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New insights into the neurobiological mechanisms of major depressive disorders

Marc Fakhoury *

Department of Neuroscience, Faculty of Medicine, University of Montreal, Montreal, Quebec, H3C 3J7, Canada

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ABSTRACT

Objective: To review the current evidence about the neurobiological mechanisms in major depressive disorders (MDD) and the key findings from studies using neuroimaging tools and animal models.
Method: This paper gives an overview of the role of genetic and environmental factors in the pathophysiology of MDD and describes the structural changes in brain structures of depressed individuals. A closer look is given at the molecular processes and neurotransmitters implicated in this mental disorder. Moreover, this paper discusses key findings from recent research using animal models and their relevance for clinical applications.
Results: Although the exact cause of MDD is not known, there is enough evidence showing that genetic, psychological and environmental factors significantly increase the risk of developing this disease. Individuals affected by MDD exhibit a reduced volume of structures such as the amygdala, hippocampus and basal ganglia, as well as altered level of neurotransmitters in the brain.
Conclusion: The studies presented in this review show promising results that could shed light on the molecular mechanisms of MDD. However, more work needs to be done to better understand this psychiatric disorder and promote the development of new treatment strategies.

1. Introduction

Major depressive disorders (MDD) are characterized by a persistent feeling of sadness and by a loss of interest. Also called major depression or clinical depression, this disorder can lead to a variety of emotional and physical problems. This disease can be found worldwide, but they may be cultural factors that increase the risk of getting MDD. It was shown that 20% of adults might suffer an episode of major depression at some point during their lifetime. Moreover, women tend to me more affected than man in general, specially after experiencing a major event such as parental death, hostile family environment, miscarriage and divorce [1].

Despite the fact that the exact cause of MDD is not known, they are several factors that can influence its emergence. The most probable causes are genetic, psychological and biological. Although family, adoption and twin studies have all indicated the importance of genetics in clinical depression, this disease is mainly associated with environmental factors such as stress. MDD often follows a traumatic emotional experience and can also be precipitated by pharmacological agents or drug abuse [2]. Other studies have linked the appearance of these symptoms to damage caused to the cerebellum [3,4]. Changes in the levels or activity of neurotransmitter can also cause depression in individuals [5].

While the level and extent of depression varies among individuals, there exist common signs and symptoms associated with this disease. A person affected with depression loses the ability to feel joy and pleasure and most often feels agitated and aggressive. It is sometimes referred to as unipolar depressive disorder, to be distinguished from depression, which alternates with episodes of mania called bipolar depression [6]. Other symptoms of MDD include poor concentration and memory, as well as thoughts of death or suicide [7]. MDD is also associated with an increased risk of cardiovascular disease, osteoporosis and diabetes [8,9], and it is linked to risk factors such as smoking and alcohol dependence [10,11].

Although family and primary care physicians have greatly increased the recognition and treatment of this disorder, MDD remains an unresolved treatment challenge [12,13]. A better understanding of its neurobiological mechanisms will help open up new avenues for therapeutic strategies. This paper will discuss the hypotheses regarding the neurochemical bases for affective disorders, as well as the effectiveness of conventional diagnosis tools and antidepressant treatments. A closer look will also be taken at the use of animal models to study the neurophysiology of MDD and identify the brain circuit involved in this disorder.

2. Role of genetics in MDD

Genetic studies are crucial because they help clinical researchers develop new therapeutic strategies by defining the origin, progression and nature of the disease. MDD seems to occur from one generation to the next in some families but may also affect people with no family history of depression. Twin studies show a heritability of up to 50%, and family studies among first-degree relatives indicate a 2-fold to 3-fold increase

* Tel.: +1-514-710-7060.
E-mail address: marc.fakhoury@umontreal.ca.

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in the risk of being affected by MDD [14]. Scientists have also discovered a region in the human genome that appears to be associated with an increase in the risk of developing MDD. A study conducted by Abkevich et al. [15] has performed a genome scan on 945 individuals with MDD and 162 with bipolar disorder (BPD). They observed a highly significant linkage signal at 12q23, confirming a previously BPD identified locus [16]. By identifying the 12q23 region as a locus that increases the risk of both BPD and MDD, this study highlighted the fact that there exists a genetic overlap between these two disorders.

Genetic factors play a major role in the development of MDD, and several genes that are associated with depressive symptomatology have been identified and are worth mentioning [14]. Table 1 illustrates a list of candidate genes that play an important role in the pathophysiology of this disease. Since MDD is characterized by an altered level of serotonin (5-HT), genes that are involved in 5-HT synthesis or inhibition could potentially influence the progression of major depression [17]. Factors that could alter 5-HT level include the serotonin transporter protein (5-HTT), the 5-HT receptors (such as 5-HTR2A) and the tryptophan hydroxylase 2 (TPH2). Genetic variations of FK506 binding protein 5 (FKBP5) could also increase the vulnerability to stress and mood disorders [18].

Neurotrophic factors, which are a family of protein responsible of the growth of neuron cells, are also highly involved in the regulation of MDD [19]. The brain-derived neurotrophic factor (BDNF) is one example of a neurotrophic factor, but others include the insulin-like growth factor (IGF), the fibroblast growth factor (FGF) and the vascular endothelial growth factor (VEGF). They are mostly involved in the plasticity of neuronal networks, and they can also stimulate neurogenesis in the hippocampus [19]. People affected by MDD often have a dysregulation of several members of neurotrophic factors [20], and most of the antidepressant drugs currently used today are aimed at restoring their normal levels in the brain. In addition to fostering personalized medicine, these establishing biomarkers could lead to the characterization of novel mechanisms for developing therapeutic strategies. In a genome-based therapeutic drugs for depression (GENDEP), the expression of several potential genes was examined in depressed individuals, before and after treatment with selective antidepressant drugs [21]. The severity of depressive episodes in these individuals was measured by the Montgomery–Asberg Depression Rating Scale (MADRS), and the treatment was considered successful when the MADRS score was reduced by at least 50% [21]. Successful antidepressant response was associated with an increase in the levels of BDNF and VGF, suggesting a role of these neurotrophic factors in the regulation of MDD [21]. Enzymes and neuropeptides also seem to be involved in the pathophysiology of MDD. A genome-wide association study that is composed of more than 2000 depressed individuals showed that adenylate cyclase and galanin play an important role in 5-HT signaling and the development of MDD [22].

3. Genetics and environmental interactions

We still do not know how many genes are involved in MDD, but it is very doubtful that any one gene can cause depression in a large group of people. It is rather the combination of genetic changes that predispose someone of being affected by MDD. Moreover, genetic factors appear to have a much serious implication with MDD when combined with environmental factors, such as stress or a traumatic experience. Indeed, stress is the main cause of MDD and seems to trigger this disorder in almost every individual with particular set of genes that render them more vulnerable to this disease. Neurological studies have shown that stress and anxiety, along with its corresponding physiological symptoms, play an important role in precipitating episodes of MDD [23]. A longitudinal study of more than 500 adult twins has provided evidence of a gene–environment interaction by showing that a polymorphism of the 5-HTT gene could moderate the influence of stressful life events on MDD [24]. By analyzing the 5-HTT genotype and the history of episodes of major depression of each participant, it was shown that individuals with one or two copies of the short allele of the 5-HTT polymorphism exhibited more depressive symptoms, in relation to stressful life events, compared to individuals homozygous for the long allele [24]. Another study examined the interaction between gene polymorphisms and traumatic events, by following 124 patients with recurrent MDD following a traumatic experience during childhood [25]. It was shown that the interaction between certain genetic polymorphisms with early traumatic events significantly increased the risk for depressive symptoms, suggesting that childhood trauma is associated with the onset of MDD [25].

Other interesting studies using epigenetics have indicated that changes in certain gene expression are associated with MDD. Unlike simple genetics based on changes to the DNA sequence, epigenetics study the changes in gene expression that can be caused by a number of biological processes such as DNA methylation or histone acetylation. It has been shown that DNA methylation of BDNF is linked to the pathophysiology of depressive due to reduced neural levels of BDNF in the brain [26]. DNA methylation patterns can also be modified in response to environmental factors by a complex interplay of several independent DNA methyltransferases, such as DNMT1, DNMT3A and DNMT3B [27]. Environmental factors known to trigger epigenetic changes include malnutrition, lack of vitamins and high consumption of alcohol and nicotine. There is also evidence showing that epigenetic traits induced by environmental factors can be inherited. Indeed, maternal diet could lead to epigenetic variations and altered DNA methylation in the offspring [28]. When female mice were given dietary methyl supplements prior to and during pregnancy, their offsprings exhibited increased level of DNA methylation, which significantly affected their phenotype and general health [28]. The susceptibility to mood disorders can also be altered by epistatic interactions between genes. For instance, interaction between certain genes involved in the regulation of the hypothalamus-pituitary-adrenal (HPA) axis could increase the risk of depression [29].

4. Brain structures involved in MDD

With the advances in imaging technology, there is now enough evidence showing a close association between mood disorders and changes in both the function and the structure of brain areas. For instance, depression is associated with the neurogenesis of the hippocampus, a center for both mood and memory [30,31]. Loss of hippocampal neurons is found in some depressed individuals and correlates with impaired memory and dysthymic mood [32]. It is also well known that patients with major depression have significant volume reduction in

Table 1
Candidate genes involved in the pathophysiology of MDD.

Gene	Location	Name	Function
5-HTR2A	Chromosome 13	Hydroxytryptamine receptor 2A	G-protein-coupled serotonin receptor that can activate signal transduction inside the cell
5-HTT	Chromosome 17	Serotonin transporter protein	Transports serotonin from synapses to presynaptic neurons
BDNF	Chromosome 11	Brain-derived neurotrophic factor	Promote the survival of neurons by preventing apoptosis
FGF	Chromosome 4	Fibroblast growth factor	Important growth factor that ameliorates hippocampal neurogenesis
FKBP5	Chromosome 6	FK506 binding protein 5	Involved in immunoregulation and in the modulation of stress and anxiety
IGF	Chromosome 12	Insulin-like growth factor 1	Regulates processes involved in MDD, such as synaptic plasticity, adult neurogenesis and differentiation
TPH2	Chromosome 12	Tryptophan hydroxylase 2	Involved in serotonin synthesis
VEGF	Chromosome 6	Vascular endothelial growth factor	Increases endothelial cell number and promotes neurogenesis, neuronal cell survival and synaptic plasticity