Review Article

Neurobiology of Major Depressive Disorder

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We survey studies which relate abnormal neurogenesis to major depressive disorder. Clinically, descriptive gene and protein expression analysis and genetic and functional studies revised here show that individual alterations of a complex signaling network, which includes the hypothalamic-pituitary-adrenal axis; the production of neurotrophins and growth factors; the expression of miRNAs; the production of proinflammatory cytokines; and, even, the abnormal delivery of gastrointestinal signaling peptides, are able to induce major mood alterations. Furthermore, all of these factors modulate neurogenesis in brain regions involved in MDD, and are functionally interconnected in such a fashion that initial alteration in one of them results in abnormalities in the others. We highlight data of potential diagnostic significance and the relevance of this information to develop new therapeutic approaches. Controversial issues, such as whether neurogenesis is the basis of the disease or whether it is a response induced by antidepressant treatments, are also discussed.

1. Introduction

Major depressive disorder (MDD) is one of the most common psychiatric diseases. MDD is not only characterized by profound dysregulation of affect and mood but is also associated with other abnormalities including cognitive dysfunction, sleep and appetite disturbance, fatigue, and many other metabolic, endocrine, or inflammatory alterations (see [1, 2]). The existence of MDD as a medical condition has been recognized with the term melancholia in texts dating up to the ancient Greece, but the current diagnostic criteria remain to some degree arbitrary. In addition, account must be taken of the fact that almost all individuals have experienced a transient depressed mood state at some time in their life. In fact, there is controversy in whether MDD is best conceptualized as a disease or as the extreme of a continuum of increasingly disturbed affective regulation. MDD is often termed unipolar depressive disorder to be distinguished from depression which alternates with episodes of mania which is termed bipolar depression. The latter is potentially distinguishable by functional neuroimaging approaches [3].

The purpose of this review is to summarize information accumulated in the last two decades concerning gene and protein expression changes in MDD [4]. These data suggest that the pathophysiology of this disease is related to disturbed adult neurogenesis [5, 6] and, without doubt, will help develop new therapeutic and diagnostic tools in the near future [2, 7]. Due to the complexity of the subject, we will exclude from this review well-established monoamine neurochemical alterations in MDD which are the basis for most current treatments [8]. Anatomical identification of the brain regions altered in MDD has also advanced in the last decade with the employment of modern functional neuroimaging techniques (see [9]), but a detailed analysis of the anatomy and histopathology of the disease is also out of the scope of the present review.

Adult neurogenesis is a topic of increasing interest in neuroscience. In the last decade it has been shown that, rather than being architecturally stable, the mammalian central nervous system retains potential to remove neurons and glia, and to establish new neural circuits. Two major cerebral zones, the subventricular region of the lateral ventricles, and the subgranular region of the gyrus dentatus, contain proliferating neural precursors able to provide neurons to be functionally integrated into neuronal networks. Neurogenesis in the sub-ventricular region provides neurons to the olfactory bulbus and is functionally implicated in olfaction. Adult born neurons produced in the gyrus dentatus are involved in major hippocampal functions and appear to be the target of diseases which impair memory and learning [10].
The etiology of depression is unknown (see review by [11]). MDD can be spontaneous but often follows a traumatic emotional experience or can be a symptom of other diseases, most often neurological (e.g., stroke, multiple sclerosis, or Parkinson disease) or endocrine (Cushing's disease, hypothyroidism). MDD can also be triggered or precipitated by pharmacological agents or drug abuse [12]. The prevalence is higher in women (in the range of 1.5 to 2.5) and nearly 50% of the risk for depression is due to genetic factors [13]. These factors may influence both overall risk of illness and the sensitivity of individuals to the environmental adversities.

2. Neurotrophins and Depression

Histological and functional neuroimaging studies revealed synaptic and structural plasticity alterations in different regions of the brain, including the frontal cortex and hippocampus in MDD patients [14–17]. In pathophysiological terms, it was proposed that these alterations could prevent the brain from making appropriate adaptive responses to environmental stimuli [18]. These facts have directed attention of neuroscientists to the study of neurotrophins in depression as they are neuron survival factors of critical importance for the establishment and maintenance of neural circuits during development and in adult subjects [19–21].

Neurotrophins constitute a family of 4 distinct secreted growth factors (nerve growth factor, NGF; brain-derived neurotrophic factor, BDNF; neurotrophin-3, NT-3; and neurotrophin-4, NT-4) which upon binding to membrane receptors in the target neurons activate an intracellular cascade which promotes survival and trophic effects. Each neurotrophin binds with high affinity to specific members of the tyrosine kinase receptor family (Trk receptors; NGF binds to TrkA, BDNF and NT-4 binds to TrkB and, NT-3 binds not only to TrkC but also to the other Trk receptors with low affinity). In addition, all the neurotrophins bind with low affinity to p75 (NTR), which not only is a very different receptor, responsible for storing and transporting neurotrophins, but also promotes neuronal cell death to sculpt neuronal circuits during development.

Initial preclinical studies showing that expression of BDNF was downregulated in the dentate gyrus and hippocampus of rats subjected to chronic stress [22] have attracted interest of researchers on the potential involvement of BDNF in depression. Research accumulated in the last decade indicates that this neurotrophin is a central target in the pathogenesis of depression and suicidal behaviour [23, 24]. Expressions of BDNF, BDNF-regulated genes, and the receptor TrkB are decreased in postmortem brain samples from depressed humans [25] and in circulating lymphocytes of depressed patients during a drug-free period [26]. Consistent with these findings, serum levels of BDNF are also decreased in MDD patients [27, 28] and polymorphisms in the BDNF gene may be predictive of the chronicity of the disease [29]. Moreover, expression of BDNF is upregulated both in human and experimental animals by antidepressant treatments, including electroconvulsive therapy and repetitive transcranial magnetic stimulation [30–34]. In addition, BDNF (and also NT3) produced antidepressant effect on behavioral models of depression [35, 36] which are abolished in mice deficient in TrkB receptor [37]. Together these findings support a causal implication of BDNF in the genesis of MDD. Discrepancies present in the literature concerning the occasional absence of BDNF upregulation by different classes of antidepressants have been attributed to the route of administration, the doses of drugs employed, or, remarkably, a differential effect of the different antidepressants on the transcription on the four different exons present in the BDNF gene [23]. However, it must be mentioned that BDNF heterozygous knockout mice do not display anxious or depressive-like behaviors [38].

The expression of the BDNF receptor TrkB is also upregulated by chronic electroconvulsive seizure and antidepressant drug treatments [39]. Furthermore, increase of BDNF signaling by overexpression of the full length TrkB gene in mice results in an antidepressant-like behavioral response [40]. However, the implication of TrkB in depression pathophysiology bears more complexity because the TrkB gene in addition to the active full length isoform has a truncated isoform which modulates negatively BDNF signaling [23]. In fact, mutant mice with a forebrain directed deficiency in TrkB exhibit symptoms of attention-deficit disorder rather than depressive behaviour [41].

The formation of BDNF takes place by proteolytic cleavage of a larger precursor protein termed proBDNF. ProBDNF is able to bind the low-affinity receptor p75NTR exerting an opposite effect to that of BDNF/TrkB signaling [42, 43]. Consistent with this finding, it has been found that the serum levels and the expression of both proBDNF and p75NTR in circulating lymphocytes are up-regulated in MDD [44]. According to these facts it has been proposed that not only the expression of BDNF and TrkB but also the ratio between BDNF-TrkB and proBDNF-p75NTR is dysregulated in MDD [44]. Evidence from a role of the p75NTR receptor in depression is also supported by genetic evidence, because the missense Ser205Leu polymorphism of this gene appears to have a protective effect against the development of MDD in women [45].

The involvement of other neurotrophins and receptors in MDD has received less attention. Expressions of NT-3 and two members of the related family of glial cell line-derived neurotrophic factor, GDNF and ARTN, were found down-regulated in circulating blood cells of patients with MDD but not in bipolar disorder [46].

3. MicroRNAs and Depression

From the beginning of the present century, it was recognized that the genome, in addition to produced mRNA destined to form proteins which regulate cell function, generates also small units of noncoding RNA, termed microRNA (miRNA). miRNAs are regulatory molecules which control gene function by cleaving or repressing the translation of
target mRNAs. miRNAs are very conserved among the different species and participate critically in most biological processes. Three aspects of miRNA is particularly relevant in medicine: (1) dysregulation of specific miRNAs are associated to many diseases; (2) levels of miRNAs can be identified and quantified by RT-PCR in the serum serving as biomarkers of different diseases; and (3) they can be silenced in vivo by administration of miRNAs inhibitors (antagomir) or employed as exogenous therapeutic agents to influence gene transcription and protein synthesis.

miRNAs, as neurotrophins, are involved in neuron survival, synaptogenesis, and neural plasticity, and their implication in psychiatric diseases is beginning to be explored (see [47]). Alterations of various miRNAs, including miR-30e, miR-182, and miR-132 have been implicated in MDD [47–50]. Remarkably, miR-132, and miR-182 regulate negatively the expression of BDNF and were found to show increased serum levels in MDD patients [50]. In preclinical studies, miR-212, which also regulates the expression of BDNF, was overexpressed in the dentate gyrus and serum after electroconvulsive stimulation [51]. Together these findings suggest that future functional studies of miRNA will provide significant advances in the understanding of psychiatric diseases including the design of novel treatments (see review [6]).

4. Stress Hormones and Depression

A large number of clinical and basic researches indicate that MDD is associated with a maladaptive response to stress, due to dysfunction of the hypothalamic-pituitary-adrenal axis (HPA axis) [52–54]. Abnormal hormone dynamics is a constant feature in mood disorders and can precede the onset of MDD [55] supporting the involvement of the HPA axis in this disease [56]. Stress hormonal alterations observed in MDD include impaired inhibition of cortisol release by dexamethasone, elevated cortisol values, increased excretion of cortisol and an overactive response to psychological stressors. Assays to evaluate HPA dysfunction, such as the dexamethasone suppression test or the dexamethasone/corticotropin releasing hormone test, have been useful to establish objective parameters in the diagnosis of endogenous mood disorders and to predict response to antidepressant treatment [57–59].

Regardless of whether these alterations are at the origin (i.e., Cushing disease) or are a consequence of MDD, it is important to remark that the elevated levels of stress and glucocorticoid hormones interfere with normal hippocampal neurogenesis [60] contributing to the development of the disease. Consistent with this interpretation, a glucocorticoid receptor target gene, the serum- and glucocorticoid-inducible kinase 1 (SGKI) which inhibits hippocampal neurogenesis, is upregulated in depressed patients and in animal models of depressive behavior [60]. In addition, there is evidence for a role of corticosteroids modifying the function of BDNF, suggesting a functional crosstalk between stress hormones and BDNF signaling of potential implication in the pathogenesis of MDD [61].

5. Inflammation and Depression

Evidence for immune system involvement in the pathophysiology of major depressive disorder is abundant and solid (see reviews [62–64]). As mentioned above, a characteristic feature observed in MDD patients is the elevation of glucocorticoids. However, in spite of the potent anti-inflammatory effect of glucocorticoids, MDD patients exhibit elevated levels of circulating proinflammatory cytokines, including interleukin-1, interleukin-6, tumor necrosis factor alpha, and some soluble interleukin receptors [28, 65–67]. The proinflammatory cytokines not only participate in the innate immune response and inflammation but also have important metabolic and endocrine effects including neurotransmitter metabolism, neuroendocrine function, and neural plasticity. Remarkably, administration of interleukin-6 induces depressive-like behaviors and neutralizes the antidepressant effect of fluoxetine in experimental animals [68]. In a similar fashion, people treated with inflammatory cytokines such as interferon alpha develop depression that is indistinguishable from depression in nonmedically ill populations (see [69]). Furthermore, expression of different cytokines and genes implicated in cell death is up-regulated in postmortem brain tissue of MDD patients suggesting local inflammatory, apoptotic, and oxidative stress in brain regions involved in reward-related behaviors [70]. The involvement of cytokines in behavior and in different functions of the nervous system is also sustained by the presence of specific receptors in hippocampus and hypothalamic nuclei [71]. Remarkably, proinflammatory cytokines stimulate the hypothalamic-pituitary-adrenal axis, activate the secretion of growth hormone, and inhibit thyroid-stimulating hormone secretion [72]. All these endocrine effects are associated with MDD.

A striking finding about the role of proinflammatory cytokines in MDD is that, in contrast with the elevated levels in the blood, the level of interleukin-6 in cerebrospinal fluid is reduced in MDD patients and the decreased level is predictive of future depression in old women [73].

6. Gut Microbiota and Depression

There is growing evidence for the occurrence of a functional interplay between gut microbiota and brain function (brain-gut axis). According to this view the microbiota can influence brain chemistry and consequently behavior. Consistent with this idea, it has been found that the composition of gut microbiota in animal models of depression and chronic stress shows differences with that of healthy animals [74]. Leptin [75], ghrelin [76], cholecystokinin [77], and other various factors are signaling peptides produced in the gastrointestinal system with a direct influence on the central nervous system, including modulation of neurogenesis, which might be implicated in MDD. However, at the present, we are still far from assigning a role for disbalances in the gut microbiota in the pathophysiology of depression and alterations in gut flora may be secondary to abnormal gastrointestinal dynamics in MDD patients.
7. Concluding Remarks: Adult Neurogenesis and MDD

The evidence surveyed in this review supports a primary involvement of disturbed adult neurogenesis and altered synaptic connectivity in the origin of MDD (see reviews [11,78]). In adult mammals, neurogenesis is sustained by two specialized niches of neural progenitors, the subventricular zone of the lateral ventricles and the subgranular zone of the hippocampal dentate gyrus [79]. Preclinical studies have shown that hippocampal neurogenesis is altered in chronic stress which is considered as an animal model of clinical depression [80]. In addition, most studies point to hippocampal neurogenesis as the target for antidepressant treatments [80–83]. As listed in this review, deficient neurogenesis may be caused by distinct primary alterations of a complex signaling network which includes, at least, the following players: dysfunction of the hypothalamic-pituitary-adrenal axis; deficient production of neurotrophins; abnormalities in the expression of MiRNAs; dysregulation of proinflammatory cytokines; and, even, the abnormal delivery of gastrointestinal signaling peptides. Any of these alterations appear to promote a similar phenotype characterized by major mood alteration. In addition, all of those factors are functionally interconnected in such a fashion that initial alteration in one of them results in abnormalities in the others. However, whether the reduced neurogenesis is the cause of MDD or whether neurogenesis is only necessary to ameliorate the disease needs to be clarified. Postmortem studies in humans have found no change in cell proliferation between major depression patients and control samples [84]. Furthermore, no depressive-like behavior was induced by experimental inhibition of cell proliferation in the hippocampus of animal models [85]. And, most striking, increased neurogenesis has been implicated in the induction of anxious behavior in mice questioning the simplistic view that more newborn neurons are always better for mental health [86]. A further explanation is that changes in adhesion molecules, like neural cell adhesion molecule (NCAN) associated with neurogenesis and also with synaptic plasticity, may play a central role in MOD [11].

Regardless of whether the role of hippocampal neurogenesis in MDD concerns the etiology or the antidepressant treatment, it is likely that future treatments of MDD will be designed to target neurogenesis and neural plasticity as a central factor in the pathogenesis of this disorder. Potential candidates for this purpose are different families of secreted factors with positive influence in neurogenesis. Remarkably, FGFs, which are a family of growth factors involved in the control of proliferation and neuroplasticity, have been recently implicated in the pathophysiology of MDD [87]. Several ligands of the FGF family, such as FGF-2, are expressed in the adult brain and become downregulated in individuals suffering from MDD [88]. In addition, exogenous FGF-2 has antidepressant effect on animal models of depressed behavior [89]. Vascular endothelial growth factor (VEGF) is an angiogenic growth factor which promotes hippocampal neurogenesis [90] implicated also in the pathophysiology of MDD [91]. SB100B is a protein associated with MDD which is expressed and secreted by glial cells and other nonneural cell lineages implicated in synaptogenesis and neuronal survival [92]. A number of recent studies have observed that SB100B is increased in the hippocampus, serum, and cerebrospinal fluid of MDD patients, most likely reflecting a response of glial cells to neural damage (see [93] and references therein) and also that the basal levels of serum may predict the outcome of the therapeutic response to antidepressants [94].

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

References

[1] P. J. Fitzgerald, “Gray colored glasses: is major depression partially a sensory perceptual disorder?” Journal of Affective Disorders, 2013.

[2] U. E. Lang and S. Borgwardt, “Molecular mechanisms of depression: perspectives on new treatment strategies,” Cell Physiol Biochem, vol. 31, pp. 761–777, 2013.

[3] J. C. Fournier, M. T. Keener, J. Almeida, D. M. Kronhaus, and M. L. Phillips, “Amygdala and whole-brain activity to emotional faces distinguishes major depressive disorder and bipolar disorder,” Bipolar Disorder, 2013.

[4] L. Mandelli and A. Serretti, “Gene environment interaction studies in depression and suicidal behavior: an update,” Neuropsychology and Biobehavioral Reviews, 2013.

[5] M. M. Lee, A. Reif, and A. G. Schmitt, “Major depression: a role for hippocampal neurogenesis?” in Behavioral Neurobiology of Depression and Its Treatment, vol. 14 of Current Topics in Behavioral Neurosciences, pp. 153–179, Springer, Berlin, Germany.

[6] F. Katelijn Hansen and K. Obrietan, “MicroRNA as therapeutic targets for treatment of depression,” Neuropsychiatric Disease and Treatment, vol. 2013, pp. 1011–1021, 2013.

[7] C. A. Altar, M. P. Vawter, and S. D. Ginsberg, “Target identification for CNS diseases by transcriptional profiling,” Neuropsychopharmacology, vol. 34, no. 1, pp. 18–54, 2009.

[8] J. H. Meyer, N. Ginovart, A. Boovarala et al., “Elevated monoamine oxidase levels in the brain: an explanation for the monoamine imbalance of major depression,” Archives of General Psychiatry, vol. 63, no. 11, pp. 1209–1216, 2006.

[9] V. Krishnan and E. J. Nestler, “Linking molecules to mood: new insight into the biology of depression,” American Journal of Psychiatry, vol. 167, no. 11, pp. 1305–1320, 2010.

[10] J. B. Aimone, W. Deng, and F. H. Gage, “Adult neurogenesis: integrating theories and separating functions,” Trends in Cognitive Sciences, vol. 14, no. 7, pp. 325–337, 2010.

[11] R.S. Wainwright and A. M. L. Galea, “The neural plasticity theory of depression: assessing the roles of adult neurogenesis and PSA-NCAM within the hippocampus,” Neural Plasticity, vol. 2013, Article ID 805497, 14 pages, 2013.

[12] A. Kenneson, J. S. Funderburk, and S. A. Maisto, “Substance use disorders increase the odds of subsequent mood disorders,” Drug and Alcohol Dependence, 2013.

[13] M. Fava and K. S. Kendler, “Major depressive disorder,” Neuron, vol. 28, no. 2, pp. 335–341, 2000.

[14] G. Rajkowska, “Histopathology of the prefrontal cortex in major depression: what does it tell us about dysfunctional monoaminergic circuits?” Progress in Brain Research, vol. 126, pp. 397–412, 2000.
[15] D. Cotter, D. Mackay, S. Landau, R. Kerwin, and I. Everall, "Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder," *Archives of General Psychiatry*, vol. 58, no. 6, pp. 545–553, 2001.

[16] D. Cotter, D. Mackay, G. Chana, C. Beasley, S. Landau, and I. P. Everall, "Reduced neuronal size and glial cell density in area 9 of the dorsolateral prefrontal cortex in subjects with major depressive disorder," *Cerebral Cortex*, vol. 12, no. 4, pp. 386–394, 2002.

[17] S. Campbell and G. MacQueen, "An update on regional brain volume differences associated with mood disorders," *Current Opinion in Psychiatry*, vol. 19, no. 1, pp. 25–33, 2006.

[18] R. S. Duman, "Pathophysiology of depression: the concept of synaptic plasticity," *European Psychiatry*, vol. 17, no. 3, pp. 306–310, 2002.

[19] S. L. Oliveira, M. M. Pillat, A. Cheffer, C. Lameu, T. T. Schweindt, and H. Ulrich, "Functions of neurotrophins and growth factors in neurogenesis and brain repair," *Journal of the International Society for Advancement Cytometry*, vol. 83, no. 1, pp. 76–89, 2013.

[20] C. K. Callaghan and A. M. Kelly, "Neurotrophins play differential roles in short and long-term recognition memory," *Neurobiology of Learning and Memory*, vol. 104, pp. 39–48.

[21] C. Jiang and S. R. Salton, "The role of neurotrophins in major depressive disorder," *Translational Neuroscience*, vol. 4, no. 1, pp. 46–58, 2013.

[22] M. A. Smith, S. Makino, R. Kvetnansky, and R. M. Post, "Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus," *Journal of Neuroscience*, vol. 15, no. 3 I, pp. 1768–1777, 1995.

[23] Y. Dwivedi, "Brain-derived neurotrophic factor: role in depression and suicide," *Neuropsychiatric Disease and Treatment*, vol. 5, no. 1, pp. 433–449, 2009.

[24] B.-H. Lee and Y.-K. Kim, "The roles of BDNF in the pathophysiology of major depression and in antidepressant treatment," *Psychiatry Investigation*, vol. 7, no. 4, pp. 231–235, 2010.

[25] A. Tripp, H. Oh, J. P. Guilloux, K. Martinowich, D. A. Lewis, and E. Sibille, "Brain-derived neurotrophic factor signaling and subgenual anterior cingulate cortex dysfunction in major depressive disorder," *American Journal of Psychiatry*, vol. 169, no. 11, pp. 1194–1202, 2012.

[26] G. N. Pandey, Y. Dwivedi, H. S. Rizavi, X. Ren, H. Zhang, and M. N. Pavuluri, "Brain-derived neurotrophic factor gene and protein expression in pediatric and adult depressed subjects," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 34, no. 4, pp. 645–651, 2010.

[27] F. Karege, G. Perret, G. Bondolfi, M. Schwald, G. Bertschy, and J.-M. Aubry, "Decreased serum brain-derived neurotrophic factor levels in major depressed patients," *Psychiatry Research*, vol. 109, no. 2, pp. 143–148, 2002.

[28] Y.-K. Kim, S.-D. Won, J.-W. Hur et al., "Exploration of biological markers of suicidal behavior in major depressive disorder," *Psychiatry Investigation*, vol. 4, no. 1, pp. 13–21, 2007.

[29] Y. Lee, S. W. Lim, S. Y. Kim et al., "Association between the BDNF Val66Met polymorphism and chronicity of depression," *Psychiatry Investigation*, vol. 10, pp. 56–61, 2013.

[30] B. Chen, D. Dowlatshahi, G. M. MacQueen, J.-F. Wang, and L. T. Young, "Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication," *Biological Psychiatry*, vol. 50, no. 4, pp. 260–265, 2001.

[31] C. A. Altar, R. E. Whitehead, R. Chen, G. Wörtwein, and T. M. Madsen, "Effects of electroconvulsive seizures and antidepressant drugs on brain-derived neurotrophic factor protein in rat brain," *Biological Psychiatry*, vol. 54, no. 7, pp. 703–709, 2003.

[32] M. B. Müller, N. Toschi, A. E. Kresse, A. Post, and M. E. Keck, "Long-term repetitive transcranial magnetic stimulation increases the expression of brain-derived neurotrophic factor and cholecystokinin mRNA, but not neuropeptide tyrosine mRNA in specific areas of rat brain," *Neuropsychopharmacology*, vol. 23, no. 2, pp. 205–215, 2000.

[33] A. S. Gonul, F. Akdeniz, F. Taneli, O. Donat, C. Eker, and S. Vahip, "Effect of treatment on serum brain-derived neurotrophic factor levels in depressed patients," *European Archives of Psychiatry and Clinical Neuroscience*, vol. 255, no. 6, pp. 381–386, 2005.

[34] U. E. Lang, M. Bajbouj, J. Gallinat, and R. Hellweg, "Brain-derived neurotrophic factor serum concentrations in depressive patients during vagus nerve stimulation and repetitive transcranial magnetic stimulation," *Psychopharmacology*, vol. 187, no. 1, pp. 56–59, 2006.

[35] J. A. Siuciak, D. R. Lewis, S. J. Wiegand, and R. M. Lindsay, "Antidepressant-like effect of brain-derived neurotrophic factor (BDNF)," *Pharmacology Biochemistry and Behavior*, vol. 56, no. 1, pp. 131–137, 1996.

[36] Y. Shirayama, A. C.-H. Chen, S. Nakagawa, D. S. Russell, and R. S. Duman, "Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression," *Journal of Neuroscience*, vol. 22, no. 8, pp. 3251–3261, 2002.

[37] T. Saarelainen, P. Hendolin, G. Lucas et al., "Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects," *Journal of Neuroscience*, vol. 23, no. 1, pp. 349–357, 2003.

[38] G. M. MacQueen, K. Ramakrishnan, S. D. Croll et al., "Performance of heterozygous brain-derived neurotrophic factor knockout mice on behavioral analogues of anxiety, nociception, and depression," *Behavioral Neuroscience*, vol. 115, no. 5, pp. 1145–1153, 2001.

[39] M. Nibuya, S. Morinobu, and R. S. Duman, "Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments," *Journal of Neuroscience*, vol. 15, no. 11, pp. 7539–7547, 1995.

[40] E. Koponen, T. Rantamäki, V. Voikar, T. Saarelainen, E. MacDonald, and E. Castrén, "Enhanced BDNF signaling is associated with an antidepressant-like behavioral response and changes in brain monoamines," *Cellular and Molecular Neurobiology*, vol. 25, no. 6, pp. 973–980, 2005.

[41] B. Zörner, D. P. Wolfer, D. Brandis et al., "Forebrain-specific trkB-receptor knockout mice: behaviorally more hyperactive than ‘depressive’," *Biological Psychiatry*, vol. 54, no. 10, pp. 972–982, 2003.

[42] M. Zagrebelsky, A. Holz, G. Dechant, Y.-A. Barde, T. Bonhoeffer, and M. Korte, "The p75 neurotrophin receptor negatively modulates dendrite complexity and spine density in hippocampal neurons," *Journal of Neuroscience*, vol. 25, no. 43, pp. 9989–9999, 2005.

[43] R. S. Duman, "Brain-derived neurotrophic factor serves as a common component of antidepressant actions," *Neuropsychopharmacology*, vol. 54, no. 10, pp. 1069–1077, 2005.

[44] L. Zhou, J. Xiong, Y. Lim et al., "Upregulation of blood proBDNF and its receptors in major depression," *Journal of Affective Disorders*, vol. 150, no. 3, pp. 776–784, 2013.
Neural Plasticity 7

[77] C. Becker, B. Zeau, C. Rivat, A. Blugeot, M. Hamon, and J.-J. Benoliel, "Repeated social defeat-induced depression-like behavioral and biological alterations in rats: involvement of cholecystokinin," *Molecular Psychiatry*, vol. 13, no. 12, pp. 1079–1092, 2008.

[78] F. R. Bambico and C. Belzung, "Novel insights into depression and antidepressants: a synergy between synaptogenesis and neurogenesis?" *Current Top Behavioral Neurosciences*, vol. 15, pp. 243–291, 2013.

[79] G.-L. Ming and H. Song, "Adult neurogenesis in the mammalian central nervous system," *Annual Review of Neuroscience*, vol. 28, pp. 223–250, 2005.

[80] H. Jun, S. M. Q. Hussaini, M. J. Rigby, and M. H. Jang, "Functional role of adult hippocampal neurogenesis as a therapeutic strategy for mental disorders," *Neural Plasticity*, vol. 2012, Article ID 854285, 20 pages, 2012.

[81] L. Santarelli, M. Saxe, C. Gross et al., "Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants," *Science*, vol. 301, no. 5634, pp. 805–809, 2003.

[82] C. Anacker, P. A. Zunszain, A. Cattaneo et al., "Antidepressants increase human hippocampal neurogenesis by activating the glucocorticoid receptor," *Molecular Psychiatry*, vol. 16, no. 7, pp. 738–750, 2011.

[83] Z. W. Peng, F. Xue, H. N. Wang et al., "Paroxetine up-regulates neurogenesis in hippocampus-derived neural stem cell from fetal rats," *Molecular and Cellular Biochemistry*, vol. 375, pp. 105–113, 2013.

[84] A. Reif, S. Fritzen, M. Finger et al., "Neural stem cell proliferation is decreased in schizophrenia, but not in depression," *Molecular Psychiatry*, vol. 11, no. 5, pp. 514–522, 2006.

[85] M. N. Jayatissa, K. Henningsen, M. J. West, and O. Wiborg, "Decreased cell proliferation in the dentate gyrus does not associate with development of anhedonic-like symptoms in rats," *Brain Research*, vol. 1290, pp. 133–141, 2009.

[86] J. Fuss, N. M. B. Ben Abdallah, F. W. Hensley, K.-J. Weber, R. Hellweg, and P. Gass, "Deletion of running-induced hippocampal neurogenesis by irradiation prevents development of an anxious phenotype in mice," *PLoS One*, vol. 5, no. 9, Article ID e12769, 2010.

[87] C. A. Turner, S. J. Watson, and H. Akil, "The fibroblast growth factor family: neuromodulation of affective behavior," *Neuron*, vol. 76, pp. 160–174, 2012.

[88] S. J. Evans, P. V. Choudary, C. R. Neal et al., "Dysregulation of the fibroblast growth factor system in major depression," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 101, no. 43, pp. 15506–15511, 2004.

[89] J. Jarosik, B. Legutko, S. Werner, K. Unsicker, and O. V. B. Halbach, "Roles of exogenous and endogenous FGF-2 in animal models of depression," *Restorative Neurology and Neuroscience*, vol. 29, no. 3, pp. 153–165, 2011.

[90] K. Jin, Y. Zhu, Y. Sun, X. O. Mao, and L. Xie, "Greenberg DA. Vascular endothelial growth factor stimulates neurogenesis in vitro and in vivo," *Proceedings of the National Academy of Sciences*, vol. 99, pp. 11946–11950, 2002.

[91] A. Clark-Raymond and A. Halaris, "VEGF and depression: a comprehensive assessment of clinical data," *Journal of Psychiatric Research*, vol. 47, pp. 1080–1087, 2013.

[92] R. Donato, G. Sorci, F. Riuzzi et al., "Si100B's double life: intracellular regulator and extracellular signal," *Biochimica et Biophysica Acta*, vol. 1793, no. 6, pp. 1008–1022, 2009.

[93] T. Gos, M. L. Schroeter, W. Lessel et al., "Si100B-immunopositive astrocytes and oligodendrocytes in the hippocampus are differentially afflicted in unipolar and bipolar depression: a post-mortem study," *Journal of Psychiatric Research*, vol. 47, no. 11, pp. 1694–1699, 2013.

[94] B.S. Jang, H. Kim, S.W. Lim, K.W. Jang, and D.K. Kim, "Serum Si100B levels and major depressive disorder: its characteristics and role in antidepressant response," *Psychiatry Investigation*, vol. 5, no. 3, pp. 193–198, 2008.