We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 7

Biological Markers and Genetic Factors of Major Depressive Disorder

Hwa-Young Lee and Yong-Ku Kim

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/54388

1. Introduction

Major depressive disorder (MDD) is very prevalent and severe psychiatric disorder with prevalence estimates ranging 5% to 20% [1, 2] and has been a growing public health concern due to its recurrent, deliberate, and lethal nature. According to projections, MDD will become the second leading cause of disability worldwide by the year 2020. [3]

MDD is considered to be a clinically heterogeneous disorder which result from multiple genes interacting with environmental factors such as early stressful life events [4] and the diagnosis is based on a patient's symptoms, not on laboratory test.

Although recent decades have witnessed a tremendous revolution in the development of antidepressant drugs, the neurochemical effects that underlie the therapeutic action of these agents remain largely unknown. Antidepressant drugs acutely increase levels of monoamines, but it takes 2–3 weeks to show a clinical response after the administration of an antidepressant drug, [5] and the initial response rate in patients with major depressive disorders is about 70%. [6]

For the further understanding of the pathogenesis or the prediction of treatment response of MDD, biological approach for depression is needed.

The term 'biological marker' means biological change associated with depression that could be used to indicate the presence and severity of the condition and predict drug or other treatments' response as well as the clinical prognosis. So, the research for biological markers of depressive disorders is helpful for finding diagnostic method and useful to distinguish the effectiveness and early improvement after antidepressant administration.

Although work in this area has been inconclusive, many animal, post-mortem, clinical, and genetic studies have produced results implicating at least 3 neurobiological systems in the

pathogenesis in major depression: dysfunction in the serotonergic system, hyperactivity of the hypothalamic-pituitary-adrenal axis, and decreased neuroplasticity. Additionally, other neurotransmitters, biochemical factors including inflammatory markers, neurophysiologic markers and neuroimaging markers may be associated with MDD.

In this chapter, we discuss biological markers involved in the pathogenesis of major depressive disorder.

2. Biological marker and genetic factor

2.1. Neurotransmitters

2.1.1. Serotonergic system

It has been hypothesized that a deficit in serotonin may be a crucial determinant in the pathophysiology of major depression. The serotonin system has been widely investigated in studies of major depression. The innervations of the serotonin system project from the dorsal raphe nucleus to all of the regions of the brain, including the cerebral cortex and hippocampus. Decreased function and activity of the serotonergic system in patients with major depression have been also confirmed in postmortem, serotonin transporter and serotonin receptor studies.

In suicide victims with major depression, enhanced radioligand binding of an agonist to inhibitory serotonin-1A autoreceptors in the human dorsal raphe nucleus provides pharmacological evidence to support the hypothesis of diminished activity of serotonin neurons. [7]

A trend of decreased 5-HT1A receptor expression appears to be a robust finding in major depression. A functional genetic variant of the 5-HT1A receptor, the C-1019G promoter polymorphism (rs6295), has been investigated in major depression. The G allele was more frequent in major depression. [8] By contrast, polymorphisms of HTR1A showed no association in Caucasians, while a significant association was observed in several studies of Asians. [9]

Imipramine binds to the serotonin transporter (5-HTT) on platelets, and it has been suggested that decreased platelet imipramine binding may be a putative biological marker of depressive disorder. A meta-analysis has shown that imipramine binding to platelets is indeed a robust biological marker of depression. [10]

Tryptophan hydroxylase (TPH), which has two isoforms (TPH1 and TPH2), is one of the rate limiting factors in serotonin synthesis, Postmortem studies have reported significantly higher numbers and higher densities of TPH immunoreactive neurons in the dorsal raphe nuclei of alcohol dependent, depressed suicide victims [11] when compared to controls. We have found that the TPH2 -703G/T SNP may have an important effect on susceptibility to suicidal behavior in those with major depressive disorder. Additionally, an increased frequency of the G allele of the TPH2 SNP is associated with elevated risk of suicidal behavior itself rather than with the diagnosis of major depression. [12]

Collectively, serotonin receptor, TPH and 5-HTT studies suggest that deficient or impaired serotonin activity is involved in major depression.

2.1.2. Noradrenergic and dopaminergic systems

The mechanism of action of tricyclic and monoamine oxidase inhibitor antidepressants involves the monoaminergic neurobiology. Recently, dual-acting antidepressants such as serotonin norepinephrine reuptake inhibitors (SNRIs) are introduced and have presented clinicians with a wider range of antidepressants. The action of the antidepressants is based on alterations in the functions of neurotransmitter systems and changes in the monoamine systems. [13, 14] Catecholamine metabolites, particularly 3-methoxy-4-hydroxy phenylglycol (MHPG), did not sufficiently distinguish depressed from other groups. Work in this area then underwent a subtle but significant shift toward the use of catecholamine metabolites to predict the response to tricyclic antidepressants. [15, 16] Nonetheless, research into the levels of monoamine transmitters and their metabolites have not found convincing evidence of a primary dysfunction into a particular transmitter system in depression, or a critical role in helping predict antidepressant response. [17]

The norepinephrine (NE) system has been studied in depression, particularly the action of NE reuptake inhibitors and SNRIs, which act at the NE transporter. Although polymorphisms the NET gene have not shown consistent association regarding susceptibility to depression, [18-20] but it cannot be denied that it may be an important candidate.

The Antidepressant effect of mirtazapine appears to be related to the dual enhancement of central noradrenergic and serotonergic neurotransmission via the blockade of adrenergic α2 receptors. [21-23] Previous studies have outlined the functional aspects of α2 receptors in depression, reporting reduced α2 inhibition of platelet adenylate cyclase activity [24] and increased adrenergic α2 agonist-induced platelet aggregation in depressed patients. [25] Three genes that encode human adrenergic α2 receptors have been cloned: α2a, α2B, and α2C. [26] The adrenergic α2a receptor (ADRA2A) subtype is expressed in the central nervous system and peripheral tissues. [27] According to this classification, the classic α2 receptor studied in mood disorders is the α2a receptor.

Previous study didn't show any association between this polymorphism and mood disorders, including depressive and bipolar disorders. [28] Regarding the prediction of antidepressant treatment, the ADRA2A −1291C/G genotypes did not show consistent results. [29, 30]

The dopamine (DA) system is also highly asssocitated with the symptomatology of depression, with the proposed pathophysiology of melancholic depression involving decreased DA transmission. [31] A VNTR in exon 15 of the DA transporter gene (SLC6A3), which affects the expression levels of the transporter, [32] is associated with a faster onset of antidepressant-treatment response. [33] The DA receptors have also been involved in pharmacogenetic studies of antidepressants in depression. The exon 3 VNTR of the DRD4 gene was also investigated in antidepressant drug response, with some studies finding no

association, [34, 35] and one study finding a significant modulation of this polymorphism on various antidepressant drugs. [36]

2.2. Hypothalamic-pituitary- adrenal axis (HPA axis)

Hyperactivity of the hypothalamic-pituitaryadrenal (HPA) axis is one of the most consistent neuroendocrine abnormalities in major depressive disorder. [37] Specifically, patients with MDD show increased concentrations of cortisol in the plasma, urine and cerebrospinal fluid (CSF) and an exaggerated cortisol response to adrenocorticotrophic hormone (ACTH). [38-40] The corticosteroid receptor hypothesis has been proposed for the pathogenesis of MDD, which focuses on impaired corticosteroid receptor signalling, leading to a reduced negative feedback of cortisol, an increased production of corticotropin-releasing hormone (CRH) and hypercortisolism. [38]

Interestingly, cortisol and CRH affect the serotonin (5-HT) system. [39, 41] During the stress response, glucocorticoids (GCs) stimulate all these features of 5-HT transmission. [42] Conversely, 5-HT transmission is impaired and noradrenergic transmission in the hippocampus is suppressed during chronic psychosocial stress and hypercortisolism, which is similar to the series of events evident during depression. [43] It is reported HPA axis dysregulation could be a trait genetically determined which contributes to an increased risk for depression. From the fact that this trait is found both in affected subjects and in healthy relatives with a high familial risk, HPA axis is an interesting candidate endophenotype for affective disorders. [44, 45]

Studies investigating the hypothetical causes of an impaired regulation of HPA axis in depression have mainly focused on two elements: i) glucocorticoid receptor (GR) feedback mechanisms and ii) CRH signaling system.

Reduced GR function has been pointed out as the responsible of diminished sensitivity to cortisol which would lead to an inefficient feedback mechanism. [46] On the other hand, CRH peptide mediates the regulation of HPA axis as well as autonomic and behavioral responses in front of stress. [47] Moreover, dysregulation of HPA axis has also been suggested to play a central role in the mechanisms of action of antidepressants. [38, 48] Normalization of disturbances at HPA axis has been considered a prerequisite of a proper clinical response to antidepressant treatment. [39, 49]

It was reported that Bcl1 polymorphism was associated with the susceptibility to MDD, not the prediction of treatment response. [50] Genetic association studies have yielded preliminary evidence for a role of GR genetic variations in the genetic vulnerability for MDD. Taken together, the evidence for a role of GR and the GR gene in the neurobiology of MDD is building rapidly. [51]

2.3. Neuroplasticity

A time-lag in clinical response after the administration of an antidepressant drug suggests that alterations in monoamine metabolism alone cannot explain the entire antide-

http://dx.doi.org/10.5772/54388

pressant effect. In this respect, it was suggested that the mechanism of action might be associated with intracellular signal transduction pathways that are linked to the expression of specific genes. [52]

The neural plasticity hypothesis proposes that depression results from an inability to make appropriate adaptive responses to stress. [53] By stimulating intracellular pathways, antidepressants lead to upregulation of cAMP response element-binding (CREB) protein and an increase in the expression of neurotrophic factors, particularly BDNF. Brain-derived neurotrophic factor (BDNF), an important member of the neurotrophin family, affects the survival and function of neurons in the central nervous system and is abundant in the brain and peripheral nervous system. BDNF is the neurotrophic factor in the focus of intense research for the last years. BDNF acts on neurons at both presynaptic and postsynaptic sites by binding to its tyrosine kinase receptor TrkB, and internalization of the BDNF TrkB complex-signalling endosome. [54]

It has many effects on the nervous system, such as neuronal growth, differentiation, and repair. [55] It has been shown that stress decreases the synthesis of hippocampal BDNF in adult animals [33, 56] and induces atrophy of the apical dendrites of CA3 neurons. [57-59] Growing evidence suggests that BDNF may play a crucial role in depression. [60-63] So far, considerable work on the involvement of neurotrophic factors in the pathophysiology of depression has been carried out. Direct infusion of BDNF into the rat midbrain has antidepressant effects in the learned helplessness and forced swim behavioral models of depression in rodents. [62] In addition, long-term antidepressant drug treatment and electroconvulsive therapy can increase BDNF expression. [64]

BDNF and serotonin (5-hydroxytryptamine, 5-HT) are known to regulate synaptic plasticity, neurogenesis and neuronal survival in the adult brain. These two signals co-regulate one another such that 5-HT stimulates the expression of BDNF, and BDNF enhances the growth and survival of 5-HT neurons. [65]

Several lines of research show that the BDNF molecule is probably the ''final common pathway'' for different antidepressant approaches. These include antidepressants [64], electroconvulsive therapy, [64, 66] exercise [67, 68] and repetitive transcranial magnetic stimulation. [69] A large body of evidence, in humans, shows the similar result with direct measurements of BDNF in the bloodstream. [70-72] Treatment of depressed patients with antidepressants increases the serum BDNF levels close to the levels of normal controls. [73-75] In addition, they support the possibility that the enhancement of BDNF expression may be an important element in the clinical response to antidepressant treatment. [76]

Measurements of BDNF levels in sera or plasma in previous studies have been challenged. Our research group has also examined plasma BDNF levels among patients with major depression who both have and have not attempted suicide. One study found that plasma BDNF levels were significantly lower among depressed patients than among normal controls. [77]

The BDNF gene has several polymorphic markers, including an intronic microsatellite (GT)n dinucleotide repeat [78] and a functional coding region single-nucleotide polymorphism (SNP) at position 196/758, which results in a valine (Val) to methionine (Met) amino acid

change at codon 66 (rs6265). Because this codon lies in region of the BDNF precursor protein that is cleaved away, it is not apparent in the mature BDNF protein. On pharmacogenetic study of BDNF, it was suggested that the Val66Met polymorphism of BDNF is associated with citalopram efficacy, with Met allele carriers responding better to citalopram treatment. [79] However, other studies suggested that BDNF polymorphism does not affect the clinical outcome of antidepressant administration. [80, 81]

2.4. Neuroimaging marker

Positron emission tomography (PET) imaging studies have revealed multiple abnormalities of regional cerebral blood flow (CBF) and glucose metabolism in brain regions. In PET imaging of unmedicated subjects with major depression, regional CBF and metabolism are consistently increased in the amygdala, orbital cortex, and medial thalamus, and decreased in the dorsomedial/dorsal anterolateral PFC and anterior cingulate cortex ventral to the genu of the corpus callosum (subgenual PFC) relative to healthy controls. [82, 83] These circuits have also been implicated more generally in emotional behavior.

Recent neuroimaging studies have focused on the neurobiological abnormalities that are associated with MDD, such as dysfunctional or structural differences in cerebral regions, including the prefrontal cortex, amygdala, anterior cingulate cortex (ACC), and hippocampus, in patients with MDD compared with healthy controls. [84-87]

Reductions in hippocampal volume may not antedate illness onset, but volume may decrease at the greatest rate in the early years after illness onset. [87] In the absence of a significant correlation between hippocampal volume and age in either post-depressive or control subjects, a significant correlation with total lifetime duration of depression was found. This suggest that repeated stress during recurrent depressive episodes may result in cumulative hippocampal injury as reflected in volume loss. [88]

Previous structural magnetic resonance imaging (MRI) studies using region-of-interest (ROI) analyses have shown a variety of findings. [89, 90] These inconsistencies can be explained by the variability in the ROI criteria among studies and an inconsistency in ROI validation. [89, 91, 92] Consequently, voxel-based morphometry (VBM) [93] is being increasingly used as a viable alternative methodology for detecting structural abnormalities in patients with neuropsychiatric disorders, including MDD. [94-97] Previous MDD VBM studies have also shown reduced gray matter density in the hippocampus. [95, 96, 98] Recently, it is reported that gray matter density of several regions associated with emotion regulation, particularly dorsal raphe nucleus, was lower in MDD patients. [99]

Findings to directly compare unipolar depressed and bipolar depressed individuals, [100] more widespread abnormalities in white matter connectivity and white matter hyperintensities in bipolar depression than unipolar depression, habenula volume reductions in bipolar but not unipolar depression, and differential patterns of functional abnormalities in emotion regulation and attentional control neural circuitry in the two depression types.

Neuroimaging technology has provided unprecedented opportunities for elucidating the anatomical correlates of major depression. [82] Nowadays, researches that combine brain

http://dx.doi.org/10.5772/54388

imaging and genetics have been emerging. The first imaging genetics research reported that carriers of the short allele of the serotonin transporter promoter polymorphism exhibit greater amygdala neuronal activity, as assessed by functional magnetic resonance imaging, in response to fearful stimuli compared with individuals homozygous for the long allele. [101] Since then, however, it has been reported that homozygosity for the l or s allele is associated with decreased hippocampal volumes in patients with major depression. [102, 103] Even though these results inconsistent, future direction for imaging genetics is promising.

3. Conclusions

Major depressive disorder is considered to be a clinically heterogeneous disorder and the diagnosis is based on a patient's symptoms, not on laboratory test. So, the pathogenesis of major depressive disorder is not clear. MDD results from multiple genes interacting with environmental factors such as early stressful life events. Although recent decades have witnessed a tremendous revolution in the development of antidepressant drugs, the neurochemical effects that underlie the therapeutic action of these agents remain largely unknown. Antidepressants alter the levels of neurotransmitters such as serotonin in the synaptic cleft several minutes after their administration, and this alters the activity of the neurotransmission system. Nevertheless, an improvement in the symptoms of depression takes 2–6 weeks of treatment, during which time the neuronal response and morphology of cells change.

The research results for the monoamine system, hyperactivity of the hypothalamic-pituitary-adrenal axis, decreased neuroplasticity, and neuroimaging will be helpful to understand the pathogenesis of major depressvie disorder. To find biological markers for diagnosing MDD and predicting the individual responses to antidepressants, genetic case-control association studies are used widely because they are relatively easy to conduct and can discover genetic variants with small influences on phenotype.

Researchers have searched for biological markers of diagnosis and treatment response, and will try to understand the pathogenesis of depression and the mechanisms underlying the delayed response to antidepressant treatment.

Author details

Hwa-Young Lee[1] and Yong-Ku Kim[2*]

*Address all correspondence to: yonkgu@korea.ac.kr

1 Department of Psychiatry, College of Medicine, Soonchunhyang University, Republic of Korea

2 Department of Psychiatry, College of Medicine, Korea University, Republic of Korea

References

[1] Bierut, L.J., et al., Major depressive disorder in a community-based twin sample: are there different genetic and environmental contributions for men and women? Arch Gen Psychiatry, 1999. 56(6): p. 557-63.

[2] Hamet, P. and J. Tremblay, Genetics and genomics of depression. Metabolism, 2005. 54(5 Suppl 1): p. 10-5.

[3] Murray, C.J. and A.D. Lopez, Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet, 1997. 349(9063): p. 1436-42.

[4] Caspi, A., et al., Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science, 2003. 301(5631): p. 386-9.

[5] Hindmarch, I., Expanding the horizons of depression: beyond the monoamine hypothesis. Hum Psychopharmacol, 2001. 16(3): p. 203-218.

[6] Nemeroff, C.B., Psychopharmacology of affective disorders in the 21st century. Biol Psychiatry, 1998. 44(7): p. 517-25.

[7] Stockmeier, C.A., et al., Increase in serotonin-1A autoreceptors in the midbrain of suicide victims with major depression-postmortem evidence for decreased serotonin activity. J Neurosci, 1998. 18(18): p. 7394-401.

[8] Lemonde, S., et al., Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. J Neurosci, 2003. 23(25): p. 8788-99.

[9] Horstmann, S. and E.B. Binder, Pharmacogenomics of antidepressant drugs. Pharmacol Ther, 2009. 124(1): p. 57-73.

[10] Ellis, P.M. and C. Salmond, Is platelet imipramine binding reduced in depression? A meta-analysis. Biol Psychiatry, 1994. 36(5): p. 292-9.

[11] Bonkale, W.L., G. Turecki, and M.C. Austin, Increased tryptophan hydroxylase immunoreactivity in the dorsal raphe nucleus of alcohol-dependent, depressed suicide subjects is restricted to the dorsal subnucleus. Synapse, 2006. 60(1): p. 81-5.

[12] Yoon, H.K. and Y.K. Kim, TPH2 -703G/T SNP may have important effect on susceptibility to suicidal behavior in major depression. Prog Neuropsychopharmacol Biol Psychiatry, 2009. 33(3): p. 403-9.

[13] Blier, P. and C. de Montigny, Current advances and trends in the treatment of depression. Trends Pharmacol Sci, 1994. 15(7): p. 220-6.

[14] Delgado, P.L., et al., Monoamines and the mechanism of antidepressant action: effects of catecholamine depletion on mood of patients treated with antidepressants. Psychopharmacol Bull, 1993. 29(3): p. 389-96.

[15] Schildkraut, J.J., The catecholamine hypothesis of affective disorders: a review of supporting evidence. 1965. J Neuropsychiatry Clin Neurosci, 1995. 7(4): p. 524-33; discussion 523-4.

[16] Mooney, J.J., et al., Urinary 3-methoxy-4-hydroxyphenylglycol and the depression-type score as predictors of differential responses to antidepressants. J Clin Psychopharmacol, 1991. 11(6): p. 339-43.

[17] Delgado, P.L., Depression: the case for a monoamine deficiency. J Clin Psychiatry, 2000. 61 Suppl 6: p. 7-11.

[18] Ryu, S.H., et al., Association between norepinephrine transporter gene polymorphism and major depression. Neuropsychobiology, 2004. 49(4): p. 174-7.

[19] Chang, C.C., et al., Lack of association between the norepinephrine transporter gene and major depression in a Han Chinese population. J Psychiatry Neurosci, 2007. 32(2): p. 121-8.

[20] Zill, P., et al., Identification of a naturally occurring polymorphism in the promoter region of the norepinephrine transporter and analysis in major depression. Neuropsychopharmacology, 2002. 26(4): p. 489-93.

[21] Herman, G.M., Pharmacology of Antidepressant: Selectivity or Multiplicity? J Clin Psychiatry 1999. 60 suppl 17: p. 4-8.

[22] Kasper, S., Efficacy of antidepressants in the treatment of severe depression: the place of mirtazapine. J Clin Psychopharmacol, 1997. 17 Suppl 1: p. 19S-28S.

[23] Preskorn, S.H., Selection of an antidepressant: mirtazapine. J Clin Psychiatry, 1997. 58 Suppl 6: p. 3-8.

[24] Siever, L.J., et al., Platelet alpha-adrenergic binding and biochemical responsiveness in depressed patients and controls. Psychiatry Res, 1984. 11(4): p. 287-302.

[25] Garcia-Sevilla, J.A., et al., Alpha 2-adrenoceptor-mediated inhibition of platelet adenylate cyclase and induction of aggregation in major depression. Effect of long-term cyclic antidepressant drug treatment. Arch Gen Psychiatry, 1990. 47(2): p. 125-32.

[26] Bylund, D.B., et al., International Union of Pharmacology nomenclature of adrenoceptors. Pharmacol Rev, 1994. 46(2): p. 121-36.

[27] Lorenz, W., et al., Expression of three alpha 2-adrenergic receptor subtypes in rat tissues: implications for alpha 2 receptor classification. Mol Pharmacol, 1990. 38(5): p. 599-603.

[28] Ohara, K., et al., Polymorphism in the promoter region of the alpha 2A adrenergic receptor gene and mood disorders. Neuroreport, 1998. 9(7): p. 1291-4.

[29] Lee, H.Y., et al., Association of the adrenergic alpha 2a receptor--1291C/G polymorphism with weight change and treatment response to mirtazapine in patients with major depressive disorder. Brain Res, 2009. 1262: p. 1-6.

[30] Wakeno, M., et al., The alpha 2A-adrenergic receptor gene polymorphism modifies antidepressant responses to milnacipran. J Clin Psychopharmacol, 2008. 28(5): p. 518-24.

[31] Geracitano, R., et al., On the effects of psychostimulants, antidepressants, and the antiparkinsonian drug levodopa on dopamine neurons. Ann N Y Acad Sci, 2006. 1074: p. 320-9.

[32] Fuke, S., et al., The VNTR polymorphism of the human dopamine transporter (DAT1) gene affects gene expression. Pharmacogenomics J, 2001. 1(2): p. 152-6.

[33] Smith, M.A., et al., Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. J Neurosci, 1995. 15(3 Pt 1): p. 1768-77.

[34] Serretti, A., et al., No association between dopamine D(2) and D(4) receptor gene variants and antidepressant activity of two selective serotonin reuptake inhibitors. Psychiatry Res, 2001. 104(3): p. 195-203.

[35] Serretti, A., et al., Dopamine receptor D4 is not associated with antidepressant activity of sleep deprivation. Psychiatry Res, 1999. 89(2): p. 107-14.

[36] Garriock, H.A., et al., Number of risk genotypes is a risk factor for major depressive disorder: a case control study. Behav Brain Funct, 2006. 2: p. 24.

[37] Holsboer, F., The rationale for corticotropin-releasing hormone receptor (CRH-R) antagonists to treat depression and anxiety. J Psychiatr Res, 1999. 33(3): p. 181-214.

[38] Holsboer, F., The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology, 2000. 23(5): p. 477-501.

[39] Holsboer, F. and N. Barden, Antidepressants and hypothalamic-pituitary-adrenocortical regulation. Endocr Rev, 1996. 17(2): p. 187-205.

[40] Nemeroff, C.B., The corticotropin-releasing factor (CRF) hypothesis of depression: new findings and new directions. Mol Psychiatry, 1996. 1(4): p. 336-42.

[41] De Kloet, E.R., et al., Brain corticosteroid receptor balance in health and disease. Endocr Rev, 1998. 19(3): p. 269-301.

[42] Meijer, O.C. and E.R. de Kloet, Corticosterone and serotonergic neurotransmission in the hippocampus: functional implications of central corticosteroid receptor diversity. Crit Rev Neurobiol, 1998. 12(1-2): p. 1-20.

[43] Wolkowitz, O.M., et al., Ketoconazole administration in hypercortisolemic depression. Am J Psychiatry, 1993. 150(5): p. 810-2.

[44] Holsboer, F., et al., Altered hypothalamic-pituitary-adrenocortical regulation in healthy subjects at high familial risk for affective disorders. Neuroendocrinology, 1995. 62(4): p. 340-7.

[45] Modell, S., et al., Hormonal response pattern in the combined DEX-CRH test is stable over time in subjects at high familial risk for affective disorders. Neuropsychopharmacology, 1998. 18(4): p. 253-62.

[46] Pariante, C.M. and A.H. Miller, Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. Biol Psychiatry, 2001. 49(5): p. 391-404.

[47] Arborelius, L., et al., The role of corticotropin-releasing factor in depression and anxiety disorders. J Endocrinol, 1999. 160(1): p. 1-12.

[48] Nemeroff, C.B. and M.J. Owens, Treatment of mood disorders. Nat Neurosci, 2002. 5 Suppl: p. 1068-70.

[49] Nemeroff, C.B., The role of corticotropin-releasing factor in the pathogenesis of major depression. Pharmacopsychiatry, 1988. 21(2): p. 76-82.

[50] Lee, H., et al., Association of glucocorticoid receptor polymorphisms with the susceptibility to major depressive disorder and treatment responses in Korean depressive patients. Acta Neuropsychiatrica, 2009. 21(1): p. 11-17.

[51] Claes, S., Glucocorticoid receptor polymorphisms in major depression. Ann N Y Acad Sci, 2009. 1179: p. 216-28.

[52] Duman, R.S., et al., Neuronal plasticity and survival in mood disorders. Biol Psychiatry, 2000. 48(8): p. 732-9.

[53] Popoli, M., M. Gennarelli, and G. Racagni, Modulation of synaptic plasticity by stress and antidepressants. Bipolar Disord, 2002. 4(3): p. 166-82.

[54] Lu, B., BDNF and activity-dependent synaptic modulation. Learn Mem, 2003. 10(2): p. 86-98.

[55] Lewin, G.R. and Y.A. Barde, Physiology of the neurotrophins. Annu Rev Neurosci, 1996. 19: p. 289-317.

[56] Nibuya, M., et al., Repeated stress increases catalytic TrkB mRNA in rat hippocampus. Neurosci Lett, 1999. 267(2): p. 81-4.

[57] Gould, E., et al., Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. J Neurosci, 1997. 17(7): p. 2492-8.

[58] Gould, E., et al., Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. Proc Natl Acad Sci U S A, 1998. 95(6): p. 3168-71.

[59] Magarinos, A.M. and B.S. McEwen, Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: involvement of glucocorticoid secretion and excitatory amino acid receptors. Neuroscience, 1995. 69(1): p. 89-98.

[60] Duman, R.S., G.R. Heninger, and E.J. Nestler, A molecular and cellular theory of depression. Arch Gen Psychiatry, 1997. 54(7): p. 597-606.

[61] Altar, C.A., Neurotrophins and depression. Trends Pharmacol Sci, 1999. 20(2): p. 59-61.

[62] Siuciak, J.A., et al., Antidepressant-like effect of brain-derived neurotrophic factor (BDNF). Pharmacol Biochem Behav, 1997. 56(1): p. 131-7.

[63] Chen, B., et al., Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. Biol Psychiatry, 2001. 50(4): p. 260-5.

[64] Nibuya, M., S. Morinobu, and R.S. Duman, Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. J Neurosci, 1995. 15(11): p. 7539-47.

[65] Mattson, M.P., S. Maudsley, and B. Martin, BDNF and 5-HT: a dynamic duo in age-related neuronal plasticity and neurodegenerative disorders. Trends Neurosci, 2004. 27(10): p. 589-94.

[66] Altar, C.A., et al., Effects of electroconvulsive seizures and antidepressant drugs on brain-derived neurotrophic factor protein in rat brain. Biol Psychiatry, 2003. 54(7): p. 703-9.

[67] Oliff, H.S., et al., Exercise-induced regulation of brain-derived neurotrophic factor (BDNF) transcripts in the rat hippocampus. Brain Res Mol Brain Res, 1998. 61(1-2): p. 147-53.

[68] Garcia, C., et al., The influence of specific noradrenergic and serotonergic lesions on the expression of hippocampal brain-derived neurotrophic factor transcripts following voluntary physical activity. Neuroscience, 2003. 119(3): p. 721-32.

[69] Muller, M.B., et al., 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, 2000. 23(2): p. 205-15.

[70] Karege, F., et al., Decreased serum brain-derived neurotrophic factor levels in major depressed patients. Psychiatry Res, 2002. 109(2): p. 143-8.

[71] Karege, F., et al., Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. Biol Psychiatry, 2005. 57(9): p. 1068-72.

[72] Shimizu, E., et al., Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. Biol Psychiatry, 2003. 54(1): p. 70-5.

[73] Aydemir, O., A. Deveci, and F. Taneli, The effect of chronic antidepressant treatment on serum brain-derived neurotrophic factor levels in depressed patients: a preliminary study. Prog Neuropsychopharmacol Biol Psychiatry, 2005. 29(2): p. 261-5.

[74] Gervasoni, N., et al., Partial normalization of serum brain-derived neurotrophic factor in remitted patients after a major depressive episode. Neuropsychobiology, 2005. 51(4): p. 234-8.

[75] Gonul, A.S., et al., Effect of treatment on serum brain-derived neurotrophic factor levels in depressed patients. Eur Arch Psychiatry Clin Neurosci, 2005. 255(6): p. 381-6.

[76] Russo-Neustadt, A., et al., Physical activity-antidepressant treatment combination: impact on brain-derived neurotrophic factor and behavior in an animal model. Behav Brain Res, 2001. 120(1): p. 87-95.

[77] Lee, B.H., et al., Decreased plasma BDNF level in depressive patients. J Affect Disord, 2007. 101(1-3): p. 239-44.

[78] Proschel, M., et al., Dinucleotide repeat polymorphism at the human gene for the brain-derived neurotrophic factor (BDNF). Hum Mol Genet, 1992. 1(5): p. 353.

[79] Choi, M.J., et al., Brain-derived neurotrophic factor gene polymorphism (Val66Met) and citalopram response in major depressive disorder. Brain Res, 2006. 1118(1): p. 176-82.

[80] Kang, R.H., et al., Brain-derived neurotrophic factor gene polymorphisms and mirtazapine responses in Koreans with major depression. J Psychopharmacol, 2010. 24(12): p. 1755-63.

[81] Tsai, S.J., et al., Association study of a brain-derived neurotrophic-factor genetic polymorphism and major depressive disorders, symptomatology, and antidepressant response. Am J Med Genet B Neuropsychiatr Genet, 2003. 123B(1): p. 19-22.

[82] Drevets, W.C., Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. Curr Opin Neurobiol, 2001. 11(2): p. 240-9.

[83] Manji, H.K., W.C. Drevets, and D.S. Charney, The cellular neurobiology of depression. Nat Med, 2001. 7(5): p. 541-7.

[84] Canli, T., et al., Brain activation to emotional words in depressed vs healthy subjects. Neuroreport, 2004. 15(17): p. 2585-8.

[85] Frodl, T., et al., Hippocampal and amygdala changes in patients with major depressive disorder and healthy controls during a 1-year follow-up. J Clin Psychiatry, 2004. 65(4): p. 492-9.

[86] Henriques, J.B., Davidson, R.J., Decreased responsiveness to reward in depression. COGNITION AND EMOTION, 2000. 15(5): p. 711-724.

[87] MacQueen, G.M., et al., Course of illness, hippocampal function, and hippocampal volume in major depression. Proc Natl Acad Sci U S A, 2003. 100(3): p. 1387-92.

[88] Sheline, Y.I., et al., Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J Neurosci, 1999. 19(12): p. 5034-43.

[89] Konarski, J.Z., et al., Volumetric neuroimaging investigations in mood disorders: bipolar disorder versus major depressive disorder. Bipolar Disord, 2008. 10(1): p. 1-37.

[90] Lorenzetti, V., et al., Structural brain abnormalities in major depressive disorder: a selective review of recent MRI studies. J Affect Disord, 2009. 117(1-2): p. 1-17.

[91] Goldstein, J.M., et al., Cortical abnormalities in schizophrenia identified by structural magnetic resonance imaging. Arch Gen Psychiatry, 1999. 56(6): p. 537-47.

[92] Wolkin, A., et al., Structural magnetic resonance image averaging in schizophrenia. Am J Psychiatry, 1998. 155(8): p. 1064-73.

[93] Ashburner, J. and K.J. Friston, Voxel-based morphometry--the methods. Neuroimage, 2000. 11(6 Pt 1): p. 805-21.

[94] Leung, K.K., et al., Neural correlates of attention biases of people with major depressive disorder: a voxel-based morphometric study. Psychol Med, 2009. 39(7): p. 1097-106.

[95] Shah, P.J., et al., Cortical grey matter reductions associated with treatment-resistant chronic unipolar depression. Controlled magnetic resonance imaging study. Br J Psychiatry, 1998. 172: p. 527-32.

[96] Vasic, N., et al., Gray matter reduction associated with psychopathology and cognitive dysfunction in unipolar depression: a voxel-based morphometry study. J Affect Disord, 2008. 109(1-2): p. 107-16.

[97] Cheng, Y.Q., et al., Brain volume alteration and the correlations with the clinical characteristics in drug-naive first-episode MDD patients: a voxel-based morphometry study. Neurosci Lett, 2010. 480(1): p. 30-4.

[98] Bergouignan, L., et al., Can voxel based morphometry, manual segmentation and automated segmentation equally detect hippocampal volume differences in acute depression? Neuroimage, 2009. 45(1): p. 29-37.

[99] Lee, H.Y., et al., Demonstration of decreased gray matter concentration in the midbrain encompassing the dorsal raphe nucleus and the limbic subcortical regions in major depressive disorder: an optimized voxel-based morphometry study. J Affect Disord, 2011. 133(1-2): p. 128-36.

[100] Almeida, J.R. and M.L. Phillips, Distinguishing between Unipolar Depression and Bipolar Depression: Current and Future Clinical and Neuroimaging Perspectives. Biol Psychiatry, 2012.

[101] Hariri, A.R., et al., Serotonin transporter genetic variation and the response of the human amygdala. Science, 2002. 297(5580): p. 400-3.

http://dx.doi.org/10.5772/54388

[102] Frodl, T., et al., Reduced hippocampal volumes associated with the long variant of the tri- and diallelic serotonin transporter polymorphism in major depression. Am J Med Genet B Neuropsychiatr Genet, 2008. 147B(7): p. 1003-7.

[103] Eker, M.C., et al., Smaller hippocampus volume is associated with short variant of 5-HTTLPR polymorphism in medication-free major depressive disorder patients. Neuropsychobiology, 2011. 63(1): p. 22-8.

IntechOpen

IntechOpen