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Review Article

Neurotrophin Bdnf and Novel Molecular Targets in Depression Pathogenesis

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Abstract

In studying the pathophysiology of depressive disorders, both genetic background and environmental exposures should be considered. Elevated levels of glucocorticoids, stress hormones, caused by dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis have been confirmed in both patient and animal models of depression. Such elevations disturb the beneficial functions of brain-derived neurotrophic factor (BDNF), which is essential for neuronal survival and synaptic plasticity in the central nervous system (CNS). Recently, it has been suggested that nutritional status also influences mood. Indeed, some evidence suggests possible interactions between diabetes, BDNF expression, and function of glucagon-like peptide 1 (GLP-1) which regulates insulin secretion and appetite. In this review paper, we provide current information on molecules including GLP-1 that putatively interact with BDNF signaling and respond to environmental conditions.

INTRODUCTION

In addition to genetic conditions, environmental factors contribute to the pathophysiology of mental disorders including depression. Interestingly, Branchi et al. demonstrated that environment is a major factor in treatment efficacy with selective serotonin reuptake inhibitors (SSRI) in mouse models of depression [1], indicating an importance of profiling other biological makers to discover new targets for depression treatment. Dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis due to chronic stress results in increased levels of stress hormones, glucocorticoids, secreted from the adrenal cortex. In the CNS, although acute effects of glucocorticoids on synaptic function such as regulation of glutamatergic and GABAergic synapses has been revealed [2,3], the effects of chronic glucocorticoid stress may have adverse influences the brain function [4]. On the other hand, reduced expression/function of brain-derived neurotrophic factor (BDNF), a critical regulator of synaptic plasticity, is also involved in mental disorders through its interaction with the glucocorticoid system. We reported a negative effect of chronic glucocorticoid exposure on BDNF-stimulated increases in synaptic maturation [5]. Interestingly, cyclin-dependent kinase 5 (CDK5) -dependent regulation of glucocorticoid and BDNF systems was shown [6,7]. Ultimately, molecules such as CDK5 may be promising targets for depression treatment via their effects on both glucocorticoid- and BDNF-mediated functions.

Recently, a possible relationship between diabetes and depressive disorders has been established [8-10], implying that nutritional status may be integral in the pathophysiology of depression. As expected, reduced plasma levels of BDNF and memory impairment in patients with diabetes have been reported [11]. Glucagon-like peptide 1 (GLP-1), which is derived from the enteroendocrine L-cells in the distal intestine and exerts physiological effects including insulin secretion, may also be involved in depression. Interestingly, dysfunction of memory caused by streptozotocin (STZ) was rescued by a GLP-1 analog [12]. In this paper, we show recent evidence concerning BDNF signaling and functionality, novel stress-related candidates including GLP-1, and depression-like behavior.

BDNF/TrkB system and CNS disorders

BDNF influences CNS neurons via activation of the TrkB receptor, which is also responsive to neurotrophin-4. Although nerve growth factor and neurotrophin-3 also influence TrkA and

TrkC, respectively, growing evidence suggests a critical role of the BDNF/TrkB system in synaptic plasticity of both developing and adult CNS neurons, and its involvement in a variety of CNS diseases including psychiatric disorders (Ref. 4; Figure 1). It is well known that phospholipase C gamma (PLCgamma), phosphoinositide 3-kinase/Akt (PI3K/Akt), and extracellular signal-regulated kinase (ERK) signals are stimulated after TrkB activation, which maintains cell survival and regulates synaptic function (Figure 1). Therefore, BDNF-mediated synaptic function has been identified as a potential treatment target of neurodegenerative diseases such as Alzheimer's disease [13]. In addition, it is suggested that an alteration in BDNF expression/function contributes to the pathophysiology of psychiatric diseases including depression. Decreased mRNA levels of BDNF in both hippocampus and prefrontal cortex (PFC) were confirmed with postmortem tissue from suicide subjects [14]. So far, a variety of evidence suggests a close relationship between BDNF expression levels and depression [15-17]. Gene expression profiling reveals targets for mental disorder treatments, though change of BDNF expression is well supported in rodent models [18]. The regulation of *Bdnf* gene expression is complex and influenced by nine promoters [19]. Specifically, promoter IV is suggested to be involved in the activity-dependent regulation of *Bdnf* genes in hippocampal, cortical and amygdala regions, and suppressed function of the promoter in the depressive disorder and/or suicide has been demonstrated [20,21]. Hing et al. showed that the C allele of rs12273363, which is a polymorphism associated with mood disorders, negatively modulates activity of promoter IV using primary neurons [20]. In postmortem brain (Wernicke area of cerebral cortex) samples from suicide subjects, increased DNA methylation in the region of the BDNF promoter/exon IV compared with control subjects, and decreased amounts of *Bdnf* transcript IV were observed [21].

Interestingly, effects of antidepressants, including fluoxetine (SSRI), phenelzine (MAOI; Monoamine oxidase inhibitors), duloxetine (SNRI; Serotonin and Norepinephrine reuptake inhibitors), and imipramine (TCA; Tricyclic antidepressants), have been investigated using mice lacking BDNF production via the promoter IV function (BDNF-KIV mice) [22]. Sakata et al. showed that these four different classes of antidepressants (fluoxetine, phenelzine, duloxetine, and imipramine) demonstrated an antidepressant-like effect in the tail suspension test, though no increase in hippocampal BDNF mRNA and protein was found, suggesting that the antidepressant effect does not require BDNF production through promoter IV activity [22]. Further investigation of BDNF expression levels as well as extensive examination of BDNF/TrkB signaling focusing on molecules associated with TrkB is needed.

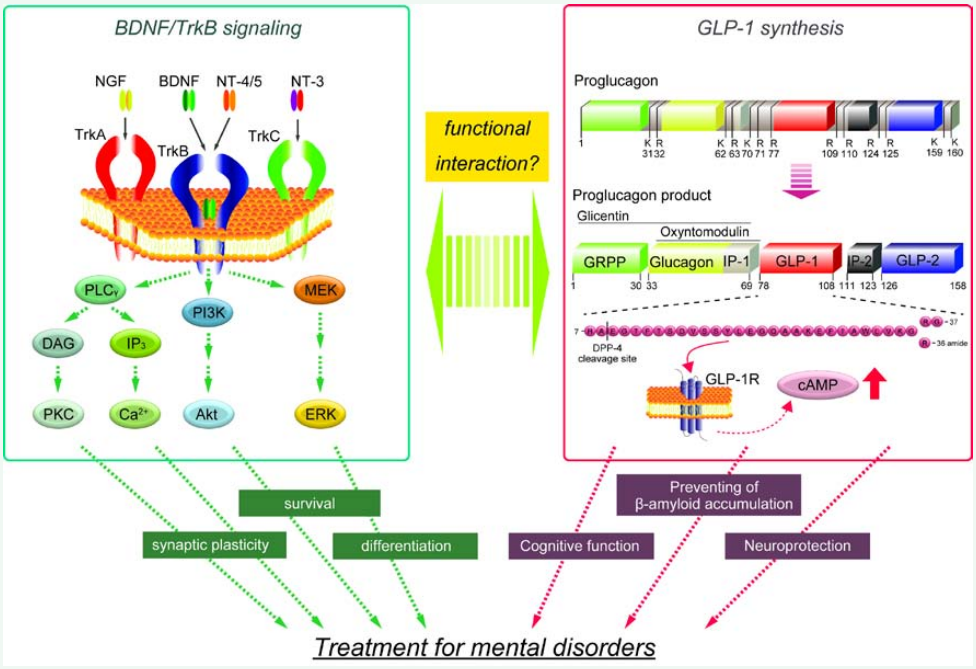

Figure 1 BDNF signaling and GLP-1 function for treatment of mental disorders.

Left; BDNF/TrkB signaling in CNS neurons. Nerve growth factor (NGF) and neurotrophin-3 (NT-3) activate TrkA and TrkC, respectively. BDNF and neurtrophin-4/5 (NT-4/5) stimulate TrkB. The stimulated TrkB receptor triggers activation of phospholipase Cγ (PLCγ), phosphoinositide 3-kinase (PI3K), and mitogen-activated/extracellular-regulated kinase (MEK) intracellular signaling pathways. Diacylglycerol (DAG)-protein kinase C (PKC) and inositol trisphosphate (IP3)-Ca2+ are downstream of PLCγ signaling to regulate synaptic plasticity. Akt and extracellular signal-regulated kinase (ERK) are downstream of PI3K and MEK, respectively, which are involved in cell survival and differentiation. For details, please see [4]. Right; GLP-1 synthesis from proglucagon. K (lysine) and R (arginine) indicate the position of cleavage site by prohormone convertase. Proglucagon products in intestinal L-cells and brain are composed of glicentin (GRPP; glicentin-related pancreatic polypeptide, glucagon, and IP-1; intervening peptide-1), GLP-1, intervening peptide-2 (IP-2), and glucagon-like peptide-2 (GLP-2) (We referred to the description by [52]). The DPP-4 cleavage site in GLP-1 is located in the N-terminal of alanine at position 2. It is well known that GLP-1 has important physiological roles including insulin secretion and appetite regulation. In CNS neurons, it has been shown that GLP-1 increases cAMP via the GLP-1 receptor, which is involved in cognitive function, preventing β-amyloid accumulation, and neuroprotection. It is possible that BDNF signaling, GLP-1 function, and interaction between both systems are promising targets to treat for mental disorders.

Depression models and BDNF signaling

In animal models of depressive disorder, curcumin, an herbal medicine, demonstrates an antidepressant effect [23]. In the forced swim test (FST), curcumin application (21 days of 40 mg/kg) achieved a significant decrease in immobility that rivaled results seen with fluoxetine treatment. Furthermore, the chronic treatment with curcumin upregulated BDNF expression, and increased levels of phosphorylated ERK (pERK) in the amygdala. Interestingly, co-application of an ERK pathway inhibitor canceled the beneficial effects of curcumin on behavior [23], suggesting that activation of ERK signaling is essential for the antidepressant effect elicited by curcumin. Chronic mild stress (CMS) in rodents is a well-known model of depression. Recently, alterations in both BDNF and pERK levels have been reported after CMS with or without antidepressant treatment. Rats exposed to five weeks of CMS consisting of unpredictable mild stress (grouped caging, tilted cage, wet cage, water or food deprivation, continuous lightning, stroboscopic lightning, or white noise) exhibited decreased sucrose intake, with reversal of anhedonic behavior induced by reboxetine treatment [24]. In this system, CMS exposure decreased hippocampal BDNF and pERK compared to controls, though reboxetine normalized these reduced levels of BDNF and pERK. On the other hand, expressions of IGF-1R (a receptor for insulin-like growth factor) in hippocampal and frontal cortex regions, and of BDNF in the frontal cortex were unchanged after CMS, indicating a region-specific response to stress. The antidepressant effect of orcinol glucoside (OG, herbal extract obtained from the Curculigo orchioides Gaertn) and its possible mechanism has been demonstrated. Ge et al. reported that serum corticosterone levels were increased following CMS, and the increased corticosterone was improved by OG treatment. In the FST and tail suspension test, OG treatment exhibited an antidepressant effect. OG treatment upregulated hippocampal pERK and BDNF, suggesting a possible role of ERK signaling in the OG-dependent antidepressant effect [25]. Using a combination of genome-wide microarray analysis and pathway analysis by the Database for Annotation, Visualisation and Integrated Discovery (DAVID), Barreto et al. demonstrated that BDNF/TrkB signaling in rat prefrontal cortex was influenced by sub-chronic restraint stress (1 hour restraint in a tube/day, for 5 days). Importantly, transcript levels for PI3K and ERK (not for PLCgamma) pathways were reduced after exposure to sub-chronic restraint stress [26]. In their system, as transcript levels were examined before inducing depression-like behavior, they found that abnormalities in BDNF signaling might contribute to the onset of depression [26]. In cultured cortical neurons obtained from rat cerebral cortex, we reported that BDNF-stimulated ERK signaling is attenuated following glucocorticoid exposure [4,5]. While ERK activation is essential to maintain expression of synaptic proteins including NR2A, a subunit of NMDA-type glutamate receptors, glucocorticoid exposure inhibits BDNF-mediated synaptic function [4,5]. Testosterone, a gonadal hormone, has an antidepressant effect, as gonadectomized rats exhibit depression-like behavior. Carrier and Kabbaj showed that suppression of ERK2 in the hippocampal dentate gyrus of gonadectomized rats with testosterone replacement resulted in anhedonia, suggesting ERK2 has a role in the antidepressant effects of testosterone [27]. Interestingly, in addition to both total and activated ERK1, activated levels of ERK2 were not changed by testosterone supplementation in hippocampal tissue of gonadectomized rats, while reduced total ERK2 was reversed by testosterone [27].

Glutamatergic neurotransmission and antidepressants

Recently, abnormal glutamatergic neurotransmission is suggested to play a role in the pathophysiology of depressive disorders. Decreased NR2A and NR2B subunits of NMDA receptors, but not NR1, are observed in prefrontal cortical tissue from patients with major depression [28]. This postmortem study also indicated reduced PSD95 protein [28], which plays a role in the scaffolding for NMDA receptors in postsynaptic sites, identifying regulation of glutamatergic neurotransmission as a possible target of treatment for depression. Indeed, blockading of NMDA receptors is thought to be a potential therapeutic target. Specifically, low-dose application of ketamine (30 min, 3.0 mg/kg) induced an acute antidepressant response in the FST in wild mice, although the effect of ketamine was not observed in *Bdnf* KO mice [29]. The acute ketamine treatment upregulated hippocampal BDNF protein expression, while the level of Bdnf mRNA was unchanged, suggesting that translation of BDNF is required for the beneficial action of ketamine [29]. Additionally, co-application with antidepressant treatment has been investigated. Rats receiving both ketamine and imipramine for 60 minutes showed lesser immobility time in the FST compared to results with each respective agent alone [30]. The combined application with ketamine and antidepressant achieved synergistic upregulation of BDNF protein in the PFC, hippocampus, and amygdala. The levels of pPKA in the hippocampus and amygdala as well as pPKC in the PFC were also increased [30]. Reduced activity of PKA and an elevation of 5-HT_{2A} receptors (serotonin 2A receptors) were shown in postmortem PFC from persons with major depression, while no differences in levels of 5-HT_{1A}, 5-HT_{2c} and in activity of PKC between those with depression and controls were observed [31].

Novel targets of antidepressants

Both clinical and animal model studies demonstrate that glucocorticoids (corticosterone in rodents, and cortisol in humans), stress hormones, are involved in depression [32-34]. Increased plasma levels of glucocorticoids due to dysfunction of the HPA axis caused by chronic stress may damage the CNS, resulting in the onset of depressive disorder. It has been reported that activity of both glucocorticoid receptor (GR; a low affinity receptor for glucocorticoids) and mineralocorticoid receptor (MR; high affinity one) are regulated by CDK5. CDK5 interacts with the ligand binding domain of the GR and induces serine phosphorylation in the N-terminal of GR, influencing transcriptional activity of the receptor [6]. CDK5 also regulates the MR-dependent transcriptional activity via phosphorylation of serine and threonine in the N-terminal region of MR, influencing the expression of BDNF in cortical neurons [35]. Interestingly, an association between the TrkB receptor and CDK5 was also reported. In addition to classical autophosphorylation of tyrosine residues, serine (S478) phosphorylation was also found [36]. Lai et al. has shown that mice lacking S478 phosphorylation in TrkB exhibit impaired hippocampal long-term potentiation (LTP) and spatial memory, suggesting involvement of CDK5 regulation in

TrkB-mediated synaptic function [7]. Because CDK5 interacts with both BDNF/TrkB signaling and the glucocorticoid system, focusing on CDK5 function may be beneficial to search for novel antidepressant candidates.

Acid sphingomyelinase has been demonstrated as a novel target of future antidepressants. The ceramide system is well known as a regulator of various neuronal aspects including cell death, and its involvement in the pathophysiology of a variety of brain diseases such as Alzheimer's disease has been suggested [37]. Though sphingomyelinase induce ceramide production, Gulbins et al. showed that the ceramide system acts downstream of antidepressant application [38]. They found that antidepressants (amitriptyline and fluoxetine) decreased acid sphingomyelinase activity and ceramide levels in hippocampal tissue, and improved depression-like behavior in corticosterone-stressed mice [38]. Importantly, direct injections of ceramide into hippocampal tissue of mice caused depression-like behavior [38]. Taken together, the sphingomyelinase/ceramide system is interesting as a new treatment target, because different classes of antidepressants similarly influence sphingomyelinase/ceramide signaling. P75, a common low-affinity receptor for neurotrophins including BDNF, can increase intracellular ceramide by activation of sphingomyelinase, which will affect structural and functional cell fate [39]. Interestingly, when examining differences in levels of neurotrophin receptors in postmortem brains between suicide and control subjects, hippocampal mRNA levels of TrkA and TrkC, and cortical mRNA levels of TrkA were decreased in suicide subjects, while p75 mRNA was increased in both hippocampus and PFC of suicide subjects [40]. As negative regulation including apoptosis in neurons by p75 has been well demonstrated [39], it is possible that p75 signaling and collaboration with Trk receptors may be useful when studying functional status of the brain.

Diabetes and BDNF

Increasing evidence raises the possibility that nutritional status affects the CNS. Cohort studies have demonstrated that risk of type 2 diabetes is moderately increased after use of antidepressant medications [8], while anti-diabetic drugs increase the risk of depression in young people [9], indicating a possible interaction between diabetes and depression. The meta-analytic research also supports the possibility of a close relationship between depression and metabolic syndrome [10].

Importantly, serum BDNF concentration was decreased in diabetic patients and animals. Proliferative diabetic retinopathy patients exhibit lower levels of serum BDNF compared with diabetic patients without complications [41]. In addition to BDNF levels, TrkB expression in retinal tissue of STZ-induced diabetic rats was drastically decreased [41]. In diabetic patients, decreased serum BDNF was observed in combination with lower scores in immediate and delayed memory [11]. It has been reported that plasma BDNF levels are inversely proportional to plasma glucose levels, while BDNF polymorphisms are not related to diabetes [42]. High-fat diets (HFD) impaired learning and memory followed by a change in dopamine metabolism in juvenile mice [43]. In addition, hippocampal LTP in the CA1 region was completely abolished in genetically obese mice [44]. These studies suggest that obesity is one of the greatest risk factors for anxiety and/or depressive disorders. As expected, diet-induced obese mice display depressive symptoms with accompanying decreases in hippocampal BDNF (but not TrkB) expression [45]. In turn, the effect of BDNF on the development of obesity was examined with injections of BDNF in the ventromedial nucleus of rats, revealing that BDNF attenuated increases in body weight of obese animals [46]. Ventromedial and dorsomedial hypothalamic BDNF deleted mice (produced by expressing cre recombinase under the α-calcium/calmodulin-dependent protein kinase II promoter) exhibit hyperphagia, obesity, leptin resistance, an increase of bone mass, and white adipose tissue, without any change in sympathetic signaling [47,48]. It is possible to use BDNF as a useful status marker of metabolic disease-related depression, though further investigation is needed to understand whether decreased plasma BDNF is a cause, or a consequence of diabetes and/or obesity.

Glucagon-like peptide 1 (GLP-1) and mental disorders

As shown above, nutritional status influences neuronal function in the CNS, with recent evidence implicating involvement of the gut hormone, GLP-1 [49,50]. It is well known that luminal nutrients stimulate gut hormone secretion through the activation of nutrient receptors to control a variety of physiological responses including gut motility, digestion, absorption, metabolism, and appetite [51]. Proglucagon gene product, GLP-1, generated via post translational processing by prohormone convertase 1/3, is rich in the enteroendocrine L-cells located in distal intestine and brain tissues (Ref. 52, 53; please see Figure 1). GLP-1 has critical physiological roles including insulin secretion, appetite regulation, and neuroprotection through the activation of GLP-1 receptors (GLP-1R) [54]. The biologically active forms of GLP-1 are GLP-1 (7-37) and GLP-1 (7-36) amide, and both are cleaved by dipeptidyl peptidase-4 (DPP-4) to convert into inactive forms. Therefore, DPP-4 inhibitors (for example, vildagliptin, sitagliptin, and alogliptin) are applied to elevate active GLP-1 concentration to treat diabetic patients [55]. Constitutively active GLP-1 analogues, such as exendin-4 (Ex-4) and liraglutide, are available for diabetes treatment [56]. Recently, GLP-1 therapy is targeted not only for metabolic diseases [55,57] but also for brain illness including Alzheimer's disease and depression [58]. Intracerebroventricular administration of STZ induces significant dysfunction of spatial learning and memory and decreases the number of CA1 normal neurons [12]. The STZ-administered animals showed an increase of phosphorylated tau, which was reversed by subcutaneous injection of Ex-4 [12]. The combination of intraperitoneal STZ and intrahippocampal lipopolysaccharide injection caused a more severe impairment in cognitive function through the NF-κB-related inflammatory response than that by solo STZ application, though continuous daily intraperitoneal application of Ex-4 reversed this cognitive impairment [59]. It has been reported that Ex-4 also improves novel object cognitive dysfunction in mice induced by a weight drop concussive head trauma device as a model of mild traumatic brain injury [60]. Although GLP-1 analogs are recognized to penetrate the blood-brain barrier [61,62], the direct effect of GLP-1 in the brain was examined by using intracerebral application. For example, liraglutide attenuated HFD and amyloid-β25-35-caused deficits in LTP of the hippocampal CA1 region and improved spatial memory function [63,64]. Application with vildagliptin and

sitagliptin (DPP-4 inhibitors, respectively) for 21 days exerted preventive effects against brain dysfunction in insulin-resistant rats produced by HFD treatment [65]. These DPP-4 inhibitors (for 12 weeks) delayed amyloid accumulation in brains of Alzheimer's disease model transgenic mice generated by expressing both a chimeric mouse/human amyloid precursor and a mutant human presenilin 1 [66]. Another DPP-4 inhibitor, saxagliptin, upregulated hippocampal GLP-1, and reduced accumulation of amyloid and phosphorylated tau in STZ-injected rats [67]. In contrast, Kim et al. demonstrated that oral administration of sitagliptin boosted tau phosphorylation in Otsuka Long Evans Tokushima Fatty rats, a type 2 diabetic animal model exhibiting hyperphagia, hyperglycemia, and hyperinsulinemia [68]. So far, a variety of physiological regulatory peptides have been identified as substrates of DPP-4 [69], though further study using molecular techniques are required to consider the efficacy of DPP-4 inhibitors.

BDNF and GLP-1-mediated signaling

Activation of GLP-1R triggers an increase in cAMP concentration in cortical [60,70,71] and hippocampal neurons [72]. Ex-4 protected cortical neurons from cell death induced by oxygen/glucose deprivation through the activation of PKA, followed by an increase in cAMP levels [70]. cAMP response element-binding protein (CREB) functions as a transcriptional factor regulating synaptic function downstream of cAMP induction [73]. In human islet, Ex-4 stimulates phosphorylation of CREB (pCREB, an active form) and protects β-cell against hypoxia and cytokines [74]. GLP-1-related signaling also exerts protective effects on differentiated human neuroprogenitor cells and stimulates BDNF production through the CREB system [75]. Geniposide, a GLP-1R agonist, has been shown to protect PC12 cells by using the PKA/CREB system [76]. In the ventromedial nucleus of the hypothalamus in animal models, intraportal administration of GLP-1 increased BDNF levels with an associated increase of c-fos positive cells [77]. Such BDNF production regulates pancreatic glucagon secretion, suggesting a role for BDNF in regulation of glucose metabolism [77]. Interestingly, marked upregulation of BDNF in thalamostriatum and forebrain tissue in mice by alogliptin (a highly selective DPP-4 inhibitor) has been reported [78]. Investigation into the interplay between GLP-1, BDNF, and putative molecules in the CNS may contribute to clarifying the relationship between diabetes and mental disorders.

CONCLUDING REMARKS

A functioning serotonergic system is critical for mood stability, with elevated serotonin levels improving depressive symptoms. As such, the effect of antidepressants, especially SSRIs, on alterations in serotonergic levels has been intensely studied. Interestingly, research has demonstrated that increased serotonin in the brain also negatively affects mood [79]. Although socioeconomic status is speculated to affect mental health [80], Branchi et al. demonstrated that fluoxetine application increased brain BDNF expression, decreased corticosterone levels, and decreased depressive behaviors in mice under the enriched housing condition, while mice under stressful conditions exhibited reduced BDNF, increased glucocorticoid levels, and an enhanced depression-like phenotype [1]. Taken together, this suggests that environmental factors should be considered when treating depression, along with managing serotonergic levels in the brain. Thus, targeting common regulators of glucocorticoids and BDNF may be beneficial, as it is well known that levels of plasma glucocorticoids and of brain BDNF are sensitive to stressful conditions [4]. As shown in this review, nutritional status is considered an important environmental factor involved in depression pathogenesis. Detailed study of the interactions between neuropeptide GLP-1, BDNF, and the HPA-axis may be highly promising in elucidating the pathophysiology of depression.

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