World Journal of Experimental Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5493/wjem.v5.i2.103

World J Exp Med 2015 May 20; 5(2): 103-109
ISSN 2220-315X (online)

REVIEW

Mood disorders: A potential link between ghrelin and leptin on human body?

Stalo Zarouna, Greta Wozniak, Anastasia Ioannis Papachristou

Stalo Zarouna, Psychology Department, University of Cyprus, Nicosia 1678, Cyprus
Greta Wozniak, Basic Medical Science, Medical Pharmacology, Medical School, University of Cyprus, Nicosia 1678, Cyprus
Anastasia Ioannis Papachristou, School of Medicine, University of Crete, Voutes Campus, Heraklion, GR-71003 Crete, Greece
Author contributions: All authors contributed to this paper.
Conflict-of-interest: None conflict of interest.

Correspondence to: Greta Wozniak, MD, PhD, Assistant Professor of Basic Medical Science, Medical Pharmacology, Medical School, University of Cyprus, Kallipoleos 75, Nicosia 1678, Cyprus. greta@ucy.ac.cy
Telephone: +357-22-895221
Fax: +357-22-895221
Received: September 26, 2014
Peer-review started: September 28, 2014
First decision: December 17, 2014
Revised: January 9, 2015
Accepted: January 30, 2015
Article in press: February 2, 2015
Published online: May 20, 2015

Abstract

Leptin and ghrelin are two hormones associated with multiple physiological functions, especially energy balance. Leptin is an adipocyte-secreted hormone discovered in 1950 and ghrelin which was found in 1999, is a peptide hormone produced and secreted in the stomach. A number of previous studies showed that these hormones could be associated with different types of mood disorders. The results of previous studies, nevertheless, are confounded by diverse sample selection and different methodologies. A search for related articles in the PubMed database was attempted. The search covered studies, reports, reviews and editorials published in the last ten years. Older references served as auxiliary sources for comparison purposes. However, due to the different results of the studies, there is a need for more investigation in order to establish the exact biochemical mechanisms that are responsible for these diseases and ghrelin's and leptin's effects on mood.

Key words: Mood disorders; Ghrelin; Leptin

Core tip: Mood disorders are affecting a major amount of the world population. Considering the multiple factors that are contributing in the development of mood disorders, this review emphasizes on the role of leptin and ghrelin hormones. These two hormones have a key role in energy balance but they also have an effect on other physiological functions too, therefore we emphasize on the recent findings which raise a potential link between the hormones and the disorders of mood.

Zarouna S, Wozniak G, Papachristou AI. Mood disorders: A potential link between ghrelin and leptin on human body? *World J Exp Med* 2015; 5(2): 103-109 Available from: URL: http://www.wjgnet.com/2220-315X/full/v5/i2/103.htm DOI: http://dx.doi.org/10.5493/wjem.v5.i2.103

INTRODUCTION

Mood disorders (MD) cover a wide range of mental illnesses and many studies have examined different aspects of them, such as their effect on social life of a person and how they are evolutionary changing through the years. Anxiety disorders and major

depressive disorder (MDD) are the most prevalent mental disabilities and affect a large amount of the world population[1]. The etiology of MDs is diverse. Genetic factors like family history, as well as psychological and socioeconomic features have a key role on the development of MDs[2-4]. As far as genetic factors are concerned, there has been a great deal of research on a specific gene called brain-derived neurotrophic factor (BDNF), which has an important role to the pathophysiology of MDs but which might also contribute to the therapeutic mechanisms, by exerting antidepressant effects[5,6]. BDNF is involved in neuronal plasticity, and has antidepressant effects probably due to its interaction with serotonin systems[7,8]. This interaction monitors the development and plasticity of the neural circuits which have a role in MDs. Likewise, antidepressant drugs can alter the levels of neurotrophic factors and therefore are able to contribute in neuronal plasticity[9].

Different parts of the brain are involved in the regulation of mood and the expression of emotions, as well as other functions, like reward processing[10]. Neuroimaging and neuropathological studies support that the medial prefrontal cortex, the caudolateral orbital cortex, the amygdala, the hippocampus and the ventromedial parts of the basal ganglia are networks which modulate emotional behavior[10]. There is evidence that the function of these structures is altered in patients with MDs[11-13]. For example, in cases of stress and long-term depression, the hippocampus and the prefrontal cortex are subjected to atrophy while amygdala is subjected to hyperaction[14]. Another important site of the brain that associates with MDs is the hypothalamic-pituitary-adrenal axis (HPA) which consists of the hypothalamus, the pituitary and adrenal cortex[15]. The regulation of the HPA-axis depends on the inputs that the paraventricular nucleus receives but it is also auto-regulatory. The auto-regulation is important for allostasis and it is hypothesized that allostatic change may link to MDs[15]. Moreover, a dysregulation of the HPA axis it is often connected with MDD.

The areas of the brain mentioned above are not only associated to MDs but they also have an important role in feeding behavior and nutrition hormones. Whether food choice and mood have a negative or a positive relationship depends on the psychological and the neurohormonal characteristics of a person[16]. The correlation of MDs and food intake is supported by the irregularities of the HPA axis function[17]. Danaei *et al*[18] reported that obesity has become a pandemic in the last five decades. Numerous studies have showed that obesity and MDs are related. More specifically, depression and major depression are reported as risks factors for developing obesity particularly for women[19-25].

There is evidence that obesity may be a risk factor for anxiety disorders too[26,27]. Under normal conditions, the brain is activated to confront perceived threats, by altering the HPA axis and by entering into an anabolic state. When an individual faces chronic stress, however, the metabolism shifts to catabolic state[28].

HPA axis is not the only region of the brain that is affected by MDs. The cortex, the limbic system, the midbrain and the brainstem are also subjected to changes[29]. When the physiological pathways are activated due to chronic stress, cortisol rises, and appetite hormones as well as weight are altered[30]. The reinforced motivation for food is caused by the increased secretion of glucocorticoids and which in turn leads to obesity[31].

Another hypothesis which supports the relation between obesity and MDs refers to the inefficiency of leptin signaling[32]. Leptin is a 16-kDa protein which is encoded by the obese (*ob*) gene and is mainly secreted by the white adipose tissue[33]. Leptin suppresses food intake, whereas another hormone called ghrelin stimulates appetite. Ghrelin, is a hormone secreted from stomach but it can be found in small amounts in the brain too[34]. Surprisingly, obese individuals have high circulating leptin levels, in contrast to the orexigenic hormone which is found in low levels. This suggests that obese people are leptin-resistant[35].

In this review, we focus on recent findings regarding the role of ghrelin and leptin in the regulation of MDs such MDD, and we refer to the mechanism of the pathophysiology of MD. This review points at the potential link between ghrelin and leptin on human body and MDs, as they serve as complementary hormones with multiple functions. This review takes into account information from 2004 to 2014 on the leptin and ghrelin hormones and more specifically, their function in the central nervous system (CNS), and their potential role in MDs.

LEPTIN'S ROLE IN MOOD REGULATION

Leptin has a key role in energy intake and expenditure. Specifically, circulating leptin sends information to the hypothalamus about the changes of energy intake and how much energy is stored in the adipose tissue[36]. Leptin is produced peripherally in the adipose tissue so it is essential to cross the blood-brain barrier to act inside the brain[37]. It is believed that the transportation of leptin into the brain follows a saturable system and crosses the blood-brain barrier *via* LepRs which are located in nonneural cells in the meninges, choroid and blood vessels[38,39]. The transportation of leptin becomes more intensive in the hypothalamic ARC (Arcuate Nucleus), a major site for leptin signaling and resistance[38]. Leptin affects two types of neurons in the ARC; a group of neurons secrets the protein POMC (proopiomelanocortin) together with cocaine and amphetamine-regulated transcript (CART), whereas the other class of neurons expresses neuropeptide Y (NPY) and AgRP (agouti-related protein)[40]. The NPY and AgRP peptides are expressed with the reduction of leptin, while CART and POMC are suppressed[41].

The HPA is a brain area that was systematically

Table 1 Leptin in patients with mood disorders according study's since 2004

Ref.	Findings
Westling *et al*[51]	Low CSF leptin in MDD women
Atmaca *et al*[52]	Low in OCD + D
Esel *et al*[57]	High in women but not in men
Gecici *et al*[54]	High in patients with atypical depressive disorder but not with non-atypical
Jow *et al*[50]	Low
Emul *et al*[53]	No difference
Pasco *et al*[47]	High in females non-smokers
Jimenez *et al*[46]	High in patients with post-stroke depression
Hafner *et al*[56]	High in men with social isolation and depressed
Lawson *et al*[45]	Low
Hafner *et al*[55]	High in normal-weight women
During antidepressant therapy	
Himmerich *et al*[42]	High after successful treatment

CSF: Cerebrospinal fluid; MDD: Major depressive disorder; OCD + D: Obsessive compulsive disorder + depression.

found to be associated with MDs. In depression, the overstimulation of HPA axis caused by glucocorticoid receptor resistance increase leptin synthesis and secretion[42]. Thus, studies on mouse models showed that leptin might modulate HPA function. Specifically, it seems that peripheral and hippocampal administration of leptin mitigates symptoms of depression[33,43,44]. The results of some human studies are consistent with animal studies as they showed that leptin reduces symptoms of depression and had anxiolytic effects[45]. There is a study by Jimenez *et al*[46], however, which suggests that leptin might predict post-stroke depression, as higher leptin levels were found in patients with depression after stroke[46]. Similarly, a cross-sectional study by Pasco *et al*[47], demonstrated that depressive disorders can be predicted by high serum leptin levels among female non-smokers. In addition, elevated leptin levels as well as visceral fat seem to predict depressive symptoms in old men[48]. Likewise, in a longitudinal study by Milaneschi *et al*[49] high levels of leptin and abdominal adiposity were a high risk factor for the development of depressed mood over a 9-year follow up.

Studies in humans have given controversial evidence about the role of leptin in MDs. A few studies reported that depression is associated with low leptin levels independent of body mass[45,50]. Furthermore, one study revealed that female suicide attempters with MDD had lower cerebrospinal fluid leptin than in the group with other disorders, even though both groups had similar body mass index (BMI)[51]. Patients with MDD, Obsessive Compulsive Disorder (OCD) and comorbid depression were examined in various studies. It was found that these patients had significantly lower leptin levels and higher cortisol levels than healthy controls and patients without comorbid depression and MDD[52]. Furthermore, Emul *et al*[53] found that the comorbid MDD with OCD group did not have any difference compared to patients with pure OCD and controls.

On the contrary, other studies showed that patients with different types or symptoms of depression, such as atypical depressive disorders, depressed mood and sleep disturbances as well as social isolation, had higher leptin levels than a control group[47,54-56]. Researchers who investigated the effects of leptin on antidepressant treatments found out that leptin was increased during drug treatment[42,57]. As far as anxiety is concerned, Lawson *et al*[45] found that increased symptoms of anxiety were related with low levels of leptin, independent of BMI and weight, supporting that leptin is an anti-stress hormone (Table 1).

GHRELIN'S ROLE IN MOOD REGULATION

Ghrelin is a 28-amino acid peptide, secreted from stomach and functions as an orexigenic hormone, while it is increased before meals and reduced after meals[58-61]. Ghrelin is acylated [acyl ghrelin (AG)] by ghrelin O-acyl transferase in the stomach and 10%-20% of circulating ghrelin exists in this form[59]. Acylation is required for ghrelin to activate its receptor, the growth hormone secretagogue receptor (GHSR). In particular, it promotes food intake and adiposity sending a peripheral signal to the hypothalamus through the neuropeptide Y and agouti-related protein[62]. Even though AG has a major role in energy balance it also contributes in other biological functions too, such as the regulation of insulin secretion, the regulation of glucose metabolism and influences the pituitary-gonadal axis[63].

Although ghrelin is present in the stomach and other peripheral tissues like the pancreas, it is also found in smalls amounts in the hypothalamus[34,59,63]. Therefore ghrelin affects the CNS and does not act only as a hunger signal[64]. There is evidence that plasma ghrelin passes the blood-brain barrier and binds with the hippocampus thus promoting synaptic plasticity[65]. AG activates GHSR-expressing neurons of the hypothalamus to stimulate food intake and secretion of growth hormone (GH). Ghrelin acts through the GHSR thus it stimulates the secretion of the GH from the anterior lobe of pituitary[60,66,67]. As an orexigenic hormone, ghrelin has an important role in weight gain and adiposity. Druce *et al*[61] though, found that obese people do not have different ghrelin levels that lean individuals[61]. The studies that focused on the extremes of the BMI range, found that the correlation between ghrelin levels and BMI are inversed; the lower the BMI the higher are the ghrelin levels[68]. On the contrary, leptin and ghrelin are correlated positively.

As it was mentioned already, ghrelin does not only act as a hunger signal but it is also involved in reward, motivation and signaling pathways, and is in this way linked with stress, anxiety disorders and depression[69]. Carlini *et al*[70] suggest that the relation between the

Table 2 Ghrelin in patients with mood disorders according study's since 2007

Ref.	Findings
Rouach *et al*[80]	High in patients with binge-eating disorders
Schanze *et al*[62]	No difference
Kluge *et al*[78]	No difference
Barim *et al*[68]	Low
Matsuo *et al*[79]	No difference
Ishitobi *et al*[84]	High in non-responders with MDD
Ozsoy *et al*[81]	High
Treatment and ghrelin levels	
Schmid *et al*[83]	Decrease with mirtazapine

MDD: Major depressive disorder.

limbic areas and the hypothalamus create a circuit that connects emotional states and eating behavior. Moreover, Nakashima *et al*[71], found an association between a gene polymorphism and depression. Different studies in animals yielded contrasting findings. Some showed that ghrelin could be an anxiogenic hormone whereas others revealed that it can have anxiolytic and anti-depressive responses[70,72-76]. High levels of ghrelin were observed after conditions of energy insufficiency but also after acute or chronic stress[77].

In human studies too contrasting findings were reported. Some researches did not find any differences in ghrelin levels between patients with major depression and controls[62,78,79] while other researchers suggested that plasma ghrelin levels as well as pre-proghrelin mRNA levels are elevated in conditions of stress[77,80]. Ozsoy *et al*[81], for example, found higher levels in serum ghrelin levels in depressive patients, than in controls and they also found that high serum ghrelin levels were normalized by treatment. An improvement of depressive symptoms was found in men with MDD after they were administrated with ghrelin[82]. On the other hand, a reduction of ghrelin levels in MDD patients revealed a reduction of psychopathological symptoms[83,84]. Barim *et al*[68] examined patients with depression before and after treatment with citalopram and showed that the levels of ghrelin of the depression patients were lower than the ones of healthy individuals in both periods of time. This antidepressant effect of high levels of ghrelin might be associated with the restriction of food or with hyperactivity of the HPA axis in depression and anxiety which increases the stimulation of ACTH and glucocorticoids that increase ghrelin levels[76,82-86]. The change in ghrelin levels may imply a reaction to symptoms of depression, such as loss of weight and appetite[81] (Table 2).

DISCUSSION

Leptin and ghrelin are two complementary hormones that have a major impact on energy balance. Leptin restrains gastric ghrelin to secret and inhibits the stimulation of feeding[87]. It is hypothesized that these hormones control energy homeostasis through two independent systems. Leptin functions as a feedback mechanism that signals to key regulatory centers in the brain to inhibit food intake and to regulate body weight and energy homeostasis. Ghrelin stimulates the activity of neurons expressing NPY, AgRP and orexin. Furthermore, ghrelin has an inhibitory effect on POMC neurons and CRH-producing neurons[35]. Even though leptin as well as ghrelin, exert peripheral signals, evidence from studies in animals showed that leptin is also produced in the brain and that ghrelin is synthesized in neuronal cells of the hypothalamus[88,89]. Due to their multiple functions, researchers are trying to discover their effect on MDs. Many studies showed that the mechanisms that underlie their function are critical to the development and the treatment of MDs.

Studies with patients with depression seem to suggest that that the two hormones might exert antidepressant effects, due to the change of their levels in patients with depression as opposed to controls. However, the potential antidepressant effect of the hormones is not clear, as other studies did not find any changes to serum levels between patients with depression and control and some other studies even report reverse results. Particularly, some studies revealed that high levels of the hormones are associated with depression and anxiety disorders, while others showed that depressive patients have low levels of the hormones, even before and after treatment, compared to controls. It is clear however, that the neural circuits involved in the regulation of food intake *via* ghrelin and leptin, affect emotional changes too. The systems in the CNS that are involved in energy balance are associated with the regulation of emotions[90]. The ARC of the hypothalamus and the HPA axis are two critical areas both in MDs and for the secretion and synthesis of ghrelin and leptin.

Chronic stress can lead to changes in eating patterns and metabolism, and eating and metabolism may in turn affect mood. This is only a conjecture for now as it has not been thoroughly studied to date. The researchers concluded that they had identified a previously unknown role for ghrelin in regulating mood. Results of studies have shown that ghrelin levels can be increased by chronic stress and can reduce anxiety and depression-like behaviours. These findings may be relevant to conditions such as anorexia, where ghrelin levels are known increased. Much more research will be needed to look into whether this hormone plays a role in anxiety and depression in humans.

The current review indicates that leptin and ghrelin are indeed involved in the process of MDs. The variety of methodologies used in different studies over the past 10 years might be responsible for the conflicting findings. It appears that the mechanism in which these two hormones affect mood or are affected by mood could be further enlightened if a

study is repeated controlling for dual diagnosis and comorbidity, as well as the severity of depression. Focusing on MDD can be a better indicator of biological markers since melancholia can be a result of every day events. Therefore, findings for MDD can be used as a precursor for examining other MDs with closely related symptoms.

CONCLUSION

Leptin and ghrelin do not only have a key role in energy homeostasis but they have also pleiotropic effects on the CNS and periphery. The evidence from different studies on the association between MDs and the two hormones is controversial. This can be explained by the diverse characteristics of the patients participating in the studies, the various methodologies that are used and the different measurements of the levels of hormones. As a result, the role of ghrelin and leptin in MDs is not yet clearly established. It will be interesting to examine more extensively the role of the two hormones in all of the different types of MDs in order to reveal potential common features of emotional changes and changes of the hormones levels.

REFERENCES

1 **Kessler RC**, Wang PS. The descriptive epidemiology of commonly occurring mental disorders in the United States. *Annu Rev Public Health* 2008; **29**: 115-129 [PMID: 18348707]
2 **Merikangas KR**, Low NC. The epidemiology of mood disorders. *Curr Psychiatry Rep* 2004; **6**: 411-421 [PMID: 15538988 DOI: 10.1007/s11920-004-0004-1]
3 **Kalia M**. Neurobiological basis of depression: an update. *Metabolism* 2005; **54**: 24-27 [PMID: 15877309]
4 **Belmaker RH**, Agam G. Major depressive disorder. *N Engl J Med* 2008; **358**: 55-68 [PMID: 18172175 DOI: 10.1056/NEJMra073096]
5 **Hashimoto K**, Shimizu E, Iyo M. Critical role of brain-derived neurotrophic factor in mood disorders. *Brain Res Brain Res Rev* 2004; **45**: 104-114 [PMID: 15145621]
6 **Hashimoto K**. Brain-derived neurotrophic factor as a biomarker for mood disorders: an historical overview and future directions. *Psychiatry Clin Neurosci* 2010; **64**: 341-357 [PMID: 20653908 DOI: 10.1111/j.1440-1819.2010.02113.x]
7 **Craddock N**, Forty L. Genetics of affective (mood) disorders. *Eur J Hum Genet* 2006; **14**: 660-668 [PMID: 16721402 DOI: 10.1038/sj.ejhg.5201549]
8 **Martinowich K**, Lu B. Interaction between BDNF and serotonin: role in mood disorders. *Neuropsychopharmacology* 2008; **33**: 73-83 [PMID: 17882234 DOI: 10.1038/sj.npp.130157]
9 **Calabrese F**, Molteni R, Racagni G, Riva MA. Neuronal plasticity: a link between stress and mood disorders. *Psychoneuroendocrinology* 2009; **34** Suppl 1: S208-S216 [PMID: 19541429]
10 **Drevets WC**, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct Funct* 2008; **213**: 93-118 [PMID: 18704495 DOI: 10.1007/s00429-008-0189-x]
11 **Kanner AM**. Is major depression a neurologic disorder with psychiatric symptoms? *Epilepsy Behav* 2004; **5**: 636-644 [PMID: 15380113 DOI: 10.1016/j.yebeh.2004.07.008]
12 **Haldane M**, Frangou S. New insights help define the pathophysiology of bipolar affective disorder: neuroimaging and neuropathology findings. *Prog Neuropsychopharmacol Biol Psychiatry* 2004; **28**: 943-960 [PMID: 15380855 DOI: 10.1016/j.pnpbp.2004.05.040]
13 **Brambilla P**, Glahn DC, Balestrieri M, Soares JC. Magnetic resonance findings in bipolar disorder. *Psychiatr Clin North Am* 2005; **28**: 443-467 [PMID: 15826742 DOI: 10.1016/j.psc.2005.01.006]
14 **McEwen BS**. Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. *Metabolism* 2005; **54**: 20-23 [PMID: 15877308 DOI: 10.1016/j.metabol.2005.01.008]
15 **Watson S,** Mackin P. HPA axis function in mood disorders. *Psychiatry* 2006; **5**: 166-170 [DOI: 10.1383/psyt.2006.5.5.166]
16 **Gibson EL**. Emotional influences on food choice: sensory, physiological and psychological pathways. *Physiol Behav* 2006; **89**: 53-61 [PMID: 16545403]
17 **Soczynska JK**, Kennedy SH, Woldeyohannes HO, Liauw SS, Alsuwaidan M, Yim CY, McIntyre RS. Mood disorders and obesity: understanding inflammation as a pathophysiological nexus. *Neuromolecular Med* 2011; **13**: 93-116 [PMID: 21165712 DOI: 10.1007/s12017-010-8140-8]
18 **Danaei G**, Ding EL, Mozaffarian D, Taylor B, Rehm J, Murray CJ, Ezzati M. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. *PLoS Med* 2009; **6**: e1000058 [PMID: 19399161 DOI: 10.1371/annotation/0ef47acd-9dcc-4296-a897-872d182cde57]
19 **Maniam J**, Morris MJ. The link between stress and feeding behaviour. *Neuropharmacology* 2012; **63**: 97-110 [PMID: 22710442 DOI: 10.1016/j.neuropharm.2012.04.017]
20 **McIntyre RS**, Konarski JZ, Wilkins K, Soczynska JK, Kennedy SH. Obesity in bipolar disorder and major depressive disorder: results from a national community health survey on mental health and well-being. *Can J Psychiatry* 2006; **51**: 274-280 [PMID: 16986816]
21 **Simon GE**, Von Korff M, Saunders K, Miglioretti DL, Crane PK, van Belle G, Kessler RC. Association between obesity and psychiatric disorders in the US adult population. *Arch Gen Psychiatry* 2006; **63**: 824-830 [PMID: 16818872 DOI: 10.1001/archpsyc.63.7.824]
22 **Mather AA**, Cox BJ, Enns MW, Sareen J. Associations of obesity with psychiatric disorders and suicidal behaviors in a nationally representative sample. *J Psychosom Res* 2009; **66**: 277-285 [PMID: 19302884 DOI: 10.1016/j.jpsychores.2008.09.008]
23 **de Wit L**, Luppino F, van Straten A, Penninx B, Zitman F, Cuijpers P. Depression and obesity: a meta-analysis of community-based studies. *Psychiatry Res* 2010; **178**: 230-235 [PMID: 20462641 DOI: 10.1016/j.psychres.2009.04.015]
24 **Atlantis E**, Baker M. Obesity effects on depression: systematic review of epidemiological studies. *Int J Obes* (Lond) 2008; **32**: 881-891 [PMID: 18414420 DOI: 10.1038/ijo.2008.54]
25 **McElroy SL**, Kotwal R, Malhotra S, Nelson EB, Keck PE, Nemeroff CB. Are mood disorders and obesity related? A review for the mental health professional. *J Clin Psychiatry* 2004; **65**: 634-651, quiz 730 [PMID: 15163249]
26 **Gariepy G**, Nitka D, Schmitz N. The association between obesity and anxiety disorders in the population: a systematic review and meta-analysis. *Int J Obes* (Lond) 2010; **34**: 407-419 [PMID: 19997072 DOI: 10.1038/ijo.2009.252]
27 **Bazhan N**, Zelena D. Food-intake regulation during stress by the hypothalamo-pituitary-adrenal axis. *Brain Res Bull* 2013; **95**: 46-53 [PMID: 23590931 DOI: 10.1016/j.brainresbull.2013.04.002]
28 **Jauch-Chara K**, Oltmanns KM. Obesity--a neuropsychological disease? Systematic review and neuropsychological model. *Prog Neurobiol* 2014; **114**: 84-101 [PMID: 24394671 DOI: 10.1016/j.pneurobio.2013.12.001]
29 **Dallman MF,** Pecoraro NC, La Fleur SE, Warne JP, Ginsberg AB, Akana SF, Laugero KC, Houshyar H, Strack AM, Bhatnagar S, Bell ME. Glucocorticoids, chronic stress, and obesity. *Prog Brain Res* 2006; **153**: 75-105 [PMID: 16876569 DOI: 10.1016/S0079-6123(06)53004-3]
30 **Vicennati V**, Pasqui F, Cavazza C, Pagotto U, Pasquali R. Stress-related development of obesity and cortisol in women. *Obesity* (Silver Spring) 2009; **17**: 1678-1683 [PMID: 19300426 DOI: 10.1038/oby.2009.76]
31 **Dallman MF**. Stress-induced obesity and the emotional nervous

system. *Trends Endocrinol Metab* 2010; **21**: 159-165 [PMID: 19926299 DOI: 10.1016/j.tem.2009.10.004]
32 **Taylor V**, MacQueen G. Associations between bipolar disorder and metabolic syndrome: A review. *J Clin Psychiatry* 2006; **67**: 1034-1041 [PMID: 16889445 DOI: 10.4088/JCP.v67n0704]
33 **Lu XY**. The leptin hypothesis of depression: a potential link between mood disorders and obesity? *Curr Opin Pharmacol* 2007; **7**: 648-652 [PMID: 18032111 DOI: 10.1016/j.coph.2007.10.010]
34 **Korbonits M**, Goldstone AP, Gueorguiev M, Grossman AB. Ghrelin--a hormone with multiple functions. *Front Neuroendocrinol* 2004; **25**: 27-68 [PMID: 15183037 DOI: 10.1016/j.yfrne.2004.03.002]
35 **Klok MD**, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. *Obes Rev* 2007; **8**: 21-34 [PMID: 17212793 DOI: 10.1111/j.1467-789X.2006.00270.x]
36 **Brennan AM**, Mantzoros CS. Drug Insight: the role of leptin in human physiology and pathophysiology--emerging clinical applications. *Nat Clin Pract Endocrinol Metab* 2006; **2**: 318-327 [PMID: 16932309 DOI: 10.1038/ncpendmet0196]
37 **Roubos EW**, Dahmen M, Kozicz T, Xu L. Leptin and the hypothalamo-pituitary-adrenal stress axis. *Gen Comp Endocrinol* 2012; **177**: 28-36 [PMID: 22293575 DOI: 10.1016/j.ygcen.2012.01.009]
38 **Oswal A**, Yeo G. Leptin and the control of body weight: a review of its diverse central targets, signaling mechanisms, and role in the pathogenesis of obesity. *Obesity* (Silver Spring) 2010; **18**: 221-229 [PMID: 19644451 DOI: 10.1038/oby.2009.228]
39 **Price TO**, Farr SA, Yi X, Vinogradov S, Batrakova E, Banks WA, Kabanov AV. Transport across the blood-brain barrier of pluronic leptin. *J Pharmacol Exp Ther* 2010; **333**: 253-263 [PMID: 20053933 DOI: 10.1124/jpet.109.158147]
40 **Coll AP**, Yeo GS, Farooqi IS, O'Rahilly S. SnapShot: the hormonal control of food intake. *Cell* 2008; **135**: 572.e1-572.e2 [PMID: 18984167 DOI: 10.1016/j.cell.2008.10.014]
41 **Ahima RS**, Osei SY. Leptin signaling. *Physiol Behav* 2004; **81**: 223-241 [PMID: 15159169 DOI: 10.1016/j.physbeh.2004.02.014]
42 **Himmerich H**, Zimmermann P, Ising M, Kloiber S, Lucae S, Kunzel HE, Binder EB, Holsboer F, Uhr M. Changes in the hypothalamic-pituitary-adrenal axis and leptin levels during antidepressant treatment. *Neuropsychobiology* 2007; **55**: 28-35 [PMID: 17556850 DOI: 10.1159/000103573]
43 **Lu XY**, Kim CS, Frazer A, Zhang W. Leptin: a potential novel antidepressant. *Proc Natl Acad Sci USA* 2006; **103**: 1593-1598 [PMID: 16423896 DOI: 10.1073/pnas.0508901103]
44 **Liu J**, Garza JC, Bronner J, Kim CS, Zhang W, Lu XY. Acute administration of leptin produces anxiolytic-like effects: a comparison with fluoxetine. *Psychopharmacology* (Berl) 2010; **207**: 535-545 [PMID: 19823809 DOI: 10.1007/s00213-009-1684-3]
45 **Lawson EA**, Miller KK, Blum JI, Meenaghan E, Misra M, Eddy KT, Herzog DB, Klibanski A. Leptin levels are associated with decreased depressive symptoms in women across the weight spectrum, independent of body fat. *Clin Endocrinol* (Oxf) 2012; **76**: 520-525 [PMID: 21781144 DOI: 10.1111/j.1365-2265.2011.04182.x]
46 **Jiménez I**, Sobrino T, Rodríguez-Yáñez M, Pouso M, Cristobo I, Sabucedo M, Blanco M, Castellanos M, Leira R, Castillo J. High serum levels of leptin are associated with post-stroke depression. *Psychol Med* 2009; **39**: 1201-1209 [PMID: 19356259 DOI: 10.1017/S0033291709005637]
47 **Pasco JA**, Jacka FN, Williams LJ, Henry MJ, Nicholson GC, Kotowicz MA, Berk M. Leptin in depressed women: cross-sectional and longitudinal data from an epidemiologic study. *J Affect Disord* 2008; **107**: 221-225 [PMID: 17727958 DOI: 10.1016/j.jad.2007.07.024]
48 **Milaneschi Y**, Simonsick EM, Vogelzangs N, Strotmeyer ES, Yaffe K, Harris TB, Tolea MI, Ferrucci L, Penninx BW. Leptin, abdominal obesity, and onset of depression in older men and women. *J Clin Psychiatry* 2012; **73**: 1205-1211 [PMID: 22687702 DOI: 10.4088/JCP.11m07552]
49 **Milaneschi Y**, Sutin AR, Terracciano A, Canepa M, Gravenstein KS, Egan JM, Vogelzangs N, Guralnik JM, Bandinelli S, Penninx BW, Ferrucci L. The association between leptin and depressive symptoms is modulated by abdominal adiposity. *Psychoneuroendocrinology* 2014; **42**: 1-10 [PMID: 24636496 DOI: 10.1016/j.psyneuen.2013.12.015]
50 **Jow GM**, Yang TT, Chen CL. Leptin and cholesterol levels are low in major depressive disorder, but high in schizophrenia. *J Affect Disord* 2006; **90**: 21-27 [PMID: 16324751 DOI: 10.1016/j.jad.2005.09.015]
51 **Westling S**, Ahrén B, Träskman-Bendz L, Westrin A. Low CSF leptin in female suicide attempters with major depression. *J Affect Disord* 2004; **81**: 41-48 [PMID: 15183598 DOI: 10.1016/j.jad.2003.07.002]
52 **Atmaca M**, Tezcan E, Kuloglu M, Ustundag B. Serum leptin levels in obsessive-compulsive disorder. *Psychiatry Clin Neurosci* 2005; **59**: 189-193 [PMID: 15823166 DOI: 10.1111/j.1440-1819.2005.01356.x]
53 **Emül HM**, Serteser M, Kurt E, Ozbulut O, Guler O, Gecici O. Ghrelin and leptin levels in patients with obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; **31**: 1270-1274 [PMID: 17597276 DOI: 10.1016/j.pnpbp.2007.05.007]
54 **Gecici O**, Kuloglu M, Atmaca M, Tezcan AE, Tunckol H, Emül HM, Ustundag B. High serum leptin levels in depressive disorders with atypical features. *Psychiatry Clin Neurosci* 2005; **59**: 736-738 [PMID: 16401252 DOI: 10.1111/j.1440-1819.2005.01445.x]
55 **Häfner S**, Baumert J, Emeny RT, Lacruz ME, Thorand B, Herder C, Koenig W, Rupprecht R, Ladwig KH. Sleep disturbances and depressed mood: a harmful combination associated with increased leptin levels in women with normal weight. *Biol Psychol* 2012; **89**: 163-169 [PMID: 22020135 DOI: 10.1016/j.biopsycho.2011.10.005]
56 **Häfner S**, Zierer A, Emeny RT, Thorand B, Herder C, Koenig W, Rupprecht R, Ladwig KH. Social isolation and depressed mood are associated with elevated serum leptin levels in men but not in women. *Psychoneuroendocrinology* 2011; **36**: 200-209 [PMID: 20692102 DOI: 10.1016/j.psyneuen.2010.07.009]
57 **Esel E**, Ozsoy S, Tutus A, Sofuoglu S, Kartalci S, Bayram F, Kokbudak Z, Kula M. Effects of antidepressant treatment and of gender on serum leptin levels in patients with major depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2005; **29**: 565-570 [PMID: 15866359 DOI: 10.1016/j.pnpbp.2005.01.009]
58 **McKibben B.** Ghrelin: The hunger hormone. *Advanced Biochemistry* 2007: 1-12
59 **Kojima M**. Discovery of Ghrelin and its Physiological Function. *J Med Sci* 2010; **3**: 92-95 [DOI: 10.2174/1996327001003020092]
60 **Toska A,** Saridi M, Rekleiti M, Wozniak G. Impact of Ghrelin and Adiponectin on Metabolic and Cardiovascular Effects. *Int J Caring Sci* 2013; **6**: 349-359
61 **Druce MR**, Wren AM, Park AJ, Milton JE, Patterson M, Frost G, Ghatei MA, Small C, Bloom SR. Ghrelin increases food intake in obese as well as lean subjects. *Int J Obes* (Lond) 2005; **29**: 1130-1136 [PMID: 15917842 DOI: 10.1038/sj.ijo.0803001]
62 **Schanze A**, Reulbach U, Scheuchenzuber M, Groschl M, Kornhuber J, Kraus T. Ghrelin and eating disturbances in psychiatric disorders. *Neuropsychobiology* 2008; **57**: 126-130 [PMID: 18552514 DOI: 10.1159/000138915]
63 **Gil-Campos M**, Aguilera CM, Cañete R, Gil A. Ghrelin: a hormone regulating food intake and energy homeostasis. *Br J Nutr* 2006; **96**: 201-226 [PMID: 16923214 DOI: 10.1079/BJN20061787]
64 **Steiger A**, Dresler M, Schüssler P, Kluge M. Ghrelin in mental health, sleep, memory. *Mol Cell Endocrinol* 2011; **340**: 88-96 [PMID: 21349316 DOI: 10.1016/j.mce.2011.02.013]
65 **Diano S**, Farr SA, Benoit SC, McNay EC, da Silva I, Horvath B, Gaskin FS, Nonaka N, Jaeger LB, Banks WA, Morley JE, Pinto S, Sherwin RS, Xu L, Yamada KA, Sleeman MW, Tschöp MH, Horvath TL. Ghrelin controls hippocampal spine synapse density and memory performance. *Nat Neurosci* 2006; **9**: 381-388 [PMID: 16491079 DOI: 10.1038/nn1656]
66 **Seoane LM**, Al-Massadi O, Lage M, Dieguez C, Casanueva FF. Ghrelin: from a GH-secretagogue to the regulation of food intake, sleep and anxiety. *Pediatr Endocrinol Rev* 2004; **1** Suppl 3: 432-437 [PMID: 16444170]
67 **Andrews ZB**. The extra-hypothalamic actions of ghrelin on neuronal function. *Trends Neurosci* 2011; **34**: 31-40 [PMID: 21035199 DOI: 10.1016/j.tins.2010.10.001]

68 **Barim AO**, Aydin S, Colak R, Dag E, Deniz O, Sahin I. Ghrelin, paraoxonase and arylesterase levels in depressive patients before and after citalopram treatment. *Clin Biochem* 2009; **42**: 1076-1081 [PMID: 19272368 DOI: 10.1016/j.clinbiochem.2009.02.020]

69 **Schellekens H**, Finger BC, Dinan TG, Cryan JF. Ghrelin signalling and obesity: at the interface of stress, mood and food reward. *Pharmacol Ther* 2012; **135**: 316-326 [PMID: 22749794 DOI: 10.1016/j.pharmthera.2012.06.004]

70 **Carlini VP**, Varas MM, Cragnolini AB, Schiöth HB, Scimonelli TN, de Barioglio SR. Differential role of the hippocampus, amygdala, and dorsal raphe nucleus in regulating feeding, memory, and anxiety-like behavioral responses to ghrelin. *Biochem Biophys Res Commun* 2004; **313**: 635-641 [PMID: 14697239 DOI: 10.1016/j.bbrc.2003.11.150]

71 **Nakashima K**, Akiyoshi J, Hatano K, Hanada H, Tanaka Y, Tsuru J, Matsushita H, Kodama K, Isogawa K. Ghrelin gene polymorphism is associated with depression, but not panic disorder. *Psychiatr Genet* 2008; **18**: 257 [PMID: 18797403 DOI: 10.1097/YPG.0b013e328306c979]

72 **Kristenssson E**, Sundqvist M, Astin M, Kjerling M, Mattsson H, Dornonville de la Cour C, Håkanson R, Lindström E. Acute psychological stress raises plasma ghrelin in the rat. *Regul Pept* 2006; **134**: 114-117 [PMID: 16540188 DOI: 10.1016/j.regpep.2006.02.003]

73 **Ochi M**, Tominaga K, Tanaka F, Tanigawa T, Shiba M, Watanabe T, Fujiwara Y, Oshitani N, Higuchi K, Arakawa T. Effect of chronic stress on gastric emptying and plasma ghrelin levels in rats. *Life Sci* 2008; **82**: 862-868 [PMID: 18343456 DOI: 10.1016/j.lfs.2008.01.020]

74 **Hansson C**, Haage D, Taube M, Egecioglu E, Salomé N, Dickson SL. Central administration of ghrelin alters emotional responses in rats: behavioural, electrophysiological and molecular evidence. *Neuroscience* 2011; **180**: 201-211 [PMID: 21303683 DOI: 10.1016/j.neuroscience.2011.02.002]

75 **Spencer SJ**, Xu L, Clarke MA, Lemus M, Reichenbach A, Geenen B, Kozicz T, Andrews ZB. Ghrelin regulates the hypothalamic-pituitary-adrenal axis and restricts anxiety after acute stress. *Biol Psychiatry* 2012; **72**: 457-465 [PMID: 22521145 DOI: 10.1016/j.biopsych.2012.03.010]

76 **Lutter M**, Sakata I, Osborne-Lawrence S, Rovinsky SA, Anderson JG, Jung S, Birnbaum S, Yanagisawa M, Elmquist JK, Nestler EJ, Zigman JM. The orexigenic hormone ghrelin defends against depressive symptoms of chronic stress. *Nat Neurosci* 2008; **11**: 752-753 [PMID: 18552842 DOI: 10.1038/nn.2139]

77 **Chuang JC**, Zigman JM. Ghrelin's Roles in Stress, Mood, and Anxiety Regulation. *Int J Pept* 2010; **2010**: 460549 [PMID: 20721341 DOI: 10.1155/2010/460549]

78 **Kluge M**, Schussler P, Schmid D, Uhr M, Kleyer S, Yassouridis A, Steiger A. Ghrelin plasma levels are not altered in major depression. *Neuropsychobiology* 2009; **59**: 199-204 [PMID: 19521111 DOI: 10.1159/000223731]

79 **Matsuo K**, Nakano M, Nakashima M, Watanuki T, Egashira K, Matsubara T, Watanabe Y. Neural correlates of plasma acylated ghrelin level in individuals with major depressive disorder. *Brain Res* 2012; **1473**: 185-192 [PMID: 22819931 DOI: 10.1016/j.brainres.2012.07.027]

80 **Rouach V**, Bloch M, Rosenberg N, Gilad S, Limor R, Stern N, Greenman Y. The acute ghrelin response to a psychological stress challenge does not predict the post-stress urge to eat. *Psychoneuroendocrinology* 2007; **32**: 693-702 [PMID: 17560728 DOI: 10.1016/j.psyneuen.2007.04.010]

81 **Ozsoy S**, Besirli A, Abdulrezzak U, Basturk M. Serum ghrelin and leptin levels in patients with depression and the effects of treatment. *Psychiatry Investig* 2014; **11**: 167-172 [PMID: 24843372 DOI: 10.4306/pi.2014.11.2.167]

82 **Kluge M**, Schüssler P, Dresler M, Schmidt D, Yassouridis A, Uhr M, Steiger A. Effects of ghrelin on psychopathology, sleep and secretion of cortisol and growth hormone in patients with major depression. *J Psychiatr Res* 2011; **45**: 421-426 [PMID: 20888580 DOI: 10.1016/j.jpsychires.2010.09.002]

83 **Schmid DA**, Wichniak A, Uhr M, Ising M, Brunner H, Held K, Weikel JC, Sonntag A, Steiger A. Changes of sleep architecture, spectral composition of sleep EEG, the nocturnal secretion of cortisol, ACTH, GH, prolactin, melatonin, ghrelin, and leptin, and the DEX-CRH test in depressed patients during treatment with mirtazapine. *Neuropsychopharmacology* 2006; **31**: 832-844 [PMID: 16237393 DOI: 10.1038/sj.npp.1300923]

84 **Ishitobi Y**, Kohno K, Kanehisa M, Inoue A, Imanaga J, Maruyama Y, Ninomiya T, Higuma H, Okamoto S, Tanaka Y, Tsuru J, Hanada H, Isogawa K, Akiyoshi J. Serum ghrelin levels and the effects of antidepressants in major depressive disorder and panic disorder. *Neuropsychobiology* 2012; **66**: 185-192 [PMID: 22948519 DOI: 10.1159/000339948]

85 **Kageyama K**, Kumata Y, Akimoto K, Takayasu S, Tamasawa N, Suda T. Ghrelin stimulates corticotropin-releasing factor and vasopressin gene expression in rat hypothalamic 4B cells. *Stress* 2011; **14**: 520-529 [PMID: 21438782 DOI: 10.3109/10253890.2011.558605]

86 **Kageyama K**, Akimoto K, Yamagata S, Sugiyama A, Murasawa S, Watanuki Y, Tamasawa N, Suda T. Dexamethasone stimulates the expression of ghrelin and its receptor in rat hypothalamic 4B cells. *Regul Pept* 2012; **174**: 12-17 [PMID: 22120831 DOI: 10.1016/j.regpep.2011.11.003]

87 **Kalra SP**, Ueno N, Kalra PS. Stimulation of appetite by ghrelin is regulated by leptin restraint: peripheral and central sites of action. *J Nutr* 2005; **135**: 1331-1335 [PMID: 15867335]

88 **Wilkinson M**, Brown R, Imran SA, Ur E. Adipokine gene expression in brain and pituitary gland. *Neuroendocrinology* 2007; **86**: 191-209 [PMID: 17878708 DOI: 10.1159/000108635]

89 **Zigman JM**, Jones JE, Lee CE, Saper CB, Elmquist JK. Expression of ghrelin receptor mRNA in the rat and the mouse brain. *J Comp Neurol* 2006; **494**: 528-548 [PMID: 16320257 DOI: 10.1002/cne.20823]

90 **Kishi T**, Elmquist JK. Body weight is regulated by the brain: a link between feeding and emotion. *Mol Psychiatry* 2005; **10**: 132-146 [PMID: 15630408 DOI: 10.1038/sj.mp.4001638]

P- Reviewer: Masaki T, Unger M **S- Editor**: Ji FF **L- Editor**: A **E- Editor**: Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com