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Depression: Recent Insights into Its Pathogenesis

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Abstract : *Depression is among the most common neuropsychiatric disorders and is responsible for a high burden to both society and the health care system. It is characterized by increasing incidence and affects all ages, while being more prevalent among women. Treatment for depression has been modulated according to the underlying pathogenesis and it is crucial to explore all pathways in order to better treat patients. Research has shown that depression has many causative factors, from gene involvement to immunological factors. Neurotransmitters, such as serotonin, dopamine and norepinephrine have also been implicated, along with the hypothalamic-pituitary-adrenal axis. Recent discoveries have also uncovered the involvement of oxidative stress in the pathogenesis of depression. Neuronal plasticity in the brain has also been linked to the advent of depression and these pathways offer new insights into this disorder.*

Keywords: *Depression, oxidative stress, pathogenesis, treatment.*

I. Introduction

Depression is a frequently occurring neuropsychiatric disorder which affects people of all ages in the modern world. It is characterized by mood alterations, changes in psychomotor activity, neuroendocrine variations and can have detrimental effects on the overall health status. Mental health is therefore an important part of the overall wellbeing and is the cause of great morbidity throughout the world.

Depression is a common cause of emotional suffering and it is associated with a decline in both well-being and daily functioning. It causes a reduction in both morale and social capacity among all ages in society [1]. Depression is more prevalent among women than among men throughout the whole life cycle and this trend is also noted in old people [2]. Although women more often experience mood-related symptoms and men describe more motivation-related symptoms and agitation [3], it has been suggested that men report depression to a lesser extent than women [4].

Considering the high degree of morbidity of depression, much research has been invested in understanding the underlying mechanisms of depression. A lot of progress has been made, with new drugs having been developed according to these new discovered pathways. There is still much to be investigated though, as with the advent of technology, new diagnostic and research methods are being available to explore the pathogenesis of the entity.

II. Incidence Of Depression

Depression is fast becoming an important medical entity with a lifetime prevalence of approximately 15-25% among women and 5-12% among men[5]. It has been predicted by the World Health Organization(WHO) that, by the year 2030, depressive illness will account for 13% of the total global burden of disease replacing cardiovascular disorders[6]. According to the WHO, almost 1 million deaths occur per year due to suicide which translates to 3000 suicide deaths everyday[7].

Depression is one of the most severe, chronic and disabling psychiatric disorder, affecting up to 20% of the world population[8]. It is characterized by emotional suffering, work impairment and a burden to relatives. Nearly half of all women and a quarter of all men will suffer from a depressive episode at some time in their life.

Depressive disorders affect millions of individuals worldwide [9] and it has been noted that depression is more prevalent among women than among men throughout the whole life cycle [10]. Depression represents a major public health concern because of the detrimental effects to the patients and society and it can lead to severe impact on mortality and morbidity, such as cardiovascular disease and metabolic syndrome. Studies have also indicated that there is a two to threefold increase in lifetime risk of developing depression among first-degree relatives [11, 12]. This high prevalence makes depression one of the most common disease and cause of handicap worldwide.

III. Treatment Of Depression

3.1. Pharmacotherapy

Depression is a treatable disease and pharmacotherapies have been present and effective for decades. The classes of drugs commonly used to treat depression are the tricyclic antidepressants, monoamine-oxidase inhibitors and selective serotonin re-uptake inhibitors. Antidepressant drugs currently have a delay of 3–6 weeks to achieve their effect and show a maximum 60–70% of therapeutic effect in depressive patients[13]. They also have multiple side effects, ranging from dizziness, tremors, decreased sex drive, blurred vision and headaches, to name but a few. For some patients, lithium treatment can augment the effects of antidepressants and some studies suggest that lithium has prophylactic effects on unipolar depression. Some second generation anti-psychotics are effective for acute treatments of major depressive disorder but few studies suggest that they effectively prevent relapse of major depressive disorder.

3.2. Electroconvulsive Therapy

Other therapies which are effective in depression are psychological therapies and Electroconvulsive therapies (ECT). ECT is a method whereby electrically induced generalised seizures are administered to a patient to initiate antidepressant effects. Animal experiments show that ECT can stimulate cell replication in the hippocampus and magnetic resonance imaging studies in humans have indicated similar effects. Moreover, functional MRI studies have also shown that ECT restores blood flow to networks that are disturbed in depression. ECT also normalises the endocrine system, including the HPA axis, which is frequently disturbed in severe depression. ECT can provide relief to people with severe depression and can be more effective than pharmacotherapies. In some severe cases where a rapid response is necessary or medications cannot be used safely, ECT can even be a first-line intervention. ECT may cause some side effects, including confusion, disorientation and memory loss but these side effects are usually short-term.

3.3. Cognitive Behaviour Therapy

Psychological therapies comprise of Cognitive behaviour therapy (CBT) and interpersonal therapy (IPT). CBT aims to show people how their thinking affects their mood and to teach them to think in a less negative way about life and themselves. It is based on the understanding that thinking negatively is a habit, and, like any other bad habit, can be broken.

3.4. Interpersonal Therapy

The goal of IPT is to help a person understand that depression and interpersonal problems are interrelated. These factors can lead them to become depressed and put them at risk for future depression. Understanding how to deal with one's own emotions and moods is an important step towards recovery. Psychological therapies are effective treatments for mild to moderate depression. However, in severe depression, acute medications are markedly more effective than placebo.

3.5. Medicinal Plants

There is also a growing trend nowadays to the use of medicinal plants for the treatment of depression. Although these remedies have been known since ancient times, there is growing research and interest into the pharmacodynamics and effectiveness of plant materials. This shift in interest is due to the fact that medicinal plants have lesser side effects than conventional antidepressants and may have a better onset of action. The list of medicinal plants which could be beneficial in depression is extensive and every country or region boasts such plants in their pharmacopoeia. A few examples of well-known antidepressant medicinal plants are St John's Wort, Ginseng, green tea polyphenols, Resveratrol, Saffron and Pepper, to name but a few. Although medicinal plants are unlikely to be effective in severe depression, there is a niche for such kind of treatment in mild to moderate depression.

IV. Pathogenesis Of Depression

The pathophysiology of depression is not fully understood although genetic factors, environmental factors and the patient's own susceptibility to depression have all been implicated. There is a genetic vulnerability to develop depression, especially bipolar depression and to a lesser extent recurrent depression.

4.1. Genetic Involvement

Many genes are implicated in regulating mood and the interactions of these different genes, together with their mechanisms, are presently being explored. Depression can result from an interaction between specific genes and environmental factors that can affect an individual's predisposition to depression. Several genetic vulnerability factors have been associated with an increased risk to develop depression, as indicated by family, twin, and adoption studies[14]. Several studies have discovered an association between depression and several

genes and these include the guanine nucleotide binding protein (G protein) beta polypeptide 3 (GNB3) gene[15], methylene tetrahydrofolate reductase (MTHFR) gene[16] and the solute carrier family 6 member 4 (SLC6A4) gene[17]. It has been noted that multiple genes need to act together in order to induce a depressive state.

4.2. DNA Methylation And miRNA

There has also been research focus on the involvement of DNA methylation and miRNA in the pathogenesis of depression. DNA methylation is a process by which methyl groups are added to DNA, causing modification to the DNA function and it has been implicated in depression, post-traumatic stress disorder and stressful events in life[18, 19]. MicroRNAs (miRNAs) are small non-coding RNAs which play a major role in post-transcriptional regulation of gene expression. Environmental factors may modify gene expression through the regulation of miRNA synthesis[20], with an example being BDNF dysregulation due to miRNAs expression modification. Up-regulation of two miRNAs, miR-132 and miR-182, have been implicated in the reduced serum levels of BDNF in depressed patients[21].

4.3. Neurotransmitters

The normal physiology of the body is affected by depression and these systems include neurotransmitters, stress hormones and neuronal plasticity. Serotonin, dopamine and norepinephrine are monoamine neurotransmitters which are implicated in the monoamine hypothesis of depression and which states that depression is caused by decreased monoamine function in the brain. This hypothesis has been formulated more than 5 decades ago and many monoamine-based drugs have been developed for the treatment of depression since then[22]. Most currently available antidepressants were developed according to this hypothesis and function by inhibiting reuptake of serotonin and/or noradrenaline. Serotonin was first discovered in 1948 as a monoamine released from platelets during blood clotting and subsequently in the brain and brainstem where it acts as a neurotransmitter[23]. Serotonin causes the release of corticotropin-releasing hormone (CRH) and a prolactin releasing factor from the hypothalamus. This in turn causes the release of adrenocorticotropin (ACTH) and prolactin from the pituitary gland. ACTH causes the release of cortisol from the adrenal cortex into the blood. Studies have shown that depression recurs in patients in whom serotonin and tryptophan have been depleted[24].

Dopamine is a neurotransmitter and neuromodulator which is involved in many functions such as motor control, motivation and reward[25]. Dopamine is metabolized to 3-4 dihydroxyphenylacetic acid (DOPAC) by the enzyme monoamine oxidase (MAO) which is in turn metabolised by the enzyme catechol-O-methyl transferase (COMT) to homovanillic acid (HVA). HVA is associated with dopamine levels in the brain and the level of HVA is used as a marker of metabolic stress[26]. In the central nervous system, norepinephrine increases arousal and alertness, enhances formation and retrieval of memory and can also increase restlessness and anxiety. The stress response is also abnormal in individuals with severe depression. Cortisol production is usually increased, the diurnal variations are reduced and the feedback mechanism of cortisol is disturbed.

4.4. Cellular Turnover

The turnover of brain cells is also linked to depression. In animal studies, antidepressant treatments such as ECT result in increased cell replication in areas thought to be important for emotional regulation, such as the amygdale, hippocampus, gyrus cinguli and prefrontal cortex. In addition, a patient's action in response to their symptoms can result in a downward spiral that increases the severity of the disease. For example, lack of interest and drive may contribute to low levels of engagement in normal activities, which in turn increases sad feelings that occur due to a reduction of pleasant and interesting tasks. The basis of cognitive behavioural therapy is to alleviate symptoms through changing the patient's thinking and actions.

4.5. Hypothalamic-Pituitary-Adrenal Axis

Research has shown that exposure to chronic stress results in hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, resulting in damaging effects to neuronal structures, which is an aspect of stress-related disorders such as depression[27]. HPA-axis hyperactivity results in increased levels of circulating glucocorticoids, as is evidenced by studies which showed that mice subjected to a variety of stressors exhibited elevated corticosterone (CORT) levels[28, 29]. Hypercorticolism has also been demonstrated in both rodents and humans expressing depressive behaviours [30]. The stress response is mediated by the HPA system, resulting in the release of CRH by the hypothalamus in response to a stressor. CRH acts on the pituitary gland, triggering the release of adrenocorticotropin (ACTH) into the bloodstream, which subsequently causes corticosteroid release from the adrenal cortex. Cortisol acts at the level of the pituitary gland and the hypothalamus and exerts a negative feedback mechanism to negate the stress response after a traumatic event. Cortisol is a major stress hormone that acts on many organs and brain areas through two types of receptors, which are the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). These receptors have

specific and selective distribution in the brain [31], with GRs being found in brain regions such as the hippocampus, amygdala and prefrontal cortex, which have been implicated in the pathogenesis of depression.

4.6. Oxidative Stress

Oxidative stress is considered an important mechanism involved in the pathophysiology of depression and several studies have reported that stress causes changes in reactive oxygen species (ROS) and glutathione (GSH) levels as well as in the activity of antioxidant enzymes in brain regions[32, 33]. Oxidative damages to macromolecules such as lipid, protein and nucleic acids by excessive ROS levels lead to neuronal dysfunction, which is associated with the development of depressive disorders[34]. GSH, an intracellular non-enzymatic thiol antioxidant, is widely involved in the occurrence of depression, mainly by regulation of ROS levels. Reactive oxygen species degrade polyunsaturated lipids, forming malondialdehyde (MDA). This compound is a reactive aldehyde and is one of the many reactive electrophile species that cause toxic stress in cells. Other enzymes which are considered to be involved in oxidative stress are lactate dehydrogenase (LDH), superoxide dismutase (SOD), glutathione reductase (GSR), catalase (CAT), glutathione peroxidise (GSH-Px) and glutathione S-transferase (GST). GST comprises a family of metabolic isozymes which are able to catalyze the conjugation of the reduced form of GSH to xenobiotic substrates for detoxification[35]. Glutathione peroxidase protects the organism from oxidative damage by reducing both lipid hydroperoxides to their corresponding alcohols and free hydrogen peroxide to water[36]. Catalase is also an enzyme which catalyzes the decomposition of hydrogen peroxide to water and oxygen[37] and is a very important enzyme in protecting the cell from oxidative damage by ROS. Superoxide dismutase is an enzyme that alternately catalyzes the dismutation of the superoxide (O_2^-) radical into either ordinary molecular oxygen or hydrogen peroxide[38]. Superoxide is produced as a by-product of oxygen metabolism and, if not regulated, is responsible for cell damage. LDH is an enzyme which is an important marker for tissue injury and raised levels in the blood suggest an increased rate of tissue destruction. LDH is an intracellular enzyme and any process causing injury to the cell will result in the release of LDH. In the clinical setup, LDH is used as a diagnostic tool in diseases such as myocardial infarction, malignant tumours, haemolytic anaemia, pancreatitis, bone fractures and meningitis.

4.7. Involvement Of Immunity

The immune system has also been implicated in the pathogenesis of depression and is referred to as the cytokine hypothesis of depression. It states that external and internal stressors trigger depressive behaviour by elevating the production of pro-inflammatory cytokines, interleukin-1 (IL-1) and IL-6, tumour necrosis factor alpha (TNFα) as well as activating cell-mediated immunity[39].

4.8. Neuronal Plasticity

Neuronal Plasticity has also been implicated in depression. It has been discovered that depression is responsible for neuronal atrophy in the brain. Neuronal plasticity is defined as changes in neural organization which may account for various forms of behavioural adaptability, either short-lasting or enduring, including maturation, adaptation to a mutable environment and compensatory adjustments in response to functional losses from aging or brain damage[40]. Neural plasticity is regulated by a family of growth factors that serve to promote the growth and survival of neurons. They are called neurotrophins and include the Nerve Growth factor (NGF), the brain derived growth factor (BDNF) and Fibroblast Growth Factor.

The Nerve Growth Factor, as the name implies, is a neuropeptide involved primarily in the regulation of growth, maintenance, proliferation and survival of target neurones. It is a modulatory factor in the HPA axis and has effects on the neuroendocrine and immune systems[41]. The Extracellular signal-regulated kinase (ERK) is also involved in synaptic plasticity and has many cellular targets. It influences a wide range of cellular functions such as learning and memory formation[42]. A downstream target of ERK pathway is the Cyclic AMP responsive element-binding protein (CREB)[43]. The latter, a transcription factor, has been shown to be essential for different physiological responses like development of behavioural sensitization and emotional behaviours by binding to different target genes[44]. It also plays a role in neuronal plasticity and long-term memory formation in the brain[45].

The Brain Derived Growth Factor is also involved in the neuronal effects of depression and takes part in neurogenesis and synaptogenesis [46]. Although the vast majority of neurons in the mammalian brain are formed prenatally, parts of the adult brain retain the ability to grow new neurons from neural stem cells[47]. BDNF plays a significant role in this neurogenesis and it can promote protective pathways, inhibit damaging ones and enhance cell survival. Exposure to stress and the stress hormone cortisol has been shown to decrease the expression of BDNF in rats, and, if exposure is persistent, can lead to an eventual atrophy of the hippocampus[48]. Atrophy of the hippocampus and other limbic structures has been shown to take place in humans suffering from chronic depression, as have clinical studies shown that individuals with depressive

disorders have low serum BDNF levels[49]. This suggests that an etiological link between the development of depression and BDNF exists.

The neurotrophin Fibroblast Growth Factor, basic (bFGF) is important for the initiation of nerve repair after trauma or injury. It also is known to promote the proliferation of immature neurons and causing the multiplication of new neurons. This growth factor is primarily found in the CNS and the brain and is responsible for stimulating neuronal growth of cells in the cortex, striatum, hippocampus, cerebellum, parasympathetic ganglia and the spinal cord. During periods of neuronal injury for example cerebral ischemia, the expression of bFGF is significantly increased.

V. Conclusion

Research into depression is an ongoing process and new insights into the pathogenesis are continuously being made. Even so, depression is a complex disease and our understanding of it is still far from being complete. The burden of depression on the society, the families of an affected individual and the person himself is consequent and it is imperative to further our knowledge into this entity.

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