Major depressive disorder: Current progress and new treatment perspective

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Abstract: Major depressive disorder (MDD) is a mental disorder that affects about 3.8% of the world population. It brings negative effect on individuals, including low mood, decreased sex desire, decreased appetite, and thought of death or suicide. Since 20th century, theories have been trying to explain the cause of major depressive disorders. Most of the theories focus on the interrelationship between social, psychological and biological causes. However, no one theory has found out the real pathopsychological causes of the diseases and treatments to this disorder are limited with medication and methods with huge side effects. The review summarizes four theories about the pathophysiology of MDD with their corresponding treatments and proposes a potential treatment of genetic approaches.

1. Introduction

In 2019, The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) has listed out the leading causes of global health-related burden. Depressive disorder is listed among the top 25 leading causes of burden worldwide [1]. Major Depressive Disorder (MDD) is defined as a mental disorder, with estimated 3.8% of the global population affected which was about 280 million people. The common onset is in one's 20s [2]. Patients with MDD commonly experience a more-than 2-week depressive episode. During this episode, patients suffer from low mood, inability to feel joy in previous enjoyable activities, poor concentration and memory, reduced sexual desire, irritability, withdrawal from social activities, and thoughts of death or suicide [2]. Suicide, most derived from MDD, is the 4th leading cause of death in 15-29-year-olds [3].

The biomedical model of medicine is the first model used to explain the potential cause of major depressive disorder. In the biomedical model, it uses "machine" to represent human body and it argued that major depressive disorder was the consequence of damage to the machine either physically or mentally [4]. This model is later replaced by the biopsychosocial model proposed by George L. Engel and Jon Romano of the University of Rochester in 1977 [5]. In the biopsychosocial model, Engel argued that the development of both physical and mental diseases was constructed by complex interaction among biological factor (genetic, biochemical, etc.), psychological factors (mood, personality, behavior, etc.) and social factors (cultural, familial, socioeconomic, medical, etc.) [6]. Unlike the biomedical theory, the biopsychosocial model blurred the distinction between human body and society. It acknowledges the importance of social and psychological triggers. Even for certain genetic diseases, a social or psychological factor is needed to trigger the onset of it [7]. In 2002, this model was adopted by the World Health Organization (WHO) as a basis of the International Classification of Function (ICF) and it is now widely accepted as a model for MDD [8]. The diathesis-stress model specifies that depression is a result of a long-lasting vulnerability, a diathesis or predisposition, that is activated by stresses in life. A vulnerability can be a genetic factor like mutation in 5-HTT gene or schematic factors, caused by childhood experience [9] [10]. A vulnerable person is more like to get negative outcome under repressive environment or with negative experience than a resilient individual. A large range of differences exists between one's vulnerability and development of a disorder [10]. This diathesis-stress model tries to explain how the interaction between diatheses (genetic or biological traits) and stressors (environmental factors) lead to mental disorders like major

depressive disorder, anxiety or schizophrenia. The biopsychosocial model and the diathesis-stress model are the major model discussing the potential causes of MDD.

Except the biomedical model, both the biopsychosocial model and the diathesis-stress model raise the importance of interaction between biological and environmental factors. Though both theories have listed out some possible biological causes for MDD like genetic factors, they focus more on the interrelationship and fail to explore the underlying pathophysiological causes of MDD.

This article reviews four theories concerning the pathophysiological causes of major depressive disorder, including the circadian rhythm hypothesis, the monoamine hypothesis, the immunological dysfunction hypothesis and the HPA-axis dysfunction hypothesis. This article also reviews current treatments on MDD involving light therapy, medication, ECT and TMS. Focusing on the monoamine hypothesis, a potential treatment with genetic approach is discussed.

2. Prevalence, symptoms and diagnosis

Major Depressive Disorder (MDD) affects about 280 million people which were about 3.8% of the world population. Females are one time more susceptible to MDD. In North America, the susceptibility is 3-5% for males and 8-10% for females [11]. Patients with MDD are more vulnerable to mental disorders. MDD negatively impacts one's socialization, general health, and sleeping and eating patterns. As mentioned above, it leads to low mood, inability to feel joy, poor concentration and memory and thoughts of death or suicide [2]. About 2-8% of adults with depression die by suicide [12]. Hard to fall asleep or oversleeping are common symptoms as well. In occasional cases, patients even experience delusions and hallucinations [13]. Depression is believed associate with quality-adjusted life expectancy (QALE) loss. Using the eight-item Patient Health Questionnaire (PHQ-8) on 2206, 2008, and 2010 Behavioral Risk Factor Surveillance System (BRFSS), Jia and the colleagues concluded that depression contribute to morality and morbidity. At age 18, QALE loss between diagnosed depression patients and healthy individuals was 28.9 year. This loss is way greater than QALE loss for patients with stroke (12.4-year loss), heart disease (10.3-year loss), asthma (7.0-year loss), smoking (11.0-year loss) and physical inactivity (8.0-year loss) [14].

With the 1980 version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) classification, major depressive disorder is categorized as mood disorder [15]. According to Robins and Guze's classification in 1970, patients have to show 5 symptoms to be diagnosed with depression, including 1) constant symptoms, 2) laboratory studies to construct a biological substrate, 3) symptoms specific enough to distinguish it from other disorders, 4) some evidence of genetic predisposition, and 5) evidence of common courses of illness [16]. DSM-5 or ICD-10 survey, along with assessments conducted by a trained practitioner, a psychiatrist, or a psychologist are used to justify the constant onset and specificity of the symptoms. Psychiatrists may require a CT scan to provide the biological substrate and to eliminate other possible pathological diseases in the diagnosis process.

ICD-10 is prevalent in European countries, while DSM-5 is widely used in the United States and non-European countries. Though ICD-10 and DSM-5 vary in terms of details, they both list depressed mood, loss of interest (anhedonia) as indispensable symptoms [15]. Supposing a patient reports five out of the nine symptoms (depressed mood, loss of interest, weight loss or gain, insomnia or hypersomnia, psychomotor agitation, fatigue, feeling worthless or guilty, decreased concentration, and thought of death) within two weeks, this patient is highly susceptible to depression with the DSM-5 criteria.

3. Pathophysiological Causes

In 2020, people with depression diagnosed increasingly as the COVID-19 pandemic spread around the world. With Patient Health Questionnaire, prevalence of depression symptoms in US was three times more than that before the COVID-19 pandemic [17]. Long in history, psychiatrists focus on the psychological or the situational causes of MDD. Concerning about its great negative impact on public, its underlying pathophysiological causes are under review. The real cause remains unknown with

several theories trying to explain it. Theories include topics on circadian rhythm, inflammation, HPA-axis dysfunction and monoamine neurotransmitters.

3.1 Circadian rhythm hypothesis

Circadian rhythm plays a crucial role in determining one's health status. Sleep abnormalities, hard to fall asleep or oversleeping, is the most pronounced symptoms of MDD patients. Studies on sleep electroencephalograms reveal characteristic changes in MDD patients, like reduced non-raped eye movement (NREM) production, disruption of sleep continuity and disinhibition of rapid eye movement (REM) sleep [18]. Dreams happen to REM sleep. A disinhibition of REM sleep increases the REM sleep duration and REM sleep density in the depressive episode.

REM sleep depends heavily on reduced a monoamine neurotransmitter, serotonin , in the brain [19]. Emotional brain processing mechanism that dependent on the normal sleep-wake regulation failed in depression. With a nonfunctional emotional brain processing, patients with MDD are more vulnerable to emotional changes. This hypothesis is justified by mood dysfunction in most of the depressed patients.

3.2 Immunological dysfunction hypothesis

MDD seems to associate with immune system abnormality. An increased level of cytokines is the most prominent. Clinical findings suggest a significant morbidity and mortality rate, and patients with MDD are often associated with inflammatory processes. Though the immunological dysfunction theory did not expect inflammation to be the predominant cause, it insists the potential role of inflammation in depression pathophysiology. This theory is mainly supported by three observations: 1) One-third of depressed patients show elevated peripheral inflammatory biomarkers even without a presence of an illness, 2) Inflammatory illnesses are associated with greater rates of MDD, and 3) Patients with elevated cytokines are facing a higher chance of getting MDD [20]. Inflammatory mediators affect multiple brain substrates, including altered monoamine and glutamine neurotransmission, glucocorticoid receptor resistance, and adult hippocampal neurogenesis. And it might also lead to more extensive affection on brain signaling patterns, cognition, and production of a constellation of symptoms, called 'sickness behavior'.

It seems like the subtle influence of immunological dysfunction and depression stands and the inflammatory mediators could help in MDD diagnosis. However, the immunological dysfunction theory fails to examine the leading underlying cause of MDD.

3.3 HPA-axis dysfunction hypothesis/CRF hypothesis

The hypothalamic-pituitary-adrenal axis (HPA axis) is a set of feedback interactions among the hypothalamus, the pituitary gland, and the adrenal glands. Due to the association with Corticotropin-releasing Hormone Receptor1 (CRHR1) and depression and the increased frequency of dexamethasone test non-suppression in people who are depressed, the HPA axis is believed to be associated with depression [21]. Patients with MDD experience changes in the setpoint of the HPA axis, resulting in altered regulation of corticotropin (ACTH) and cortisol secretory activity[22]. And the CRHR1 signaling might also be impaired in MDD, leading to increased production and secretion of corticotropin-releasing hormone (CRH). Though a superficial connection between CRF secretion and depression stands, the intrinsic mechanism of cortisol awakening response and MDD remains known. Future studies on Mouse genetic help dissect the intracellular cascade of CR signaling and further understand the interrelationship between CR signaling and MDD.

3.4 The monoamine hypothesis

The monoamine hypothesis predicts that the underlying pathological cause of Major Depressive Disorder is a deficiency in the monoamine neurotransmitter secretion inside the central nervous system. Those monoamine neurotransmitters include serotonin, norepinephrine (NE), and/or dopamine (DA) [23]. Evidence for this hypothesis comes from multiple areas.

First, the monoamine depletion study supported this hypothesis and pointed out either a direct or indirect relationship between monoamine neurotransmitter level and mood disorders [24]. A study by H. Ruhe and N. Mason used acute tryptophan depletion (ATD) or para-chlorophenylalanine (PCPA) to diminish 5-HT, serotonin. They also use acute phenylalanine/tyrosine depletion (APTD) or alpha-methyl-para-tyrosine (AMPT) to decrease NE/DA levels. With the meta-analysis, Ruhe and his colleagues conclude that a 5-HT or NE/DA level deficit could reduce mood in the surveyed population with a family history of MDD and in drug-free patients with MDD in remission. Though a 5-HT or NE/DA deficiency did not cause a mood decrease in healthy individuals, it somehow proved an indirect relationship between 5-HT and NE/DA deficiency and mood disorders.

The action of antidepressants also supports this monoamine hypothesis. Antidepressants like Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs) are the dominant medication in treating MDD [25]. And the national and international guidelines recommend SSRIs as a first-line treatment for patients with MDD. Both SSRIs and SNRIs increase monoamine neurotransmitter levels in the central nervous system by blocking the serotonin reuptake while having additional effects on various 5-HT receptor subtypes. As many patients found relief after the antidepressant approach, the monoamine hypothesis is supported, and the relationship between monoamine deficiency and MDD is believed. However, the reason for time lapses existing between medication intake and relief of the symptoms has to be elucidated.

Though the monoamine hypothesis is supported in many aspects, the study about SSRIs efficiency failed to explain the delayed symptom relief. And the study done by Ruhe failed to indicate two things: 1) there is a direct relationship between the decreased monoamine neurotransmitters' level and MDD; **2)** the deficiency in monoamine neurotransmitter level is the predominant cause of MDD.

4. Treatment

4.1 Current treatments

4.1.1 Light therapy

Light therapy was first used to treat patients with seasonal affective disorder (SAD) [26]. With 25-year research, light therapy has been associated to optimize the effect of antidepressants. The efficacy between light therapy and placebo has proved its effectiveness. Light therapy includes chronotherapeutic invention-light therapy, sleep deprivation (wake therapy) and sleep time displacement (sleep phase advance therapy). Recently, application of light therapy goes beyond the limit of ASD. It is used in non-seasonal depressive disorders like major depressive disorder and bipolar disorders [26]. The three therapy methods work together to provide or maintain long-term improvement in MDD patients.

According to the circadian rhythm hypothesis, REM sleep which relies on decreased serotonin levels is frequent and intense in patients with depression [19]. Serotonin is least active during sleep and most active during wakefulness. Light deprivation is related to reduced serotonin level and abnormalities in sleep-wake cycle, like insomnia. Light deprivation might be useful in patients showing intense REM sleep. Light exposure and sleep time displacement method are used to disrupt and rebuild regular circadian rhythm in depressed patients.

4.1.2 Antidepressants

Arisen from the monoamine hypothesis and circadian rhythm hypothesis, monoamine neurotransmitters like serotonin (5-HT) are associated with major depressive disorder. A decreased level of serotonin production contributes to onset and severity of MDD. First-line antidepressants include selective serotonin reuptake inhibitors (SSRIs) like escitalopram, paroxetine, and sertraline and serotonin-norepinephrine reuptake inhibitor (SNRIs). Those drugs work on the reuptake mechanism, increasing the level of serotonin the brain circuit. In 2014, National Institute for Health and Care Excellence reported that SSRIs had a 150% efficacy than placebo that reduced the depression scores in moderate and severe major depressive disorder [27]. Same year, the U.S. Food and Drug

Administration published a review, concluding that SSRIs could reduce risk for relapse by 52% compared with placebo [28]. The dosage varies with severity of the diseases. The response rate to first antidepressant administration ranges from 50 to 75%. The time difference between start of medication and improvement can last six to eight weeks [29].

It is unclear whether antidepressants would affect one's risk of suicide or not. Adolescents with SSRIs treatments show a higher risk of both suicidal ideations and suicidal behaviors [30]. The quantitively relationship between SSRIs intake and risk of suicidality. In 2007, U.S. has introduced a black box warning on SSRIs due its correlation with risk of suicidality in patients younger than 24 years old.

4.1.3 Electroconvulsive therapy (ECT)

Electroconvulsive therapy (ECT) works by inducing electrical seizure in a person. This approach is used with informed consent and has been the last line for treating major depressive disorders. About 50% of the patients who are resistant to other treatments report this therapy method effective, despite with unipolar or bipolar depression [31]. About half of people response relapse with twelve months [32]. The side effect of ECT includes confusion and memory loss. However, it is listed as one of the least harmful treatment for severely depressed pregnant women [33, 34]. The frequency of receiving ECT is about two to three times per week. After the treatment, patients need to intake drugs continually and some of them maintain receiving ECT.

4.1.4 Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) or deep transcranial magnetic stimulation is a noninvasive therapy method for major depressive disorder. It stimulates small regions of the brain, and it is believed as the probably most effective treatments [35].

4.2 Potential treatments

The monoamine hypothesis wins the most attention on the four hypotheses mentioned above, as it gains support from both the studies and the action of antidepressants. The serotonin level is also mentioned in the circadian rhythm hypothesis. Serotonin secretion is under investigation. Tryptophan hydroxylase (TPH) is used in serotonin production. This enzyme turns the L-tryptophan into 5-Hydroxy-L-Tryptophan, which is a precursor of 5-HT [36]. TPH1 and TPH2 are two subtypes of TPH. Though they function similarly, TPH2 works in the central nervous system while TPH1 does its job in the peripheral nervous system. In the gene encoded for TPH2, a mutation at the 41st position turns the 41st Serine into a Tyrosine. For the TPH2 to function appropriately inside the central nervous system, it needs to be activated by two protein kinases: Protein Kinase A (PKA) and Ca^{2+}/calmodulin dependent protein kinase II (PKII). PKA works exactly on Serine on TPH2.

Though the underlying mechanism of why this single mutation involving Ser41 could lead to a decrease in serotonin production remained unknown, a potential treatment involving genetic editing could be performed to fix this mutation.

5. Conclusion

Four hypotheses (the circadian rhythm hypothesis, the monoamine hypothesis, immunological dysfunction hypothesis and HPA-axis dysfunction hypothesis) propose the potential causes of major depressive disorder. The circadian rhythm hypothesis points out the relationship between sleep dysregulation and mood regulation. A dysfunction in the sleep and wake cycles lead to decreasing function of the mood regulating mechanism. The main neurotransmitter involved serotonin, mentioned in the monoamine hypothesis as well. The monoamine hypothesis emphasizes the depletion of monoamine neurotransmitters level like serotonin in brain. It gains support in 2 ways. Patients with decreased serotonin level gain enhanced symptoms and patients with MDD feel relieved by taking antidepressants which increase monoamine neurotransmitter level inside brain. The immunological dysfunction theory suggests the elevated level of cytokines and peripheral inflammatory biomarkers

contribute to the development of MDD. One-third of depressed patients show an elevated peripheral inflammatory biomarkers and patients with elevated cytokines are more likely to suffer MDD. The HPA-axis dysfunction hypothesis or the CRF hypothesis emphasizes the connection between secretion of corticotropin-releasing hormone and depression. Although all three theories proved the superficial connection between the pathophysiological changes and presence of major depressive disorder, they all fail to prove the intrinsic mechanisms or fail to explain the delay in their corresponding treatments. Current pathophysiological treatments are more like to suffer the patients while fail to provide permanent cure. The monoamine hypothesis gains most supports due to more considerable and cogent evidence. Genetic treatments on elevation of monoamine hypothesis could possibly bring eternal cure for MDD patients caused by genetic mutation on several genes. The candidates of genetic editing using CRISPR include TPH2 and BDNF. However, current technology fails to replicate the TPH2 or BDNF in large sample size and the observed effect sizes are not consistent with the polygenicity of MDD. More research is required on determining genetic candidates for MDD.

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