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Biological Markers and Genetic Factors of Major Depressive Disorder

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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-HT_{1A} receptor expression appears to be a robust finding in major depression. A functional genetic variant of the 5-HT_{1A} 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 α_2 receptors. [21-23] Previous studies have outlined the functional aspects of α_2 receptors in depression, reporting reduced α_2 inhibition of platelet adenylate cyclase activity [24] and increased adrenergic α_2 agonist-induced platelet aggregation in depressed patients. [25] Three genes that encode human adrenergic α_2 receptors have been cloned: α_2a , α_2b , and α_2c . [26] The adrenergic α_2a receptor (ADRA2A) subtype is expressed in the central nervous system and peripheral tissues. [27] According to this classification, the classic α_2 receptor studied in mood disorders is the α_2a 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 associated 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-pituitary-adrenal (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-

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 suggests 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

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 depressive 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.

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