Review on neurobiology and psychiatric aspects of depression and its newer treatments

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Abstract

Depression is a mental health condition. It is distinguished by intense, long-lasting feelings of sadness or despair. Depression can alter an individual's thoughts and feelings, as well as his or her social behavior and sense of physical well-being. It can affect people of any age, including children. and teenagers It can run in families and typically begins between the ages of between the ages of 15 and 30. The symptoms associated with depression are feeling of sadness, loneliness, hopelessness ,fatigue or loss of energy, loss of appetite, guilt ,restlessness and being easily annoyed.Drugs like selective serotonin reuptake inhibitors, Monoamine oxidase inhibitors are used for treating depression. Recently approved drugs like Zulresso used to treat postpartum depression ,esketamine is also used for treating depression.

Keywords: *Depression, Neurobiology, Neuroprogression*

Introduction:

Depression is a long-term mental illness characterised by changes in mood, thoughts, behaviour, and physical health. It is a common but deadly disease that can deprive a person of their capacity to enjoy life and bring death and reduction in ability to perform even the most basic daily tasks [1]

Depression is one of the most common and life-threatening mental illnesses, affecting over 21% of the world's population. Changes in a complex signalling network, including the hypothalamic-pituitary-adrenal axis, neurotrophin production, and proinflammatory cytokine production, may all be involved in substantial mood changes.[1]

Stress-induced increases in proinflammatory cytokines promote depression by causing oxidative and nitrosative brain damage, affecting the serotonin pathway, and contributing to glucocorticoid resistance. All of these factors influence neurogenesis in depression-related brain areas and are functionally linked, so that a change in one causes abnormality in the others.[2]

Epidemiology:

The prevalence of depression in community samples has been measured in a number of research, with prevalence rates ranging from 1.7 to 74 per thousand people. The findings on depression prevalence in urban populations are consistent with those of a survey of the complete adult population of an industrial township, which revealed a prevalence rate of 19.4 per thousand people. Depression is the

most frequent mental disorder in senior people, according to studies conducted in the community, inpatient, outpatient, and old age facilities. A rural Uttar Pradesh epidemiological study found that psychiatric morbidity was higher in the geriatric group (43.32 percent) than in the nongeriatric group (4.66 percent), with neurotic depression being the most common psychiatric morbidity, followed by manic-depressive psychosis depression and anxiety state.[3]

Risk factors for depression:

In terms of sociodemographic characteristics, studies have revealed that depression is more common in women, younger people, those from low socioeconomic backgrounds, and people who are malnourished. Depressed people had a much higher number of life events previous to the commencement of their illness (6-12 months) than healthy controls and schizophrenic patients, according to studies. When compared to patients with schizophrenia, depressed patients have a significantly higher proportion of life events related to death of a family member, personal health-related events, depression, interpersonal and social events, and a significantly lower number of life events in the form of family member illness. It has also been observed that, when compared to patients with mild depression, patients with moderate and severe depression use avoidance as a coping strategy for stressful life events more frequently, implying that it may be a maladaptive way of coping with the situation that contributes to the development of depression.[4]

Causes of disease- Genetic and environmental factors

Genetic causes:

Research into the genetics of depression is still in its early stages, and little is known about the disease's genetic origins. According to research, changes in a number of genes, each with a minor influence, combine to raise the risk of depression.

Twin studies:

Identical twins are very helpful to researchers since they both have the exact same genetic code. It has been found that when one identical twin becomes depressed the other will also develop clinical depression approximately 76% of the time. When identical twins are raised apart from each other, they will both become depressed about International Science Congress Association 81 67% of the time. Because both twins become depressed at such a high rate, the implication is that there is a strong genetic influence. Research has also been done with fraternal twins. Unlike identical twins that have the same genetic code, these siblings share only about 50% of their genetic makeup and do not necessarily look alike. Studies have shown that when one fraternal twin becomes depressed, the other also develops depression about 19% of the time. This is still a higher rate of depression when compared to overall rates for the general public, again pointing towards a genetic influence in the development of clinical depression[5]

Environmental factors:

Environmental causes of depression include events such as stress, traumatic events and childhood difficulties. These are events that can happen to anyone and they happen during our everyday lives. They are considered factors that are outside of us. Some researchers refer to these events as sociological or psychosocial factors because they are a "meeting" or "combination" of events that happen in society and the function and workings of the human mind.

- **Stress:**

There appears to be a complex interaction between stressful conditions, the individual's mind and body's response to stress, and the emergence of clinical symptoms of depression. The majority of scientists agree that for certain persons, there is a direct link between a traumatic event and the depression may emerge. There may be positive or negative stress. Example of positive stress are planning for a wedding, preparing for a new job, and moving to a new city.

Examples of negative stress are loss of a loved one, loss of a job, loss of a relationship and divorce.

Both negative and positive stress from environmental events can precede the development of depression.

- **Traumatic events:**

Traumatic events in the lives of people include loss of a loved one, a serious medical illness, the end of a marriage or significant financial loss. These types of events can destroy the sense of control and stability in a person's life, often leading to emotional distress.

- **Noise pollution:**

Noise pollution has been linked to aggression, hypertension, increased stress levels, tinnitus, hearing loss and disruptions in sleep. Specifically, tinnitus is linked to severe depression, panic attacks and forgetfulness. Continual exposure to noise pollution has also been linked to cardiovascular disease and increased blood pressure. A person with possible depressive tendencies will become even more susceptible to depression with continual, prolonged exposure to noise pollution.[6]

Neurobiology:

Depression's neurobiology includes dichotomous changes in corticolimbic brain regions. Neuronal atrophy and synaptic dysfunction are seen in the prefrontal cortex and hippocampus, whereas neuronal hypertrophy and increased synaptic activity are seen in the nucleus accumbens and amygdala.The peripheral and central immune systems, which are implicated in the neurobiology of depression, are dysregulated in subsets of depressed people. In physiological and pathological conditions, microglia, or brain-resident macrophages, integrate neuroimmune signals and mediate neuroplasticity. Neurons modulate the function and activation of microglia by sending soluble and contact-dependent signals.

The importance of the 'neurocircuit of emotion' was established by the emergence of neuroimaging techniques such as magnetic resonance imaging (MRI), positron emission tomography (PET), and functional fMRI, which has since been expanded to include other important brain areas, particularly the prefrontal cortex.

The structural changes in the brain in particular the hippocampus and PFC are believed to be due to abnormalities in neuroplasticity rather than neurodegeneration. These changes are indeed always reversible, particularly in the PFC (Prefrontal cortex) and also whether or not they predate the onset of depression.[7]

To a large extent, these abnormalities are caused by dysregulation of the HPA axis. Increased levels of circulating cortisol stimulate gene transcription and protein synthesis by activating brain receptors,allowing increased calcium entry into activated neurons and causing neuronal damage.

Glucocorticoid-induced hippocampus damage can occur either directly, through glutamate system activation, or indirectly, through BDNF reduction.The hormone CRH has direct toxicity on hippocampal neurons. Stress is linked to lower levels of BDNF, which makes neuronal survival much more difficult. Reduced hippocampal neuronal tissue, as well as a direct effect of hypercortisolaemia; decreased activity in monoaminergic neurotransmission, or other noxious factors, could all contribute to lower BDNF levels. The rise in cytokines levels may also contribute to the sustained HPA activation and abnormal IRSs may have a secondary or even a primary role in the dysregulation of the HPA axis.[8]

Neuroprogression:

The brain is constantly reorganising itself through neuroplasticity and attempting to achieve greater efficiency through neurodevelopment, but it occasionally establishes inefficient and incorrect alternative interconnection routes in a phasic and progressive process known as neuroprogression.Mild degenerative processes, intracellular signalling dysfunctions, apoptosis, and diminished plasticity and neurogenesis are all hallmarks of neuroprogression.The shrinkage of the

frontal lobes, prefrontal orbital cortex, circumvolution of the frontal corpus callosum, hippocampus, and amygdala in depressive individuals appears to represent a loss in neurogenesis, mitochondrial malfunction, and an imbalance in the HHS axis. [9]

Two scenarios that usually result in a reduction in neurogenesis can affect the decrease of 5-HT levels in DD. The following are the two scenarios:

Inhibition of serotonin synthesis: The stimulation of the tryptophan 2,3-dioxygenase (TDO) enzyme found in brain macrophages and microglial cells inhibits serotonin synthesis when hypercortisolemia is sustained. TDO activation causes the production of several neuroactive metabolites from the kynurenine pathway, as well as neurotoxics like 3-hydroxykynurenine, 3-hydroxyanthraic acid, and quinolinic acid.

Participation of proinflammatory cytokines :The proinflammatory cytokines, mainly ILs, alpha and beta IFNs, and tumor necrosis factor (TNF), are capable of modulating the functioning of macrophages, glial and endothelial cells, and even neurons, because these cells possess specific receptors for these signaling molecules.[10]

New medications:

Brexanolone:

Allopregnanolone is a neurosteroid that is produced naturally in the body from the hormone progesterone.allopregnanolone is referred to as **brexanolone.** In the United States, brexanolone was licenced for medicinal use in 2019.

Brexanolone is sold under the brand name **Zulresso** used to treat postpartum depression.Under medical supervision, it is injected into a vein over a 60-hour period.

Esketamine:

Esketamine, commonly known as (S)-ketamine or S(+)-ketamine, is a dissociative hallucinogen drug used as a general anaesthetic and as an antidepressant for the treatment of depression**.** Esketamine is the active enantiomer of ketamine in terms of NMDA receptor antagonism and is morepotent than racemic ketamine.

Esketamine sold under the brand name **Spravato** for depression and **Ketanest** for anaesthesia. (4)

Future treatment:

There are a slew of other promising depression treatments on the horizon. One is deep brain stimulation. A surgeon places electrodes in the brain during this procedure. These nodes emit non-painful zaps that change the electrical activity that is causing symptoms**.**

Conclusion:

Based on the evidence so far, it can be concluded that depressive disorder has a multifactorial aetiopathogenesis, with genetic diathesis and stress (both physical and psychological) playing major roles and acting through a variety of pathophysiological mechanisms. Reduced noradrenergic and serotonergic neurotransmission activity, a decrease in brain neurotrophins, and hyperactivity of the HPA axis and the inflammatory response system are examples of the latter. These are linked to structural and functional deficits in the corticothalamic-striatal-limbic neurocircuit, which disrupts system balance. Antidepressant drugs boost monoaminergic neurotransmission and BDNF levels, reverse some structural changes (at least in the hippocampus, boosting neo-neurogenesis), and improve corticolimbic neurocircuit function.

Acknowledgements
Authors thanks Dean Dr. Bharath,Dr. V. Madhavan, Dr. Anbu, Dr. Maheshwari E and Dr. Harish, Faculty of Pharmacy, Ramaiah University of Applied Science, Bangalore and Karnataka, India

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