Biomedical Research 2017; 28 (13): 5793-5804 *ISSN 0970-938X*
www.biomedres.info

The role of brain-gut peptides in mood disorders.

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Abstract

Recently, robust evidences have shown that brain-gut peptides play important role in mood disorders. However, the specific role of brain-gut peptides in mood disorders remains unclear. Therefore, the present review was aimed to summarize the recent advance of brain-gut peptides in mood disorders, mainly cyclothymic disorders and depressive disorders, in which dozens of brain gut peptides including cholecystokinin, ghrelin, substance P, neuropeptide Y, melatonin and opioid peptide which have been widely identified and characterized in central nervous system. We focused on the effects of these peptides in mood disorders. It may be helpful to clarify the precise mechanism of these brain-gut peptides in mood disorders.

Keywords: Peptides, Mood disorders, Substance P, Neuropeptide Y.

Accepted on May 17, 2017

Introduction

With regard to mood disorders, major depression accounts for most proportion. Major depression is a kind of disorder occurs again and again with a lifetime prevalence of up to 20% in the general population, owing to its persistent growth of prevalence, it had been becoming the most common psychiatric disorders [1]. Depression is a leading cause of morbidity and mortality in youngsters. Increased exposure to the disorder begins in the early teens and continues to deteriorate throughout adolescence, with lifetime rates approached to range from 15% to 25% [2]. The World Health Organization predicts that, by 2020, depression will be the major cause of disability in developed countries, preceded only by ischemic heart disease worldwide [3]. The classification of mood disorders is always changed for better going through [4]. The latest classification should come according with the Diagnostic and Statistical Manual of Mental Disorders-DSM-5 (2013). For this article, we discuss mood disorders mainly based on Mesh. The chief aspects are cyclothymic disorders and depressive disorders (postpartum depression, major depressive disorder, treatment-resistant depressive disorder, dysthymic disorder, premenstrual dysphonic disorder and seasonal affective disorder). Recent studies principally highlight the association between major depressive disorders and brain-gut peptides. Depression is a mood disorder with multitude of symptoms, including lowered mood, fatigue and disturbed sleep, anhedonia, low self-esteem and self-confidence, loss of appetite, and a low libido. The most common type of mood disorders is Major Depressive Disorder (MDD), with dysthymia and bipolar disorder second only to [5]. Then we will talk about brain gut peptide. Brain-gut peptide, just as its name, distributes in the gut and brain, playing a role in the gastrointestinal tract and central nervous system at the same time. We can classify brain-gut peptides into two different classes [6]: short-term signals, which are changed companying with eating, like, ghrelin, Cholecystokinin (CCK), PP, PYY, GLP-1, nesfatin-1, Oxyntomodulin (OXM), glucagon, Gastric Inhibitory Polypeptide (GIP), amylin, and so on. Long-term signals, which reflect the metabolic state of adipose tissue, such as insulin and lepton. Numerous researches have been reported about the changes of these peptides in body affected by mood disorders [7-15].

The continuing increase in lifetime expectancy has led mood disorders becoming a medical problem and economic burden. Mood disorder is one of the leading causes of death and disability, moreover, can affect the prognosis of the disease at the same time.

Here, we review recent developments and classical advents in discovery of association between brain-gut peptides with mood disorders. We will start with some major brain-gut peptides in proper order (mainly ordered by the number and depth of research articles). In each unit, we will introduce the peptide and explain its alternation in animal and human studies. Furthermore, genetic modification will be put forward and their effects in changing of brain-gut peptide introduced afterward and a conclusion will be made at the end of the article. However, further investigation is needed to determine the precise mechanism, therefore, new drugs for anti-treatment individuals and reduced side effects will be potentially found. Delineation of the neurobiological markers that reflect successful treatment response will help in the identification of new avenues for research and the development of personalized treatments for mood disorders.

Serotonin

Serotonin or 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter. Biochemically derived from tryptophan, serotonin is primarily found in the gastrointestinal tract (GI tract), blood platelets, and the central nervous system of animals, including humans. Currently, the therapies for depression are based on the hypothesis that the shortage of 5 Hydroxytryptamine (5 HT; serotonin) or noradrenaline in the brain deteriorates the condition of depression. The mainstays of treatment of depression are Selective Serotonin Reuptake Inhibitors (SSRIs) [5]. SNRIs and SSRIs inhibit reuptake of noradrenaline and/or serotonin in the brain by binding with presynaptic monoamine transporters, whereas tricyclic antidepressants have a range of activities including monoamine reuptake inhibition as well as antagonism of 5 HT2A receptors. Among them serotonin is probably one of the most significant ones, since changes in serotoninergic function have been observed in MDD, and therapeutic efficacy of serotoninergic drugs in MDD is well documented. Obviously, Serotonin acts as the most prevalent intersection among anti-depression. However, the United States explained the potential risks of antidepressants for their suicidal tendencies among populations, especially in children, adolescents and young adults [5]. The role of serotonin in depression and antidepressant treatment remains unresolved despite decades of research. Consequently, researches increasingly shifting away from the traditional monoamine hypothesis for depression pharmacology. Agomelatine, a kind of melatonin receptor 1 (MT1) and MT2 agonist, may play a positive confrontation to the side effects introduced by serotonin [5]. We describe evidence supporting its causation by a mutation in SLC18A2 (which encodes vesicular monoamine transporter 2 (VMAT2)).VMAT2 translocate serotonin into synaptic vesicles and is essential for stable mood. Serotonin shortage results in sleep and psychiatric harassment [7]. The serotonin molecular issue is taken apart in the re-ingest of serotonin and the procedure of re-take is a major target in the pharmacologic treatment [16].

Recent evidence suggests that the lateral habenula plays a significant role of the reward circuit by negative signal to the feedback system [17]. Studies also suggest that dysfunction of the lateral habenula is associated with psychiatric disorders including major depression. A number of recent studies have been listed to suggest that hyperactivity of LHb neurons may contribute to depression. Serotonin has been being centrally involved in depressive disorders. This LHb-5HT circuit does take to prove effective to the emotion alteration [18].

Engagement of limbic brain regions and frontal regulatory brain regions has been confirmed in emotion regulation. Disturbances are observed in serotonin and physiological response systems relevant to emotion regulation. Kathryn et al. [19] performed a study about adolescent with nonsuicidal self-injury and try to approach neurobiological research on emotion regulation. Reduced 5-HT2 binding in the frontal cortex has been documented in unmedicated adults with nonsuicidal self-injury. Lower CSF levels of serotonin metabolites have been found in patients with both major depression and nonsuicidal self-injury compared with major depression without nonsuicidal self-injury. Research on serotonin systems has shed some light on self-injury behaviors, however, has not yet led to clear treatment solutions. Seasonality suicides characteristic with a peak in spring and early summer. Higher suicide seasonality was found for individuals treated with Selective Serotonin Reuptake Inhibitor (SSRIs). Makris et al. [20] suggestion of serotonergic hypothesis of suicide seasonality, changes of serotonergic neurotransmission in plasma and whole blood of healthy individuals vary throughout the year, with maximum values during the summer and lowest values in the fall have been reported. Low concentration of the major serotonin metabolite 5-HIAA (5-hydroxyindoleacetic acid) in the cerebrospinal fluid is known to be related to suicidal behavior.

The pathophysiology of major depression is strongly linked to impairments in serotonin (5-HT) neurotransmission. It has been demonstrated that fluctuation of serotonergic results in depression and antidepressant effects [21]. Surveys conducted by Horvath et al. [22] present two siblings with hemiplegic migraine, depression, progressive spastic paraparesis, myelopathy, and spinal cord atrophy. Low cerebrospinal fluid serotonin metabolite (5-hydroxyindoleacetic acid), low platelet serotonin levels, and diminished serotonin transport capacity has been reported. They suggest that the systemic serotonin deficiency could be contributing to their neurodegenerative disorder. Chronic stress significantly attenuates 5-HT neurotransmission and 5-HT1A auto receptor sensitivity, and this effect could represent an endophenotypic hallmark for mood disorders. The antidepressants may reverse chronic stress-induced 5-HT and neurogenic changes. Chronic stress causes depression and depression-related behavior through monoaminergic changes in several brain regions as well as suppression of hippocampal neurogenesis, leading to altered activity in cognition- and emotion-related brain regions, as well as HPA axis dysfunction that itself exacerbates the effects of stress, including its effects on 5-HT activity. Some of these effects are reversed by antidepressant treatment, which may act by increasing hippocampal neurogenesis, leading to restoration of HPA activity and stress responsively, ameliorating deleterious stress induced 5-HT changes. Some nucleus performed relatively constant during the alteration of emotion [23].

The prominent role hypothesis in depression research is the low serotonin. A research focused on the effects of light on circadian rhythms and subsequent interaction with alertness and depression has revealed that light may influence mood through its ability to rapidly induce increases in serotonin (5-HT) turnover. Moreover, the direct antidepressant mechanisms of 5-HT has been highlighted [14]. Parker et al. [24] developed acute tryptophan depletion model and continued to provide a research tool for investigating the relevance of serotonin to depression onset. Molecular imaging of serotonin transporters in major depression had been introduced in a meta-analysis. Reduction concentration of 5-HT in the amygdala had been proved to be strictly resulting in the severity of depression

[25]. Definition of serotonergic transmission has been widely assumed to be associated with MDD. Li et al. [26] aim to investigate 5-hydroxytryptamin distribution for depression or other mental disorders. Though SSRI treatment may be effective to the platelet 5-HT levels, the concentration of 5-HT between peripheral and central area seems different or not confirmed to be associated. A considerable amount of literature [27] state that the role of serotonin maybe differs in different place. By increasing extracellular serotonin, SSRIs disrupt energy homeostasis and often worsen symptoms during acute treatment. The high serotonin and energy regulation hypotheses conjointly explain why depressive symptoms commonly worsen in acute treatment when serotonin levels are at their highest. They claim that symptom reduction is not achieved by the direct pharmacological properties of SSRIs, but by the brain's compensatory responses that attempt to restore energy homeostasis. Serotonin transmission of multiple brain regions appears to be elevated in depression symptom. They give explanation by evidence of elevated serotonin transmission can be found in both positive and negative states. Consequently, alterations in serotonin transmission are probably neither necessary nor sufficient to regulate depressive symptoms. Therefore, researchers can affect depressive symptoms by altering more proximate mechanisms. However, they did not consider atypical depression and lack valid non-human animal models.

Northoff et al. points out, useful neuroimaging, reveal serotonin play an essential role in the pathogenesis of MDD modulates neural activity, behavior, and ultimately clinical symptoms [28]. The insertion/deletion of the promoter polymorphism of the serotonin transporter gene has been shown early on to modulate anxiety-related personality traits.

According to a report conducted by the National Institute of Mental Health, 37% of patients developed treatment-resistant depression [29]. To solve the problem, atypical antipsychotics have been used in clinical therapy. Quetiapine and aripiprazole are approved by the US Food and Drug Administration for the adjunctive treatment of MDD. Quetiapine is a 5 HT2A and dopamine D2 receptor antagonist. Aripiprazole has partial agonistic activity at 5 HT1A and D2 receptors, and antagonistic activity at 5 HT2A receptors. Overexpression of platelet 5-HT1A receptors and reduced 5-HT tone may helpful as a detect probe for depression [30].

Future research should figure out how the serotonergic system and depressive symptoms change over acute, chronic, and more prolonged SSRI treatment, and after discontinuation of the treatment. The industry has struggled, so far, to improve on the current therapeutic options, partly owing to an inadequate understanding of depression etiology.

Melatonin

Melatonin is a substance that chemically called N-acetyl-5-methoxytryptamine. Melatonin is produced and secreted in the pineal gland. In healthy individuals, without disrupted chronobiology or depression, melatonin's secretion is high at night, however, with only negligible circulating concentrations during daylight hours. Therefore, light can suppress of nocturnal melatonin release. Stephenson et al. Introduces, that light modulates its antidepressant effect through the alter homeostatic process of sleep [14]. Melatonin analogues, agomelatine, a melatonin-receptor agonist and selective serotonergic receptor subtype antagonist play its hopeful role in antidepressant and anxiolytic effects [31]. Agomelatine gets its wonderful tolerability and safety advantages and may be performed as a preferred antidepressant [32]. Agomelatine, which also binds 5-HT2C receptors, has been confirmed that does not raise serotonin levels, furthermore, has less potential for the common gastrointestinal, sexual, or metabolic side-effects that characterize many other antidepressant compounds. Most of mood disorders have been illustrated in circadian rhythms. Normal chronobiology is increasingly thought to be a marker of effectiveness for antidepressant treatments. Failure to restore normal rhythms is highly predictive of ongoing symptoms or early relapses. Changes in the brain content and the ratio of MT1 to MT2 receptors have been reported in neurodegenerative disorders, significantly, similar changes reported after chronic antidepressant used. Exogenous melatonin has some antidepressant-like actions in animal models. By contrast, treatment with melatonin alone in human beings does not seem to be an effective antidepressant strategy. Agomelatine seems to be more effective in patients with more severe depression.

The alterations of melatonin secretion and its biomedical characters in mood harassment had been interpreted [33]. Causal relationships between alterations in circadian rhythms and mood disorders are strongly supported by the antidepressant efficacy of innovative pharmacological treatments which aimed at resynchronizing endogenous rhythms in depressed patients. Disturbances in circadian rhythms are an integral part of depressive mechanisms. The melatonin-related circadian hypothesis and the HPA axis-dysregulation hypothesis of depression are also closely related because melatonin and cortisol are interacting hormones with circadian rhythmic, similarly blunted in depression. A combination of buspirone and melatonin together shows antidepressant effect [34]. The preliminary findings have clinical implications and suggest that a platform of pre-clinical neurogenesis matched with confirmatory behavioral assays may be useful as a drug discovery strategy.

Literature search [35] shed their light on the relationship between melatonin and agomelatine for preventing seasonal affective disorder. However, there is no available methodologically sound evidence, indicates that melatonin or agomelatine is or is not an effective intervention for prevention of SAD and improvement of patient-centred outcomes among adults with a history of SAD.

Multiple nonselective MT1/MT2 agonists have been developed for the treatment of insomnia, circadian sleep disorders, and depression. The increasingly recognized the relevantion of melatonin receptor dimers *in vivo*, and the evaluation of dimer-specific will open new windows for pharmacy evolvement [36].

Ghrelin

Ghrelin is a peptide hormone produced by cholinergic cells in the gastrointestinal tract which comprising 28 amino acids and functions as a neuropeptide in the central nervous system. Ghrelin enters the general circulation, and acts in the hypothalamus to regulate eating behavior and energy use, growth hormone synthesis, and memory retention. Ghrelin is verified to change with stimulating food intake and body weight, also matters sleep regulation [37]. Sleep deprivation results in ghrelin elevation in the short term. The neuropeptide ghrelin plays a crucial role in appetite and reward. Ghrelin confirmed its role in building the circle of reward mechanism, what matters the emotion [8]. The expression of ghrelin receptor (GHSR1a) mRNA had been approved in some specific areas which may strictly connect with psychological alteration [38]. A small sample study stated that some common detect methods, may not be helpful [39]. Matsuo et al. [40] examined plasma concentration of acylated ghrelin after a period of fasting in Twenty-four patients with MDD and 24 healthy control subjects. They also compared brain volumes between the two groups, controlling for ghrelin level. However, there was no significant difference in plasma acylated ghrelin level between patients with MDD and healthy subjects. Ghrelin levels negatively correlated with gray matter volume of the Ventral Tegmental Area (VTA) in the total sample. The patients with MDD showed significantly smaller VTA gray matter volume compared to healthy subjects. The study indicating that ghrelin may play a role in the abnormal mesolimbic circuit that is involved in the pathophysiology of MDD. A cross-sectional study [41] was conducted in Japan for determining the association of serum leptin and ghrelin with depressive symptoms. This study gives the conclusion that lower leptin and higher ghrelin levels may be related to higher prevalence of depressive status among Japanese women. Strangely, men were excluded. However, this conclusion was given based on a cross-section study. Moreover, ghrelin and leptin were measured only a single time point, which limits the accuracy of the measurement. Obviously, this study comes with some limitations.

Agents such as clozapine, olanzapine and mirtazapine frequently trigger an increase in body weight. A study [42] was designed to reveal the relationship of maprotiline induced weight gain to serum ghrelin and adiponectin levels, as well as insulin resistance in lean subjects with depressive disorders. After 30 d of treatment with maprotiline, blood ghrelin and insulin levels increased, and adiponectin concentration decreased after the treatment period. The results indicate that treatment of lean patients with depressive disorder with maprotiline results in an increase in serum ghrelin and reduction in adiponectin levels. Maprotiline induced weight gain seems to be related both to a paradoxical increase in blood ghrelin levels as well as increased insulin resistance in patients with depressive disorder.

Ghrelin is involved in mood regulation and may have antidepressant effects. In addition, it has been shown to suppress secretion of Luteinizing Hormone (LH) and Thyroid Stimulating Hormone (TSH) in patients with major depression. However, these results may not be strong enough to elaborate this issue [43]. In a study [44] aims to investigate the role of ghrelin on psychopathology, sleep and secretion of cortisol and growth hormone in patients with major depression had been evaluated. They indicate that ghrelin can exert antidepressant effects in male patients with major depression however, no significant overall improvements of depressive symptoms were observed. Ghrelin strongly affected sleep and secretion of GH and cortisol in a partly different way in both female and male patients, and actually a partly different way as reported in healthy subjects.

Recent neuroendocrine research [8] suggests that ghrelin levels alter obviously in case of sleep deprivation. Abnormalities in the ghrelin system may contribute to the development of stress response related mood disorders. Ghrelin regulates the hypothalamic-pituitary-adrenal axis and affects anxiety and mood disorders. The neural sites of action through which the GHSR is highly expressed regulates the hypothalamic-pituitary-adrenal axis and associated stress-induced behaviors, including the centrally projecting Edinger-Westphal nucleus, the hippocampus, amygdala, locus coeruleus, and the ventral tegmental area assessed. Chronic social defeat stress in rats and mice all increase plasma ghrelin, ghrelin messenger RNA, and/or ghrelin cell number in the stomach. The potential role for ghrelin acts as a stress feedback signal that regulates these associated behaviors. Low plasma ghrelin concentrations in normal animals promote mild anxiety-like behavior. In response to acutely stressful stimuli, plasma ghrelin rises significantly and attenuates anxiety-like behavior. Psychomotor agitation and weight loss are also associated with melancholic depression, whereas lethargy and weight gain are frequently observed in atypical depression. This implies that different subtype depression may conduct individual pathway in ghrelin metabolism. Ghrelin-mediated glucocorticoid release may regulate a balance between executive control and a salience network designed to enhance survival potential by increasing vigilance and fear.

Ghrelin influences stress responses and anxiety, depression and fearful behaviors in certain contexts. However, the mechanism by which ghrelin affects mood has not been established. Studies to date report variable associations between ghrelin and mood disorders, and the use of ghrelin as an intervention has yet to be extensively investigated.

Substance P

Substance P (SP), an undecapeptide, belongs to the tachykinin family. SP binds to a family of Neurokinin (NK) receptors, preferentially acting on the metabotropic NK1 receptor. SP is widely distributed in the central, peripheral, and enteric nervous systems of many species. SP was thought to be a primarily neurotransmitter/ neuromodulator in pain transmission. The ventrolateral periaqueductal gray substance, a region essential for the perception of pain and a site rich in neurons containing the neuropeptide neurotransmitter substance P, the endogenous agonist for neurokinin-1

receptors. The gene encoding substance P is down-regulated by ΔFosB. Although the overexpression of ΔFosB did not significantly change baseline extracellular concentrations of substance P in the nucleus accumbens, it did significantly suppress substance P levels in animal model. The finding that overexpression of ΔFosB changes behavioral phenotype(from stress-sensitive to stress-resilient) may well provide a glimpse of future psychopharmacologic strategies, particularly if such manipulations have durable phenotypic effects. The role of substance P can be more useful in pharmacologic intervention [3].

Substance P dysregulation may be a point of convergence underlying the overlap of chronic inflammatory disease and mood disorders. The consequences of chronic SP signaling in the brain and periphery-signal amplification and a decrease in neuronal response threshold suggest a possible mechanism for the chronicity and coincidence of these conditions. The consequences of SP release generally function to signal a negative event and neutralize or eliminate the offending stimulus. SP carry negative emotional salience [45]. SP expression is elevated in the Cerebral Spinal Fluid (CSF) of at least a portion of depressed and anxious individuals, and increased release has been associated with expression of depressive and anxious symptoms.

SP and its primary binding site, the Neurokinin-1 receptor (NK-1r), are widely distributed throughout the brain and body. NK-1r antagonists have shown antidepressant efficacy. The available data have indicated that, in healthy individuals, acute stress does not affect serum SP levels, but during sustained stress chronic inflammation or individuals with mood disorders, serum SP levels may be elevated. SP may be inhibited initially and thus, permissive of CRH expression and increased GC release, followed by a recovery of SP levels when stress persists. SP is one of mediators involves with the alteration of emotion and mental activity [45]. The variation of SP on HPA-axis activity seems related to the stress strength and duration [46]. Regulation of SP activity has effectively been used in the treatment of anxiety and depression. The ability of an antidepressant to lower SP levels has predicted its ability to successfully decrease symptoms of depression. Dysregulation of SP may underlie the pathophysiology in a subset of anxiety and depression sufferers.

When comes to assess neuroimmune biomarkers in sweat patches and plasma of premenopausal women with major depressive disorder during remission period, neuropeptides NPY, SP and CGRP were extremely higher, however, VIP was extremely lower in patients compared to controls [9]. These biomarkers perform strong correlation with period of depression. Women with MDD, mostly in clinical remission, exhibited substantial increases in pro-inflammatory cytokines and sympathetic and sensory neuropeptides. Biomarker levels were strongly correlated with depressive symptomatology, and could account for the increased co-morbidities associated with depression. The elevated levels of SP and CGRP are consistent with previous reports of these peptides' role in pain perception, and of painful somatic symptoms correlating with depression severity in up to two thirds of patients with MDD. Both SP and its preferred receptor (NK-1R) may highly perform in peripheral sensory neurons and in mammalian brain of recurrent major depressive disorders [47], NK-1R expression is down-regulated, indicates a significant impairment of tachykinin receptor system in major depressive disorder that impacts post-receptor signaling. NK-1R has been suggested as relevant targets in depression and anxiety disorders.NK-1R knockout mice behavior differently with those depression units and barely connect with depression circumstance alters [48]. NK1 receptor antagonists may be investigated for the pharmacy treatment of emotion disorders [49]. Evidences proposed that SP might be a specialized neurotransmitter involved in the regulation of survival-type physiological responses to major stress, such as pain, injury or invasion of territory. NK1R antagonists may attenuate neural activity in the medial temporal lobe, a brain region with a crucial role in the regulation of fear and anxiety was demonstrated. The levels of SP in the CSF of patients with major depression had been reportedly elevated. Bondy et al. [50] found that the mean baseline SP serum concentration was significantly higher in depressed patients and that approximately a third of patients exhibited a decrease in SP response to antidepressant drug treatment. SP might be used as a biological marker for depression, and the results may help to identify a subgroup of depressed patients in which neuropeptides play a key role in the pathogenesis of the disorder. However, Deuschle et al. [51] could not find any difference in SP levels between the patients and healthy subjects. Neither the serum nor CSF concentrations of SP were affected by antidepressant treatment. The ineffective of NK1 receptor antagonists in the treatment of mood disorders may still need to be proven.

Preclinical and clinical studies have shown that blocking SP transmission, either by antagonists or genetic disruption, attenuates the effects of stress including changes in behavior (such as anxiety), neuronal activation and proliferation of hippocampal neurons [52]. Given such widespread interaction with systems comprising (adaptive) responses to stress, it is likely that a dysregulation of the SP/NK1 receptor system might contribute to the pathophysiology of specific stress related psychiatric disorders such as anxiety- and depressive disorders. Substance P/NKA had been confirmed taken apart in modulating CRH signaling in an animal model of depression [53].

Over the past decades, a number of neuroscientists have focused on the issue of aggressive behavior and its underlying pathophysiology. Numerous immunohistochemical studies have revealed the mediation of NK1 hypothalamic receptors in the induction of aggressive behavior [54]. Low CSF SP can be setup as an effective biological marker of the subtype of severe and chronic depression [55]. The main finding of this study was a difference in basal CSF SP concentrations between the depressed and control groups in the opposite direction to that which was hypothesized.

Calcitonin-gene-related-peptide

Calcitonin Gene-Related Peptide (CGRP), a 37-amino-acid neuropeptide, best known for its potent vasodilatory properties, has been implicated in many aspects of the depression. CGRP is one of the most abundant peptides in the central and periphery nervous system. SP may amplify pain symptoms. Post-Stroke Depression (PSD) is the most common psychological sequel after stroke. Shao et al. [56] revealed that the role of calcitonin gene-related peptide in post-stroke depression in chronic mild stress-treated ischemic rats. Numerous studies have implicated the Calcitonin Gene-Related Peptide (CGRP), a potent vasodilatory neuropeptide, as key modulator of the depression. CGRP immunoreactivity (CGRP-ir) concentration in CSF and hippocampus were increased in the PSD rats. Administration of CGRP into the ischemic rat increased depression-like behaviors in a dose-dependent manner, whereas ICV infusion of αCGRP8-37 produced antidepressant effects in PSD rats, implying that the PSD is mediated, at least partially, by endogenous CGRP receptor activation. Conclusion, central CGRP signaling surely active as a significant role in the modulation of PSD [56]. This study provides the evidence revealing the CGRP signaling pathway as an important modulator of PSD in rats. CGRP concentration in the CSF and hippocampus was increased in PSD rats, suggesting that increased CGRP levels might be a trait marker of PSD. Substance P (SP) and calcitoningene-related-peptide (CGRP), neuropeptides which are known mediators of pain, were measured every hour for 24 h in a subgroup of patients and controls. SP and CGRP, were constantly high in depressed individuals compared to controls [57]. CGRP levels were increased in subjects with depression, both in plasma and in the CSF.SP and CGRP may be useful biological markers in women with MDD. Cerebrospinal Fluid (CSF) was obtained from 32 patients with dementia, 19 healthy controls that were age-matched with the dementia patients, and 29 DSM-IV major depression patients and Calcitonin Gene-Related Peptide-Like Immunoreactivity (CGRP-LI) and Calcitonin-like Immunoreactivity (CT-LI) measured by RIA. In depression, CT-LI but not CGRP-LI was decreased and the CGRP/CT concentration ratio was increased, which is consistent with a possibility of an altered splicing process favoring CGRP mRNA.

Neuropeptide Y

Neuropeptide Y (NPY) is a 36-amino-acid peptide, highly conserved neuropeptide, belonging to the pancreatic polypeptide family, which also includes peptide YY (PYY) and Pancreatic Polypeptide (PP). Its potential role in the etiology and pathophysiology of mood and anxiety disorders has been extensively studied. NPY also has effects on feeding behavior, ethanol intake, sleep regulation, tissue growth and remodeling. Numerous studies had been put up that NPY involves in many kinds of mood or neurological disorders [58]. NPY systems may contribute to a promising target for the development of novel treatment interventions. The Y2 receptor is primarily a presynaptic receptor, potentially mediating inhibition of release of NPY, glutamate and GABA. Y2 receptor agonists have been found to be antigenic, while Y1 receptor agonists are anxiolytic. Y4 and Y5 receptors are also knock in depression-like behaviors [59]. Decreased expression of NPY has been suggested to contribute to the pathophysiology of depression. An altered NPYergic system is implicated in depression-like behaviors, conversely, increased NPY produces antidepressant-like effects. Decreased levels of CSF NPY in depressed patients had been found. ECS increased NPY protein and mRNA levels in the hippocampus, striatum and frontal and occipital cortices. Antidepressant treatments, such as chronic treatment with citalopram and repeated Electroconvulsive Therapy (ECT), have been shown to significantly increase CSF NPY levels in patients with major depression. Clinical improvement and increase in CSF NPY were strongly correlated. Vicissitudes of NPY play important roles in pathophysiology of affective disorders and major focus should be on development of NPY and its receptor agonists/ antagonists as novel treatment targets.

The rare allele of the Leu7Pro polymorphism in the *NPY* gene has been associated with higher processing into mature *NPY* and higher CSF *NPY* levels [60]. Low-expression *NPY* genotypes were also found to be overrepresented in subjects with MDD. *NPY* promoter region variation constrictly associated with neuropeptide [16]. Patients with depression were then entered into an 8 w treatment protocol and had repeated lumbar puncture procedures post-treatment. Higher NPY levels in depressed patients represent an adaptive change to the illness. Patients had been detected with significant higher CSF NPY concentration though relatively constant NPY concentration with antidepressant treatment [61].

Wang et al. [62] stated a neuropeptide Y variant (*rs16139*) associated with major depressive disorder in replicate samples from Chinese Han population. They showed a significant correlation between the SNP sites *rs16139* in NPY and the morbidity of depression. Patients with MDD have a lower frequency of *A*-allele in *rs16139* in replicate samples from Chinese Han population. The gene polymorphism loci *rs16139* of NPY was closely related to the onset of depression, although its role in the pathogenesis of MDD requires further study.

Cholecystokinin

Cholecystokinin (CCK), a neurotransmitter in the Central Nervous System (CNS), co-exists in a large portion of A10 dopamine neurons to exert some effect on dopamine behavior. CCK receptors are currently divided into CCKA and CCKB receptors. The CCKA receptors are found predominantly in the periphery, whereas the CCKB receptors are widely distributed throughout the brain. In panic disorder patients, CCK receptor function is enhanced [10]. They suggest that CCKB receptor functions are enhanced in the T cells of patients with panic disorder, and support the hypothesis that CCKB receptors are hypersensitive in panic disorder. Sensitivity to the panicogenic effects of cholecystokinin-tetrapeptide (CCK-4) is enhanced in panic disorder patients relative to Normal Controls (NC).

The studies association with prefrontal cortical circuit for depression- and anxiety-related behaviors mediated by cholecystokinin has been reported by Vialou et al. [63]. They show that induction of the transcription factor ΔFosB in mPFC, medial prefrontal cortex, specifically in the prelimbic PrL area, mediates susceptibility to stress. They demonstrated some results that Brain-wide mapping of ΔFosB had been introduced by chronic social defeat stress, ΔFosB in mPFC promotes susceptibility to stress and ΔFosB promotes CCKB induction in mPFC. Induction of ΔFosB in mPFC subregion after chronic social defeat stress, where FosB overexpression promotes stress susceptibility. We identified the CCKB receptor as one target gene regulated by ΔFosB in PrL, apparently inducing CCKB protein in susceptible mice and preventing the downregulation of CCKB expression that occurs selectively in resilient mice. This study indicate that social stress-induced behavioral deficits are mediated partly by molecular adaptations in mPFC involving ΔFosB and CCK through cortical projections to distinct subcortical targets.

A post analysis of serial concentrations of immunoreactive CCK and CRH, obtained every ten minutes from CSF continuously collected over six hours, was performed to investigate evidence of a physiologic relationship between Cholecystokinin (CCK) and Corticotrophin-Releasing Hormone (CRH) in the human CNS. The interactions between CCK and CRH are significant in the human CNS [64]. A double-blind, randomized, placebo-controlled design contained seven patients with MDD and 12 NC subjects aims to detect whether sensitivity to CCK-4 is enhanced inpatients with Major Depressive Disorder (MDD) with no history of panic attacks. They suggested that MDD patients show a response to CCK-4 that is comparable to NC. Central CCK receptors may not take significant apart in the development of MDD [65]. However, the limitation of this study is small number of study subjects. A classical study [66] indicated that IR-CCK (immunoreactive cholecystokinin) measured in lumbar CSF is principally derived from spinal cord and does not reflect possible changes in hypothalamic IR-CCK after eating.

A study about cholecystokinin system genes was aimed to investigate the associations between the genes with panic and other psychiatric disorders. This study aimed to clarify the association by investigating multiple variants within each gene and multiple phenotypes associated with panic. They suggest that the involvement of variation in the CCK system, particularly CCKBR, in the pathogenesis of panic. The variation in CCK may be involved in several anxiety phenotypes and CCKAR may be involved in the development of panic co-morbid with bipolar disorder [67]. Polymorphisms of the cholecystokinin gene promoter region in suicide victims in Japan were investigated in a study. The variation of the *CCK* gene promoter region was found to be responsible for suicidal behavior in Japanese males [68].

Somatostatin

Somatostatin is abundantly expressed in mammalian brain. The peptide binds with high affinity to six somatostatin receptors, sst1, sst2A and B, sst3 to 5, all belonging to the G-protein-coupled receptor family. Somatostatin systems subserve neuromodulatory roles in the brain, influencing motor activity, sleep, sensory processes and cognitive functions, and are altered in brain diseases like affective disorders. Consistent neuropeptide alterations in depression have been implied a state dependent decrease of cerebrospinal fluid somatostatin. Somatostatin concentration alteration associated with the state of disorders [69]. Brief report suggests that low CSF somatostatin associated with response to nimodipine in patients with affective illness. CSF somatostatin can be used to detect to measure the function of some treatment [70].

In analyzing the expression of 15 candidate genes for HIV Encephalitis (HIVE) by the presence or absence of Major Depressive Disorder (MDD), significant reductions in the expression of four cytoskeletal genes and somatostatin were noted. The substantial decrease in somatostatin RNA levels in the MDD group may play a primary role in the evolution of MDD in the setting of HIV. The somatostatin analogue vapreotide antagonizes neurokinin receptors and antagonism of neurokinin receptors would be new kind of wonderful specific pharmacy treatment in close future [71]. Lin et al. [13] suggest that (1) low SST plays a causal role in mood-related phenotypes, (2) deregulated EIF2-mediated protein translation may represent a mechanism for vulnerability of SST neurons, and (3) that global EIF2 signaling has antidepressant/anxiolytic potential. Sst genetic ablation increases anxiety/depressive-like behaviors. Stress affects the transcriptome of SST-positive neurons but not pyramidal cells. Low SST represents a robust pathological finding in MDD. Specifically, alterations in SST signaling and/or SST-bearing GABA neurons may represent a critical pathophysiological entity that contributes to sgACC dysfunction and matches to the high female vulnerability to develop MDD [72].

The wide distribution of somatostatin systems throughout nearly all brain regions suggests that they play major roles in brain functioning, whose comprehension is just at its beginning. Studies will be fruitful in term of translational research for neuropsychiatric diseases.

Opioid peptide

Opioid peptides are short sequences of amino acids that bind to opioid receptors in the brain; opiates and opioids mimic the effect of these peptides. Brain opioid peptide systems are known to play an important role in motivation, emotion, attachment behavior, the response to stress and pain, and the control of food intake. Opioid peptides mainly include enkephalins, β-endorphin adrenorphin, amidorphin, and leumorphin.

Yim et al. [73] explored prenatal β-endorphin as an early predictor of postpartum depressive symptoms in euthymic women, who develop PPD (postpartum depression) symptoms had higher levels of β-endorphin throughout pregnancy compared to women without PPD symptoms. β-endorphin may be a useful early predictor of PPD symptoms in women who do not report depressive symptoms in midpregnancy. Some of the

pathways leading to this complex disorder may be specific to subgroups of women. The dynamic changes in β-endorphin that occur throughout pregnancy could be useful in identifying women at increased risk for the development of PPD symptoms. Animal and human researches support involvement of central opioid systems in the pathophysiology of Major Depressive Disorder (MDD). Hegadoren et al. [74] investigated basal b-END levels in MDD and that have used challenge tests to examine b-END responses to a variety of experimental paradigms. A role for b-endorphin (β-END) in the pathophysiology of major depressive disorder (MDD) is suggested by both animal research and studies examining clinical populations. The major etiological theories of depression include brain regions and neural systems that interact with opioid systems and β-END. Exposure to cold is known to activate the sympathetic nervous system and increase the blood level of β–endorphin and noradrenaline and increase synaptic release of noradrenaline in the brain as well. Additionally, due to the high density of cold receptors in the skin, a cold shower is expected to send an overwhelming amount of electrical impulses from peripheral nerve endings to the brain, which could result in an anti-depressive effect. Taking cold shower seems a economically effective treatment for depression [75]. The endogenous opioid system may play a role both in the mechanism of action and response to antidepressant drugs [76]. At baseline, β-END response was similar in patients and controls. After 8 weeks of citalopram treatment in depression patients showed a significant decrease in the β-END response. A significant correlation between the β-END reduction in the response and the reduction in the HRSD score was observed. It was hypothesized that the β-END response to buspirone is decreased in depressed patients compared with normal controls suggesting a downregulation of 5-HT1A receptors in major depression.

NRDc (Nardilysinis), a metalloprotease belonging to the inverzincin/M16 family of metalloendopeptidases. NRDc is a metalloprotease that cleaves peptides, such as dynorphin-A, a-neoendorphin, and glucagon, at the N-terminus of arginine and lysine residues in dibasic moieties. NRDc may be down-regulated in brains of individuals with BD [11].

Zan et al. [77] reveals antagonism of κ-opioid receptor in the nucleus accumbens prevents the depressive-like behaviors following prolonged morphine abstinence. We hypothesize that dynorphin/κ-opioid receptor system in the NAc plays a crucial role in prolonged morphine abstinence-induced depressive-like behaviors, and the plasticity of the *prodynorphin* gene expression in the NAc contributes to the negative affective states.

In the human brain, the *prodynorphin* opioid neuropeptide gene is highly expressed in limbic-related areas such as the amygdala, hippocampus, ventral striatum, patch compartment of the dorsal striatum, entorhinal cortex, and hypothalamus. Anderson et al. [78] impaired periamygdaloid-cortex *prodynorphin* is characteristic of opiate addiction and depression. Reduced *PDYN* mRNA expression in the postmortem human amygdala nucleus of the Periamygdaloid Cortex (PAC) in both heroin abusers and MDD subjects is revealed. PMDD (premenstrual dysphoric disorder) women express lower baseline and stress-induced β-endorphin levels [79].

Others

In depression patients with coronary artery disease, endothelin-1is high [80]. Depression symptom severity predicts ET-1 elevation that has previously been linked to post-ACS survival, with the greatest risk of elevation among those with worse depression symptoms. The link between depression severity and ET-1 may identify a vulnerability to triggered ACS and poorer survival associated with depression.

The increasing of fasting plasma peptide YY concentrations is associated with patients with major depression who got weight loss [81]. Reduced CSF concentrations of NPY in patients with major depression and of reduced PYY concentrations in schizophrenia may reflect disturbed synthesis [82].

GLP-1 may be possible treatments for cognitive deficits in individuals with mood disorders [83]. Glucagon-like peptide-1 (GLP-1) and its more stable, longer-lasting analogues have been demonstrated to exert neuroprotective and anti-apoptotic effects, reduce modulate long-term potentiation and synaptic plasticity, and promote differentiation of neuronal progenitor cells. In animal models of behavior, treatment with GLP-1 receptor agonists has been demonstrated to reduce depressive behavior. GLP-1 is an endogenous 30-amino acid peptide hormone, released by intestinal L-cells in the ileum and colon after meals, which serves several significant physiological functions, including increasing beta cell sensitivity to glucose in pancreatic cells, decreasing glucagon secretion, inhibiting gastric secretion to delay absorption, and contributing to feelings of satiety. In humans, GLP-1 receptors are widespread and have been found in the cerebral cortex, hypothalamus, hippocampus, thalamus, caudate-putamen, and globus pallidum. Systematic evaluation of the effects of GLP-1 treatment in psychiatric populations who evince cognitive deficits represents a promising treatment avenue.

Electroconvulsive Therapy (ECT) is known to be an effective therapeutic option for several psychiatric conditions, especially for therapy-resistant major depressive disorders. PP elevation after administration of ECT might be a useful parameter to estimate the degree of such vagal stimulation after treatment [84].

Conclusion

Mood disorders, is a group of diagnoses in the Diagnostic and Statistical Manual of Mental Disorders (DSM) classification system where a disturbance in the person's mood is hypothesized to be the main underlying feature. The classification is known as mood (affective) disorders in International Classification of Diseases (ICD). We would propose that evaluating the precise mechanism in individuals with mood disorders appears warranted. The additional benefit

on medical comorbidity would be a significant advantage in light of the complex effects of mental and mood disorders.

Conflict of Interest

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

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