2), 167-172. http://dx.doi.org/10.4306/pi.2014.11.2.167

[36] Michael K.; Petra, S.; Martin, D.; Doreen, S.; Alexander, Y.; Manfred, U.; Axel, S. Effects of ghrelin on psychopathology, sleep and secretion of cortisol and growth hormone in patients with major depression. *J. Psychiatric Res.*, **2011**, *45*, 421-426. http://dx.doi.org/10.1016/j.jpsychires.2010.09.002

[37] Michael, L.; Ichiro, S.; Sherri, Osborne-Lawrence; Rovinsky, S.A., Anderson, J.G., Jung, S., Birnbaum, S., Yanagisawa, M., Elmquist, J.K., Nestler, E.J., Zigman, J.M. The orexigenic hormone ghrelin defends against depressive symptoms of chronic stress. *Nat. Neurosci.*, **2008**, *11(7)*, 752-753. http://dx.doi.org/10.1038/nn.2139

[38] Valeria, P. C.; Daniele, G. M.; Florencia, B.; Ghersi, M.; Ponzio, M.F.; Martini, A.C.; Schiöth, H.B.; de Cuneo, M.F.; Rodrigues, A.L.; de Barioglio, S.R. Acute ghrelin administration in reverses depressive-like behavior induced by bilateral olfactory bulbectomy in mice. *Peptides*, **2012**, *35*, 160-165. http://dx.doi.org/10.1016/j.peptides.2012.03.031

[39] Andrew C.-H. C.; Yukihiko, S.; Kyung-Ho, S.; Rachael, L. N.; Ronald, S. D. Expression of the cAMP Response Element Binding Protein (CREB) in Hippocampus Produces an Antidepressant Effect. *Soc. Biol. Psychiatry*, **2001**, *49*, 753-762. http://dx.doi.org/10.1016/S0006-3223(00)01114-8

[40] Hymie, A.; Zul, M.; Shawn, H. Neurotransmitter, peptide and cytokine processes in relation to depressive disorder: Comorbidity between depression and neurodegenerative disorders. *Prog. Neurobiol.*, **2008**, *85*, 1-74. http://dx.doi.org/10.1016/j.pneurobio.2008.01.004

[41] Djavadian, R. L. Serotonin and neurogenesis in the hippocampal dentate gyrus of adult mammals. *Acta Neurobiol*., **2004**, *64*, 189-200.

[42] Masaki, O.; Juhyon, K.; Kazuo, S. Ghrelin postsynaptically depolarizes dorsal raphe neurons in rats *in vitro*. *Peptides,* **2011**, *32*, 1606-1616. http://dx.doi.org/10.1016/j.peptides.2011.07.001

[43] Michelsen, K.A.; Schmitz, C.; Steinbusch, H.W. The dorsal raphe nucleus - from silver stainings to a role in depression. *Brain Res. Rev.*, **2007**, *55*, 329-42. http://dx.doi.org/10.1016/j.brainresrev.2007.01.002

[44] Medeiros, M.A.; Costa-e-Sousa, R.H.; Olivares, E.L.; Côrtes, W.S.; Reis, L.C. A reassessment of the role of serotonergic system in the control of feeding behavior. *An. Acad. Bras Cienc.*, **2005**, *77*, 103-11. http://dx.doi.org/10.1590/S0001-37652005000100008

[45] Caroline, H.; Mayte, Alvarez-Crespo.; Magdalena, T.; Skibicka, K.P., Schmidt, L., Karlsson-Lindahl, L., Egecioglu, E., Nissbrandt, H., Dickson, S.L. Influence of ghrelin on the central serotonergic signaling system in mice. *Neuropharmacology*, **2014**, *79*, 498-505. http://dx.doi.org/10.1016/j.neuropharm.2013.12.012

[46] Karolina P. Skibicka; Suzanne L. Dickson. Ghrelin and food reward: The story of potentialunderlying substrates. *Peptides*, **2011**, *32*, 2265-2273. http://dx.doi.org/10.1016/j.peptides.2011.05.016

[47] Alvarez-Crespo, M.; Skibicka, K. P.; Farkas, I.; Molnar, C. S.; Egecioglu, E.; Hrabovszky, E.; Liposits, Z.; Dickson, S. L. The amygdala as a neurobiological target for ghrelin in rats: neuroanatomical, electrophysiological and behavioral evidence. *PloS One*, **2012**, *7*, 420-21. http://dx.doi.org/10.1371/journal.pone.0046321

[48] Jiang, H.; Betancourt, L., Smith, R.G. Ghrelin amplifies dopamine signaling by cross talk involving formation of growth hormone secret a gogue receptor/dopamine receptor subtype 1 heterodimers. *Mol. Endocrinol*., **2006**, *20*, 1772-1785. http://dx.doi.org/10.1210/me.2005-0084

[49] Conkright, M. D.; Canettieri, G.; Screaton, R.; Guzman, E.; Miraglia, L.; Hogenesch, J. B.; Montminy, M. TORCs: transducers of regulated CREB activity. *Mol. Cell*, **2003**, *12*, 413-423. http://dx.doi.org/10.1016/j.molcel.2003.08.013

[50] Shaywitz, A. J.; Greenberg, M. E. CREB: a stimulus-induced transcription factor activated by a diverse array of extracellular signals. *Annu. Rev. Biochem.*, **1999**, *68*, 821-861. http://dx.doi.org/10.1146/annurev.biochem.68.1.821

[51] Ferrini, F.; Salio, C.; Lossi, L.; Merighi, A. Ghrelin in central neurons. *Neuropharmacol*, **2009**, *7*, 37-49. http://dx.doi.org/10.2174/157015909787602779

[52] Ulrike, B.; Christine, N.; Irmgard, C.; Doris, K.; Christoph, H.; Willhart, K. A common mechanism of action of the selective serotonin reuptake inhibitors citalopram and fluoxetine: Reversal of chronic psychosocial stress-induced increasein CRE/CREB-directed gene transcription in transgenic reporter gene mice. *Eur. J. Pharmacol.*, **2010**, *633*, 33-38. http://dx.doi.org/10.1016/j.ejphar.2010.01.016

[53] Cuellar, J. N.; Masako, I. Ghrelin-induced activation of cAMP signal transduction and its negative regulation by endocannabinoids in the hippocampus. *Neuropharmacology*, **2011**, *60*, 842-851. http://dx.doi.org/10.1016/j.neuropharm.2010.12.024

[54] Eriksson, PS.; Perfilieva, E.; Bjork-Eriksson, T.; Alborn, A.; Nordborg, C.; Peterson, D.; Gage, F. Neurogenesis in the adult human hippocampus. *Nat. Med.*, **1998**, *4*, 1313-1317. http://dx.doi.org/10.1038/3305

[55] Warner-Schmidt, J. L.; D. Ronald, S. Hippocampal Neurogenesis: Opposing Effects of Stress and Antidepressant Treatment. *Hippocampus*, **2006**, *16*, 239-249. http://dx.doi.org/10.1002/hipo.20156

[56] Jacobs, B. L. Adult brain neurogenesis and depression. *Brain, Behav. Immun.,* **2002**, *16*, 602-609. http://dx.doi.org/10.1016/S0889-1591(02)00015-6

[57] Gould, E.; Tanapat, P.; Hastings, N.B.; Shors, T.J. Neurogenesis in adulthood: a possible role in learning. *Trends Cogn. Sci*., **1999**, *3*, 186-192. http://dx.doi.org/10.1016/S1364-6613(99)01310-8

[58] Maura, B.; René, H.; Underwood, M, D.; Rosoklija, G. B.; Andrew, J.; Dwork, J.; John, M.; Victoria, A. Hippocampal Angiogenesis and Progenitor Cell Proliferation Are Increased with Antidepressant Use in Major Depression. *Biol. Psychiatry*, **2012**, *72*, 562-571. http://dx.doi.org/10.1016/j.biopsych.2012.04.024

[59] Santarelli, L.; Saxe, M.; Gross, C.; Surget, A.; Battaglia, F.; Dulawa, S.; Weisstaub, N., Lee, J., Duman, R., Arancio, O., Belzung, C., Hen, R. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science*, **2003**, *301*, 805-809. http://dx.doi.org/10.1126/science.1083328

[60] Sahay, A.; Hen, R. Adult hippocampal neurogenesis in depression. *Nat. Neurosci*., **2007**, *10*, 1110 -1115. http://dx.doi.org/10.1038/nn1969

[61] Hanson, N.D.; Owens, M.J; Boss-Williams, K.A; Weiss, J.M; Nemeroff, C.B. Several stressors fail to reduce adult hippocampal neurogenesis. *Psychoneuroendocrinology*, **2011**, *36*, 1520 -1529. http://dx.doi.org/10.1016/j.psyneuen.2011.04.006

[62] Snyder, J.S.; Soumier, A.; Brewer, M.; Pickel, J.; Cameron, H.A. Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. *Nature*, **2011**, *476*, 458-461. http://dx.doi.org/10.1038/nature10287

[63] Jessica, E. M. Implications of adult hippocampal neurogenesis in antidepressant action. *Rev. Psychiatr. Neurosci.*, **2004**, *29*, 196-205.

[64] Galea, L.; Wide, J.K.; Barr, A.M. Estradiol alleviates depressive-like symptoms in a novel animal model of post-partum depression. *Behav. Brain Res.*, **2001**, *122*, 1-9. http://dx.doi.org/10.1016/S0166-4328(01)00170-X

[65] Czeh, B.; Michaelis, T.; Watanabe, T.; Frahm, J.; De Biurrun, G.; Van Kampen, M.; Bartololomucci, A.; Fuchs, E. Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. *Proc. Natl. Acad. Sci. USA*, **2001**, *98*, 12796-12801. http://dx.doi.org/10.1073/pnas.211427898

[66] Rosenbrock, H.; Koros, E.; Bloching, A.; Podhorna, J.; Borsini, F. Effect of chronic intermittent restraint stress on hippocampal expressionof marker proteins for synaptic plasticity and progenitor

cell proliferation in rats. *Brain Res.*, **2005**, *1040*, 55-63. http://dx.doi.org/10.1016/j.brainres.2005.01.065

[67] Kathryn, A. C.; Cheryl, S. W. Cell cycle regulation, neurogenesis, and depression. *Commentary*, **2008**, *19*, 2259-2260.

[68] Herbert, E. C.; Vincent, V.; Eric, J. N. From synapse to nucleus: Novel targets for treating depression. *Neuropharmacology*, **2010**, *58*, 683-693. http://dx.doi.org/10.1016/j.neuropharm.2009.12.004

[69] Hyunju, C.; Endan, Li.; Yumi, K.; Sehee, K.; Seungjoon, P. Multiple signaling pathways mediate ghrelin-induced proliferation of hippocampal neural stem cells. *J. Endocrinol.*, **2013**, *218*, 49-59. http://dx.doi.org/10.1530/JOE-13-0045

[70] Zhao, C.; Deng, W.; Gage, F.H. Mechanisms and functional implications of adult neurogenesis. *Cell*, **2008**, *132*, 645-660. http://dx.doi.org/10.1016/j.cell.2008.01.033

[71] Li, E.; Chung, H.; Kim, Y.; Kim, D.H.; Ryu, J.H.; Sato, T.; Kojima, M.; Park, S. Ghrelin directly stimulates adult hippocampal neurogenesis: implications for learning and memory. *Endocrine J.,* **2013**, *60(6)*, 781-9. http://dx.doi.org/10.1507/endocrj.EJ13-0008

[72] Jiyeon, L.; Eunjin, L.; Yumi, K.; Endan, L.; Seungjoon, P. Ghrelin attenuates kainic acid-induced neuronal cell death in the mouse hippocampus. *J. Endocrinol.*, **2010**, *205*, 263-270. http://dx.doi.org/10.1677/JOE-10-0040

[73] Simpson, J.; Kelly, J.P. An investigation of whether there are sex differences in certain behavioural and neurochemical parameters in the rat. *Behav. Brain Res.*, **2012**, *229*, 289-300. http://dx.doi.org/10.1016/j.bbr.2011.12.036

[74] Simone, N.V.; Kate, S.; Daskalakis, Z. J.; Blumberger, D.M. Systematic review of gamma-aminobutyric-acid inhibitory deficits across the reproductive life cycle. *Arch. Womens Ment. Health*, **2014**, *17*, 87-95. http://dx.doi.org/10.1007/s00737-013-0403-6

[75] Payne, J.L.; Palmer, J.T.; Palmer, J.T., Joffe, H. A reproductive subtype of depression: conceptualizing models and moving toward etiology. *Harv. Rev. Psychiatry*, **2009**, *17(2)*, 72-86. http://dx.doi.org/10.1080/10673220902899706

[76] Winderbaum, F. J.; Alex, G. J.; Wecker, L. The role of estrogen receptor β and nicotinic cholinergic receptors in postpartum depression Progress in Neuro. *Psychopharmacol. Biol. Psychiatry*, **2013**, *40*, 199-206. http://dx.doi.org/10.1016/j.pnpbp.2012.10.002

[77] Studd, J.; Nappi, R. E. Reproductive depression. *Gynecol. Endocrinol.*, **2012**, *28*, 42-45. http://dx.doi.org/10.3109/09513590.2012.651932

[78] Hickey, M.; Bryant, C.; Judd, F. Evaluation and management of depressive and anxiety symptoms in midlife. *Climacteric*, **2012**, *15*, 3-9. http://dx.doi.org/10.3109/13697137.2011.620188

[79] Dennerstein, L.; Guthrie, J.R.; Clark, M.; Lehert, P.; Henderson, V.W. A population-based study of depressed mood in the middleaged, Australian-born women. *Menopause*, **2004**, *11*, 563-8. http://dx.doi.org/10.1097/01.GME.0000113844.74462.F6

[80] Frey, B.N.; Lord, C.; Soares, C.N. Depression during menopausal transition: a review of treatment strategies and pathophysiological correlates. *Menopause Int.*, **2008**, *14*, 123-8. http://dx.doi.org/10.1258/mi.2008.008019

[81] Studd, J. A guide to hormone therapy for the treatment of depression in women. *Climacteric*, **2011**, *14*, 637-642. http://dx.doi.org/10.3109/13697137.2011.609285

[82] Lagunas, N.; Calmarza-Font, I.; Diz-Chaves, Y.; Luis, M. Garcia-Segura. Long-term ovariectomy enhances anxiety and depressive-like behaviors in mice submitted to chronic unpredictable stress. *Horm. Behav.*, **2010**, *58*, 786-791 http://dx.doi.org/10.1016/j.yhbeh.2010.07.014

[83] Schmidt, P. J.; Rubinow, D. R. Menopause-related affective disorders: a justification for further study. *Am. J. Psychiatry*, **1991**, *148*, 844-852. http://dx.doi.org/10.1176/ajp.148.7.844

[84] Pokorski, M.; Siwiec, P. Memory, depression, and progressing old age in women. *J. Physiol. Pharmacol.*, **2006**, *57*, 297-304.

[85] Llanezaa, P.; García-Portillab, M. P.; Llaneza-Suáreza, D.; Armotta B.; Pérez-Lópezc, F. R. Depressive disorders and the menopause transition. *Maturitas*, **2012**, *71*, 120-130.

[86] Freeman, E.W.; Sammel, M.D.; Liu, L.; Gracia, C.R.; Nelson, D.B.; Hollander, L. Hormones and menopausal status as predictors of depression in women in transition to menopause. *Arch. Gen. Psychiatry*, **2004**, *61*, 62-70. http://dx.doi.org/10.1001/archpsyc.61.1.62

[87] Kaufert, P.A.; Gilbert, P.; Tate, R. The Manitoba Project: a re-examination of the link between menopause and depression. *Maturitas*, **2008**, *61*, 54-66. http://dx.doi.org/10.1016/j.maturitas.2008.09.009

[88] Schmidt, P.J.; Rubinow, D.R. Sex hormones and mood in the perimenopause. *Ann. N. Y. Acad. Sci.*, **2009**, *1179*, 70-85. http://dx.doi.org/10.1111/j.1749-6632.2009.04982.x

[89] Weber, M. T.; Maki P.M.; McDermott, M. P. Cognition and mood in perimenopause: A systematic review and meta-analysis. *J. Steroid Biochem. Mol. Biol.*, **2014**, *142*, 90-98. http://dx.doi.org/10.1016/j.jsbmb.2013.06.001

[90] Borrow, A. P.; Cameron, N.M. Estrogenic mediation of serotonergic and neurotrophic systems: Implications for female mood disorders. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry*, **2014**, *54*, 13-25. http://dx.doi.org/10.1016/j.pnpbp.2014.05.009

[91] Mark, D.; Mark, G. Ovariectomy-induced disruption of long-term synaptic depression in the hippocampal CA1 region *in vivo* is attenuated with chronic estrogen replacement. *Neurobiol. Learning Memory*, **2005**, *83*, 13-21. http://dx.doi.org/10.1016/j.nlm.2004.06.009

[92] Ágata, K.; Ana, M. D.; Sofia, I.R. P. 17-Estradiol replacement in young, adult and middle-aged female ovariectomized rats promotes improvement of spatial reference memory and an antidepressant effect and alters monoamines and BDNF levels in memory- and depression-related brain areas. *Behav. Brain Res.*, **2012**, *227*, 100-108. http://dx.doi.org/10.1016/j.bbr.2011.10.047

[93] Erin, E. S.; Pauline, M. M.; Jeffrey, R. B. Review of Estrogen Receptor α Gene (*ESR1*) Polymorphisms, Mood, and Cognition. *Menopause*, **2010**, *17*, 874-886. http://dx.doi.org/10.1097/gme.0b013e3181df4a19

[94] Osterlund, M.K.; Hurd, Y.L. Estrogen receptors in the human forebrain and the relation to neuropsychiatric disorders. *Prog. Neurobiol.*, **2001**, *64(3)*, 251-67. http://dx.doi.org/10.1016/S0301-0082(00)00059-9

[95] Weiser, M.J.; Foradori, C.D.; Handa, R.J. Estrogen receptor beta in the brain: from form to function. *Brain Res. Rev.*, **2008**, *57*, 309-320. http://dx.doi.org/10.1016/j.brainresrev.2007.05.013

[96] Roisin, W.; Susan, R. D.; Emorfia, G.; Zoe, G.; Stuart, L.; Henry, B.; Jayashri, K. Hormonal therapies for new onset and relapsed depression during perimenopause. *Maturitas*, **2012**, *73*, 127- 133. http://dx.doi.org/10.1016/j.maturitas.2012.06.011

[97] Thompson, D.S.; Spanier, C.A.; Vogel, V.G. The relationship between tamoxifen, estrogen, and depressive symptoms. *Breast J.*, **1999**, *5*, 375-82. http://dx.doi.org/10.1046/j.1524-4741.1999.98085.x

[98] Cizza, G.; Gold, P.W.; Chrousos, G.P. High-dose transdermal estrogen, corticotropin-releasing hormone, and postnatal depression. *J. Clin. Endocrinol. Metab.*, **1997**, *82*, 704. http://dx.doi.org/10.1210/jc.82.2.703

[99] Erika, Estrada-Camarena.; Carolina, Lo´ pez-Rubalcava.; Nelly, Vega-Rivera.; Soledad Re´ camier-Carballo.; Alonso Ferna´ndez-G. Antidepressant effects of estrogens: a basic approximation. *Behav. Pharmacol.*, **2010**, *21*, 5-6.

[100] Bernardi, M.; Vergoni, A.V.; Sandrini, M.; Tagliavini, S.; Bertolini, A. Influence of ovariectomy, estradiol and progesterone on the behavior of mice in an experimental model of depression. *Physiol. Behav.*, **1989**, *45(5)*, 1067- 8. http://dx.doi.org/10.1016/0031-9384(89)90238-2

[101] Frye, C. A.; Walf, A. A. Estrogen and/or progesterone administered systemically or to the amygdala can have anxiety-, fear-, and pain-reducing effects in ovariectomized rats. *Behav. Neurosci.*, **2004**, *118*, 306-313. http://dx.doi.org/10.1037/0735-7044.118.2.306

[102] Frye, C. A.; Wawrzycki, J. Effect of prenatal stress and gonadal hormone condition on depressive behaviors of female and male rats. *Horm. Behav.*, **2003**, *44*, 319-326. http://dx.doi.org/10.1016/S0018-506X(03)00159-4

[103] Estrada-Camarena, E.; Fernández-Guasti, A.; López-Rubalcava, C. Antidepressant-like effect of different estrogenic compounds in the forced swimming test. *Neuropsychopharmacology*, **2003**, *28,* 830-838.

[104] Julie, K. S.; Gerard, S.; Gilles, T.; Paul, K. M. Sex Differences in Diencephalon Serotonin Transporter Availability in Major Depression. *Biol. Psychiatry*, **2006**, *59*, 40-47. http://dx.doi.org/10.1016/j.biopsych.2005.06.012

[105] Okada, M; Hayashi, N; Kometani, M; Nakao, K; Inukai, T. Influences of ovary ectomy and continuous replacement of 17beta-estradiol on the tail skin temperature and behavior in the forced

swimming test in rats. *Jpn. J. Pharmacol.*, **1997**, *73*, 93-96. http://dx.doi.org/10.1254/jjp.73.93

[106] Natalia, L.; Isabel, Calmarza-Font.; Yolanda, Diz-Chaves.; Luis, M. Garcia-Segura. Long-term ovariectomy enhances anxiety and depressive-like behaviors in mice submitted to chronic unpredictable stress. *Horm. Behav.*, **2010**, *58*, 786-791. http://dx.doi.org/10.1016/j.yhbeh.2010.07.014

[107] Schmidt, P.J.; Nieman, L.; Danaceau, M.A.; Tobin, M.B.; Roca, CA; Murphy, J.H; Rubinow, D.R. Estrogen replacement in perimenopause-related depression: a preliminary report. *Am. J. Obstetrics Gynecol.*, **2000**, *183*, 414-20. http://dx.doi.org/10.1067/mob.2000.106004

[108] Julie, K. S.; Gerard, S.; Gilles, T.; Paul, K. M. Sex Differences in Diencephalon Serotonin Transporter Availability in Major Depression. *Biol. Psychiatry*, **2006**, *59*, 40-47. http://dx.doi.org/10.1016/j.biopsych.2005.06.012

[109] Robert, K.; Aitchison, K. J. Gender differences in antidepressant drug response. *Intl. Rev. Psychiatry*, **2010**, *22(5)*, 485-500. http://dx.doi.org/10.3109/09540261.2010.496448

[110] Smith, LJ.; Henderson, J.A.; Abell, C.W.; Bethea, C.L. Effects of ovarian steroids and raloxifene on proteins that synthesize, transport, and degrade serotonin in the raphe region of macaques. *Neuropsychopharmacology*, **2004**, *29*, 2035-2045. http://dx.doi.org/10.1038/sj.npp.1300510

[111] Di Paolo, T.; Diagle, M.; Picard, V.; Barden, N. Effect of acute and chronic 17 beta-estradiol treatment on serotonin and 5-hydroxyindole acetic acid content of discrete brain nuclei of ovariectomized rat. *Exp. Brain Res.*, **1983**, *51*, 73-76. http://dx.doi.org/10.1007/BF00236804

[112] Biegon, A.; McEwen, B.S. Modulation by estradiol of serotonin1 receptors in brain. *J. Neurosci.*, **1982***, 2*, 199-205.

[113] Sumner, B.E.H.; Fink, G. Effects of acute estradiol on 5-hydroxytryptamine and dopamine receptor subtype mRNA expression in female rat brain. *Mol. Cell Neurosci.*, **1993**, *4*, 83-92. http://dx.doi.org/10.1006/mcne.1993.1010

[114] Cyr, M.; Bosse, R.; Di Paolo, T. Gonadal hormones modulate 5-hydroxytryptamine2A receptors: Emphasis on the rat frontal cortex. *Neuroscience*, **1998**, *83*, 829-836. http://dx.doi.org/10.1016/S0306-4522(97)00445-4

[115] Sumner, B. E. H.; Grant, K. E.; Rosie, R.; Hegele-Hartung, C.; Fritzemeier, K. H.; Fink, G. Effects of tamoxifen on serotonin transporter and 5-hydroxytryptamine(2A) receptor binding sites andmRNA levels in the brain of ovariectomized rats withor without acute estradiol replacement. *Mol. Brain Res.*, **1999**, *73(1-2)*, 119-128. http://dx.doi.org/10.1016/S0169-328X(99)00243-0

[116] Fink, G.; Sumner, B. E. Oestrogen andmental state. *Nature*, **1996**, 383-306.

[117] Alves, SE;Weiland, NG; Hayashi, S; McEwen BS. Immuno cytochemical localization of nuclear estrogen receptors and progestin receptors within the rat dorsal raphe nucleus. *J. Comp. Neurol.*, **1998**, *391(3)*, 322-34. http://dx.doi.org/10.1002/(SICI)1096-9861(19980216)391:3<322::AID-CNE3>3.0.CO;2-3

[118] Stoffel, E. C.; Craft, R, M. Ovarian hormone withdrawal-induced depression in female rats. *Physiol. Behav.*, **2004**, *83*, 505-513. http://dx.doi.org/10.1016/j.physbeh.2004.08.033

[119] McEwen, B.S.; Alves, S.E. Estrogen actions in the central nervous system. *Endocr. Rev.*, **1999**, *20*, 279-307. http://dx.doi.org/10.1210/er.20.3.279

[120] Pau, K.Y.; Hess, D.L.; Kohama, S.; Bao, J.; Pau, C.Y.; Spies, H.G. Oestrogen upregulates noradrenaline release in the mediobasal hypothalamus and tyrosine hydroxylase gene expression in the brainstem of ovariectomized rhesus macaques. *J. Neuroendocrinol.*, **2000**, *12*, 899-909. http://dx.doi.org/10.1046/j.1365-2826.2000.00549.x

[121] Vetrivelan, R.; Mallick, HN.; Kumar, V.M. Tonic activity of alpha1 adrenergic receptors of the medial preoptic area contributes towards increased sleep in rats. *Neuroscience*, **2006**, *139*, 1141-1151. http://dx.doi.org/10.1016/j.neuroscience.2006.01.046

[122] Becker, J. Direct effect of 17 beta-estradiol on striatum: sex differences in dopamine release. *Synapse*, **1990**, *5*, 157-164. http://dx.doi.org/10.1002/syn.890050211

[123] Di Paolo, T.; Diagle, M.; Picard, V.; Barden, N. Effect of acute and chronic 17 beta-estradiol treatment on serotonin and 5-hydroxyindole acetic acid content of discrete brain nuclei of ovariectomized rat. *Exp. Brain Res.*, **1983**, *51*, 73-76. http://dx.doi.org/10.1007/BF00236804

[124] Johnson, M. D.; Crowley, W. R. Acute effects of estradiol on circulating luteinizing hormone and prolactin concentrations and on serotonin turnover in individual brain nuclei. *Endocrinology*, **1983**, *113*, 1935-1941. http://dx.doi.org/10.1210/endo-113-6-1935

[125] Morissette, M.; Levesque, D.; Belanger, A.; Di Paolo, T. A physiological dose of estradiol with progesterone affects striatum biogenic amines. *Can. J. Physiol. Pharmacol.*, **1990**, *68*, 1520-1526. http://dx.doi.org/10.1139/y90-231

[126] Munaro, N. I. The effect of ovarian steroids on hypothalamic 5-hydroxytryptamine neuronal activity. *Neuroendocrinology*, **1978**, *26*, 270-276. http://dx.doi.org/10.1159/000122782

[127] Cone, R. I.; Davis, G. A.; Goy, R. W. Effects of ovarian steroids on serotonin metabolism within grossly dissected and microdissected brain regions of the ovariectomised rat. *Brain Res. Bull.*, **1981**, *7*, 639-644. http://dx.doi.org/10.1016/0361-9230(81)90111-8

[128] Pecins-Thompson, M.; Brown, N. A.; Kohama, S. G.; Bethea, C. L. Ovarian steroid regulation of tryptophan hydroxylase mRNA expression in rhesus macaques. *J. Neurosci.*, **1996**, *16*, 7021-7029.

[129] Cohen, IR.; Wise, P. M. Effects of estradiol on the diurnal rhythm of serotonin activity in microdissected brain areas of ovariectomized rats. *Endocrinology*, **1988**, *122*, 2619 -2625. http://dx.doi.org/10.1210/endo-122-6-2619

[130] McQueen, J.K.; Wilson, H.; Dow, R.C.; Fink, G . Oestradiol- 17b increases serotonin transporter (SERT) binding sites and SERT mRNA expression in discrete regions of female rat brain. *J. Physiol.*, **1996**, *495*, 114.

[131] Thomas, M.L.; Bland, D.A.; Clarke, C.H.; Cunningham, K.A. Estrogen regulation of serotonin (5-HT) transporter and5-HT1A receptor mRNA in female rat brain. *Abstr. Soc. Neurosci.*, **1997**, *23*, 1501.

[132] Biegon, A.; Reches, A.; Snyder, L.; McEwen, B. S. Serotonergic and noradrenergic receptors in the rat brain: Modulation by chronic exposure to ovarian hormones. *Life Sci.*, **1983**, *32*, 2015-2021. http://dx.doi.org/10.1016/0024-3205(83)90053-X

[133] Osterlund, M. K.; Halldin, C.; Hurd, Y. L. Effects of chronic 17beta-estradiol treatment on the serotonin 5-HT(1A) receptor mRNA and binding levels in the rat brain. *Synapse*, **2000**, *35(1)*, 39-44. http://dx.doi.org/10.1002/(SICI)1098-2396(200001)35:1<39::AID-SYN5>3.0.CO;2-T

[134] Osterlund, M. K.; Hurd, Y. L. Acute 17 beta-estradiol treatment down-regulates serotonin 5HT1A receptor mRNA expres- sion in the limbic system of female rats. *Mol. Brain Res.*, **1998**, *55(1)*, 169-172. http://dx.doi.org/10.1016/S0169-328X(98)00018-7

[135] Pecins-Thompson, M.; Bethea, C. L. Ovarian steroid regulation of serotonin-1A autoreceptor messenger RNA expression in the dorsal raphe of rhesus macaques. *Neuroscience*, **1999**, *89(1)*, 267-277. http://dx.doi.org/10.1016/S0306-4522(98)00326-1

[136] Fink, G.; Sumner, B.; Rosie, R.; Wilson, H.; McQueen, J. Androgen actions on central serotonin neurotransmission: Relevance for mood, mental state and memory. *Behav. Brain Res.*, **1999**, *105(1)*, 53-68. http://dx.doi.org/10.1016/S0166-4328(99)00082-0

[137] Sumner, B. E. H.; Fink, G. Estrogen increases the density of 5-hydroxytryptamine(2A) receptors in cerebral cortex and nucleus accumbens in the female rat. *J. Steroid Biochem. Mol. Biol.*, **1995**, *54(1-2)*, 15-20. http://dx.doi.org/10.1016/0960-0760(95)00075-B

[138] Sumner, B. E. H.; Grant, K.E.; Rosie, R.; Hegele-Hartung, C.; Fritzemeier, K. H. Fink, G. Effects of tamoxifen on serotonin transporter and 5-hydroxytryptamine(2A) receptor binding sites and mRNA levels in the brain of ovary ectomized rats with or without acute estradiol replacement. *Mol. Brain Res.*, **1999**, *73(1-2)*, 119-128. http://dx.doi.org/10.1016/S0169-328X(99)00243-0

[139] Komulainen, P.; Pedersen, M.; Tuomo, H.; Bruunsgaard, H. BDNF is a novel marker of cognitive function in ageing women: The DR's EXTRA Study. *Neurobiol. Learn. Memory*, **2008**, *90*, 596-603. http://dx.doi.org/10.1016/j.nlm.2008.07.014

[140] Castre′ n E.; Rantamaki, T. The Role of BDNF and Its Receptors in Depression and Antidepressant Drug Action: Reactivation of Developmental Plasticity. *Devel. Neurobiol.*, **2010**, *22*, 289-297.

[141] Allen, A. L.; McCarson, K. E. Estrogen Increases Nociception-Evoked Brain-Derived Neurotrophic Factor Gene Expression in the Female Rat. *Neuroendocrinology*, **2005**, *81*, 193-199. http://dx.doi.org/10.1159/000087002

[142] Cavus, I.; Duman, R.S. Influence of Estradiol, Stress, and 5-HT2A Agonist Treatment on Brain-Derived Neurotrophic Factor Expression in Female Rats. *Biol. Psychiatry*, **2003**, *54*, 59-69. http://dx.doi.org/10.1016/S0006-3223(03)00236-1

[143] Scharfman, H. E.; Maclusky, N. J. Similarities between actions of estrogen and BDNF in the hippocampus: Coincidence or clue? *Trends Neurosci.*, **2005**, *28*, 79-85. http://dx.doi.org/10.1016/j.tins.2004.12.005

[144] Zhou, J.; Zhang, H.; Cohen, R. S.; Pandey, S, C. Effects of estrogen treatment on expression of BDNF and CREB expression and phosphorylation in rat amygdaloid and hippocampal structures. *Neuroendocrinology*, **2005**, *81(5)*, 294-310. http://dx.doi.org/10.1159/000088448

[145] Spencer, J. L.; Waters, E. M.; Romeo, R. D.; Wood, G. E.; Teresa M. A.; McEwen, B.S. Uncovering the mechanisms of estrogen effects on hippocampal function. *Front. Neuroendocrinol.*, **2008**, *29*, 219-237.

[146] Wu, Y. C.; Hill, R. A.; Gogos, A.; Buuse, Van Den, M. Sex differences and the role of Estrogen in animal models of schizophrenia: Interaction with BDNF. *Neuroscience*, **2013**, *239*, 67-83. http://dx.doi.org/10.1016/j.neuroscience.2012.10.024

[147] Farida, S.; Danielle, K. Lewis. Estrogen-BDNF interactions: Implications for neurodegenerative diseases. *Front. Neuroendocrinol.*, **2006**, *27*, 404-414. http://dx.doi.org/10.1016/j.yfrne.2006.09.003

[148] Galea, L. A. M.; Mark, D., Jennifer, S.; Barker, M.; Pawluski, J. L. Gonadal Hormone Modulation of Hippocampal Neurogenesis in the Adult. *Hippocampus*, **2006**, *16*, 225-232. http://dx.doi.org/10.1002/hipo.20154

[149] Galea, L. A. M. Gonadal hormone modulation of neurogenesis in the dentate gyrus of adult male and female rodents. *Brain Res. Rev.*, **2008**, *57*, 332-341. http://dx.doi.org/10.1016/j.brainresrev.2007.05.008

[150] Korosia; A. E. F. G. Nanincka; C. A. Oomenb; M. Schoutena; H. Krugersa; C. Fitzsimonsa; P. J. Lucassena. Early-life stress mediated modulation of adult neurogenesis and behavior. *Behav. Brain Res.*, **2012**, *227*, 400-409. http://dx.doi.org/10.1016/j.bbr.2011.07.037

[151] Bredy, T.W.; Grant, R.J.; Champagne, D.L.; Meaney, M.J. Maternal care influences neuronal survival in the hippocampus of the rat. *Eur. J. Neurosci.*, **2003**, *18*, 2903-9. http://dx.doi.org/10.1111/j.1460-9568.2003.02965.x

[152] Pawluski, J. L.; Brummelte, S.; Barha, C. K.; Tamara, M. Crozier; Galea, L. A. M.. Effects of steroid hormones on neurogenesis in the hippocampus of the Frontiers. *Neuroendocrinology*, **2009**, *30*, 343-357.

[153] Saravia, F.; Beauquis, J.; Pietranera, L.; De Nicola, A. F. Neuroprotective effects of estradiol in hippocampal neurons and glia of middle age mice. *Psychoneuroendocrinology*, **2007**, *32*, 480-492. http://dx.doi.org/10.1016/j.psyneuen.2007.02.012

[154] Christie, D.; Yan, L. F.; Zuoxin, W. Estrogen and adult neurogenesis in the amygdala and hypothalamus. *Brain Res. Rev.*, **2008**, *57*, 342-351. http://dx.doi.org/10.1016/j.brainresrev.2007.06.011

[155] Arimatsu, Y.; Hatanaka, H. Estrogen treatment enhances survival of cultured fetal rat amygdala neurons in a defined medium. *Brain Res.*, **1986**, *391*, 151-159. http://dx.doi.org/10.1016/0165-3806(86)90017-9

[156] Chowen, J. A.; Torres-Aleman, I.; Garcia-Segura, L. M. Trophic effects of estradiol on fetal rat hypothalamic neurons. *Neuroendocrinology*, **1992**, *56*, 895-901. http://dx.doi.org/10.1159/000126321

[157] Michael, K.; Mary, G.; Petra, S.; Lisa, G.; Martin, D.; Sara, K.; Manfred, U.; Alexander, Y.; Axel, S. Ghrelin increases slow wave sleep and stage 2 sleep and decreases stage 1 sleep and REM sleep in elderly men but does not affect sleep in elderly women. *Psychoneuroendocrinology*, **2010**, *35*, 297-304. http://dx.doi.org/10.1016/j.psyneuen.2009.07.007

[158] Barkan, A. L.; Dimaraki, E. V.; Jessup, S. K.; Symons, K. V.; Ermolenko, M.; Jaffe, C. A. Ghrelin secretion in humans is sexually dimorphic, suppressed by somatostatin, and not affected by the ambient growth hormone levels. *J. Clin. Endocrinol. Metab*., **2003**, *88*, 2180-2184. http://dx.doi.org/10.1210/jc.2002-021169

[159] Akamizu, T.; Murayama, T.; Teramukai, S.; Miura, K.; Bando, I. Plasma ghrelin levels in healthy elderly volunteers: the levels of acylated ghrelin in elderly females correlate positively with serum IGF-I levels and bowel movement frequency and negatively with systolic blood pressure. *J. Endocrinol.*, **2006**, *188*, 333-344. http://dx.doi.org/10.1677/joe.1.06442

[160] Kellokoski, E.; Poykko, S. M.; Karjalainen, A. H.; kkola, O; Heikkinen, J.; Kesäniemi, Y.A.; Hörkkö, S. Estrogen replacement therapy increases plasma ghrelin levels. *J. Clin. Endocrinol. Metab.*, **2005**, *90*, 2954-63. http://dx.doi.org/10.1210/jc.2004-2016

[161] Di Carlo, C.; Tommaselli, G. A.; Gargano, V.; Sammartino, A., Bifulco, G., Tauchmanova, L., Colao, A., Nappi, C. Effects of estrogenprogestin therapy on serum levels of RANKL, osteoprotegerin, osteocalcin, leptin, and ghrelin in postmenopausal women. *Menopause*, **2007**, *14*, 38-44. http://dx.doi.org/10.1097/01.gme.0000227855.04732.7b

[162] Lambrinoudaki, I. V.; Christodoulakos, G.E. Economou, E.V. ; Vlachou, S.A.; Panoulis, C.P.; Alexandrou, A.P.; Kouskouni, E.E.; Creatsas, G.C. Circulating leptin and ghrelin are differentially influenced by estrogen/progestin therapy and raloxifene. *Maturitas*, **2008**, *59*, 62-71. http://dx.doi.org/10.1016/j.maturitas.2007.10.003

[163] Grinspoon, S.; Miller, K. K.; Herzog, D. B.; Grieco, K. A.; Klibanski, A. Effects of estrogen and recombinant human insulin-like growth factor-I on ghrelin secretion in severe under nutrition. *J. Clin. Endocrinol. Metab.*, **2004**, *89*, 3988-3993. http://dx.doi.org/10.1210/jc.2004-0287

[164] Kellokoski, E.; Poykko, S. M.; Karjalainen, A. H.; Ukkola, O.; Heikkinen, J.; Kesaniemi, Y. A.; Horkko, S. Estrogen replacement therapy increases plasma ghrelin levels. *J. Clin. Endocrinol. Metab.*, **2005**, *90*, 2954-2963. http://dx.doi.org/10.1210/jc.2004-2016

[165] Johannes, D.; Veldhuis.; Daniel, M.; Iranmanesh, A. K.; Kristi M.;. Miles, J. M.; Cyril, Y. B. Estradiol Potentiates Ghrelin-Stimulated Pulsatile Growth Hormone Secretion in Postmenopausal Women. *J. Clin. Endocrinol. Metabol.*, **1991**, *9*, 3559-3565.

[166] Petra, K.; Paulo, R. C.; Cosma, M.; Kristi, L.; Mielke, J. M.; Cyril, M. Y. B.; Johannes, D. Veldhuis. Estrogen Supplementation Selectively Enhances Hypothalamo-Pituitary Sensitivity to Ghrelin in Postmenopausal Women. *J. Clin. Endocrinol. Metab.*, **2008**, *93*(10), 4020-4026. http://dx.doi.org/10.1210/jc.2008-0522

[167] Ichiro, S.; Toru, T.; Mami, Y.; Takashi, T.; Zhao Z.; Takafumi, S. Gastric estrogen directly induces ghrelin expression and production in the rat stomach. *J. Endocrinol.*, **2006**, *190*, 749-757. http://dx.doi.org/10.1677/joe.1.06808

[168] Marı´a, C. G.; Miguel, L.; Clara, V. A.; Felipe, C.; Manuel, Tena-Sempere.; Carlos, D. Role of ghrelin in reproduction. *Reproduction*, **2007**, *133*, 531-540.

[169] Rak, A.; Gregoraszczuk, E. L. Modulatory effect of ghrelin in prepubertal porcine ovarian follicles. *J. Physiol. Pharmacol.*, **2008**, *59*, 781-793.

[170] Michopoulos, V.; Berga, S. L.; Kaplan, J. R.; Wilson, M. E. Social subordination and polymorphisms in the gene encoding the serotonin transporter enhance estradiol inhibition of luteinizing hormone secretion in female rhesus monkeys. *Biol. Reprod.*, **2009**, *81*, 1154-1163. http://dx.doi.org/10.1095/biolreprod.109.079038

[171] Michopoulos, V.; M. Embree, K. R.; Reding, K., Sanchez, M.M., Toufexis, D., Votaw, J.R., Voll, R.J., Goodman, M.M., Rivier, J., Wilson, M.E., Berga, S.L. AgCRH receptor antagonism reverses the effect of social subordination upon central GABAA receptor binding in Estradiol-treated ovariectomized female thesus monkeys. *Neuroscience*, **2013**, *250*, 300-308. http://dx.doi.org/10.1016/j.neuroscience.2013.07.002

[172] Wenlong, Z.; Zhihai, L.; Juan, S.; Shulin, C. Expression of ghrelin in the porcine hypothalamo-pituitary-ovary axis during the estrous cycle. *Anim. Reprod. Sci.*, **2008**, *109*, 356-367. http://dx.doi.org/10.1016/j.anireprosci.2007.12.020

[173] Burger, L. L.; Dalkin, A. C.; Aylor, K. W.; Workman, L. J.; Haisenleder, D. J.; Marshall, J. C. Regulation of gonadotropin subunit transcription after ovary ectomy in the rat: measurement of subunit primary transcripts reveals differential roles of GnRH and inhibin. *Endocrinology*, **2001**, *142*, 3435-42. http://dx.doi.org/10.1210/endo.142.8.8315

[174] Olson, D. R.; Blake, C. A. Basal luteinizing hormone and folliclestimulating hormone release rates as a function of time after castration in female and male rats. *Neuroendocrinology*, **1991**, *53*, 124-33. http://dx.doi.org/10.1159/000125709

[175] Maki, M.; Ichiro, S.; Reiko, W.; Mami, Y.; Kinji, I.; Takafumi, S. Estrogen modulates ghrelin expression in the female rat stomach.

Peptides, **2004**, *25*, 289-297. http://dx.doi.org/10.1016/j.peptides.2003.12.020

[176] Horn, C. A.; Fletcher, T. P.; Carpenter, S. Effects of oestradiol-17 on peripheral plasma concentrations of LH and FSH in ovary ectomized tammars (Macropuseugenii). *J. Reprod. Fert.*, **1985**, *73*, 585-592. http://dx.doi.org/10.1530/jrf.0.0730585

[177] Rafael, Ferna´ndez-Ferna´ndez.; Manuel, Tena-Sempere.; Juan, R.; Juan, M. C.;V1´ctor, M. N.; Enrique, A.; Leonor, P. Direct stimulatory effect of ghrelin on pituitary release of LH through a nitric oxide-dependent mechanism that is modulated by estrogen. *Reproduction*, **2007**, *133*, 1223-1232. http://dx.doi.org/10.1530/REP-06-0227

[178] Iqbal, J.; Kurose, Y.; Canny, B.; Clarke, I. J. Effects of central infusion of ghrelin on food intake and plasma levels of growth hormone, luteinizing hormone, prolactin, and cortisol secretion in sheep. *Endocrinology*, **2006**, *147*, 510-9. http://dx.doi.org/10.1210/en.2005-1048

[179] Kaynard, A. H.; Pau, K. Y.; Hess, D. L.; Spies, H. G. Third-ventricular infusion of neuropeptide Y suppresses luteinizing hormone secretion in ovariectomized rhesus macaques. *Endocrinology*, **1990**, *127*, 2437-2444. http://dx.doi.org/10.1210/endo-127-5-2437

[180] Vulliemoz, N. R; Xiao, E.; Xia-Zhang, L.; Wardlaw, S. L; Ferin, M. Central infusion of AGRP suppresses pulsatile release in ovariectomized rhesus monkeys. *Endocrinology*, **2005**, *146(2)*, 784-9. http://dx.doi.org/10.1210/en.2004-1093

[181] Vulliemoz, N. R; Xiao, E.; Xia-Zhang, L.; Germond, M.; Rivier, J.; Ferin, M. Decrease in Luteinizing Hormone Pulse Frequency during a Five-Hour Peripheral Ghrelin Infusion in the Ovari ectomized Rhesus Monkey. *J. Clin. Endocrinol. Metab.*, **2004**, *89(11)*, 5718-5723. http://dx.doi.org/10.1210/jc.2004-1244

[182] Michael, K.; Doreen, S.; Manfred, U.; Axel, S. Ghrelin suppresses nocturnal secretion of luteinizing hormone (LH) and thyroid stimulating hormone (TSH) in patients with major depression. *J. Psychiatric Res.*, **2013**, *47*, 1236-1239. http://dx.doi.org/10.1016/j.jpsychires.2013.05.010

[183] Fabio, L.; Lorenza, B.; Matteo, B.; Elisa, M.; Fabio, B.; Ezio, G. Acylated Ghrelin Inhibits Spontaneous Luteinizing Hormone Pulsatility and Responsiveness to Naloxone But Not That to Gonadotropin-Releasing Hormone in Young Men: Evidence for a Central Inhibitory Action of Ghrelin on the Gonadal Axis. *J. Clin. Endocrinol. Metab.*, **2008**, *93(9)*, 3633-3639. http://dx.doi.org/10.1210/jc.2008-0049

[184] Kaynard, A. H.; Pau, K. Y.; Hess, D. L.; Spies, H. G. Third-ventricular infusion of neuropeptide Y suppresses luteinizing hormone secretion in ovariectomized rhesus macaques. *Endocrinology*, **1990**, *127*, 2437-2444 http://dx.doi.org/10.1210/endo-127-5-2437

[185] Vulliemoz, N. R.; Xiao, E.; Xia-Zhang, L.; Wardlaw, S. L.; Ferin, M. Central infusion of AGRP suppresses pulsatile release in ovariectomized rhesus monkeys. *Ann. Meeting Endocrine Soc.*, **2005**, *146*, 784-9.

[186] Kamegai, J.; Tamura, H.; Shimizu, T.; Ishii, S.; Sugihara, H.; Wakabayashi, I. Chronic central infusion of ghrelin increases hypothalamic neuropeptide Y and agouti-related protein mRNA levels and body weight in rats. *Diabetes*, **2001**, *50*, 2438-2443. http://dx.doi.org/10.2337/diabetes.50.11.2438

[187] Chen, H. Y.; Trumbauer, M. E.; Chen, A. S.; Weingarth, D.T., Adams, J.R., Frazie,r E.G., Shen, Z., Marsh, D.J., Feighner,S.D., Guan, X.M., Ye, Z., Nargund, R.P., Smith, RG, Van der Ploeg L.H., Howard, A.D., MacNeil, D.J., Qian, S. Orexigenic action of peripheral ghrelin is mediated by neuropeptide Y and agouti-related protein. *Endocrinology*, **2004**, *145*, 2607-2612. http://dx.doi.org/10.1210/en.2003-1596

[188] Vullie´moz, N. R.; Xiao, E.; Xia-Zhang, L.; Rivier, J.; Ferin, M. Astressin, B, a nonselective CRH receptor antagonist, prevents the inhibitory effect of ghrelin on LH pulse frequency in the ovariectomized rhesus monkey. *Endocrinology*, **2008**, *149*, 869-874 http://dx.doi.org/10.1210/en.2007-1350

[189] Rivier, J. E.; Kirby, D. A.; Lahrichi, S. L.; Corrigan, A.; Vale, W. W.; Rivier, C. L. Constrained corticotropin releasing factor antagonists (astressin analogues) with long duration of action in the rat. *J. Med. Chem.*, **1999**, *42*, 3175-3182. http://dx.doi.org/10.1021/jm9902133

[190] Kandi, P.; Hayslett, R. L. Nicotine and 17 -estradiol produce an antidepressant-like effect in female ovariectomized rats Brain. *Res. Bull.*, **2011**, *84*, 224-228. http://dx.doi.org/10.1016/j.brainresbull.2010.12.012

[191] Prange, A. Estrogen may well affect response to antidepressant. *J. Am. Med. Assoc.*, **1972**, *219*, 143-144.

[192] Schneider, L.; Small, G.; Clary, C. M. Estrogen replacement therapy and antidepressant response to sertraline in older depressed women. *Am. J. Geriatr. Psychiatr.*, **2001**, *9*, 393-399. http://dx.doi.org/10.1097/00019442-200111000-00007

[193] Schneider, L.; Small, G.; Hamilton, S.; Bystrisky, A.; Nemeroff; C. Meyers, B. Estrogen replacement and response to fluoxetine in surgically menopausal women. *Am. J. Geriatr. Psychiatr.*, **1997**, *5*, 97-106. http://dx.doi.org/10.1097/00019442-199721520-00002

[194] Hong, Z.; Qian, H.; Hao, X.; Lei, N.; Jiang-Ning, Z. Antidepressant-like effects of sodium butyrate in combination with estrogen in rat forced swimming test: Involvement of 5-HT1A receptors. *Behav. Brain Res.*, **2009**, *196*, 200-206. http://dx.doi.org/10.1016/j.bbr.2008.08.039

[195] Kornstein, S. G.; Schatzberg, A. F.; Thase, M. E.; Yonkers, K. A.; McCullough, J. P.; Keitner, G. I.; Keller, M. B. Gender differences in treatment response to sertraline versus imipramine in chronic depression. *Am. J. Psychiatry*, **2000**, *157*, 1445-1452. http://dx.doi.org/10.1176/appi.ajp.157.9.1445

[196] Estrada-Camarena, E.; Fernandez-Guasti, A.; Lopez-Rubalcava, C. Interaction between estrogens and antidepressants in the forced swimming test in rats. *Psychopharmacology (Berl)*, **2004**, *173*, 139-45. http://dx.doi.org/10.1007/s00213-003-1707-4

[197] Sell, S. L.; Craft, R. M.; Seitz, P. K.; Stutz, S. J.; Cunningham, K. A.; Thomas, M. L. Estradiol-sertraline synergy in ovariectomized rats. *Psychoneuroendocrinology*, **2008**, *33*, 1051-60. http://dx.doi.org/10.1016/j.psyneuen.2008.05.006

Received: November 17, 2014 Revised: January 13, 2015 Accepted: January 24, 2015