Review Article

Basic Hypothesis and Therapeutics Targets of Depression: A Review

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Abstract

Depression is a psychological disorder marked by emotional symptoms such as melancholy, anhedonia, distress mood, loss of interest in daily life activities, feeling of worthlessness, sleep disturbances and destructive tendencies. According to WHO, more than 264 million people from all age groups are suffering with depression thus, it is become a leading cause of disability and infirmity worldwide. It is estimated that 40% of risk for depression is genetic and the other 60% is non-genetic which involved acute & chronic stress, childhood trauma, viral infections and even random processes during brain development. Depression is mainly due to neurotransmitter imbalances, HPA disturbances, increased oxidative and nitrosative damage, impairment in glucose metabolism, and mitochondrial dysfunction, etc. The monoamine hypothesis is based on attenuation of monoamines such as serotonin (5-HT), norepinephrine (NE) and dopamine (DA) in the brain regions (hippocampus, limbic system and frontal cortex) that can cause depression like symptoms. Depression is also marked by increased level of corticotrophin-releasing hormone (CRH) and and impaired responsiveness to glucocorticoid hormone. The present review emits about its background knowledge, various pathophysiological pathways involved and current therapy for the depression.

Keywords: Depression, HPA axis, mitochondrial dysfunction, NMDA receptor, Serotonin, Glutamate

Introduction

Depression is one in all the two diagnostic classes that represent common mental disorders (CMDs), the other is anxiety disorder. Both are highly widespread among the community and influence the mood or feelings of affected persons. Depressive disorders are characterized by dejection, loss of pleasure, guilt feelings or low selfworth, insomnia, appetite imbalance, feelings of tiredness, and loss of concentration. At a worldwide level, according to WHO 2020 more than 264 million people from all age group are suffering with depression, equivalent to 4.4% of the world's population. India is home to an estimated fifty seven million people (18% of the the world estimate) littered with depression [1]. Depression may be caused due to neurotransmitter imbalances [2], increased oxidative and nitrosative damage in brain, HPA disturbances, impairment in glucose metabolism, and mitochondrial dysfunction, etc [3]. The monoamine hypothesis is based on attenuation of monoamines such as serotonin (5-HT), norepinephrine (NE) and dopamine (DA) in the brain regions (hippocampus, limbic system and frontal cortex) that can cause depression like symptoms. Monoaminergic neurotransmitters are metabolised by monoamine oxidase (MAO) [4,5]. Decreased antioxidant status, elevated oxidative and nitrosative stress are found in patients with depression [6]. Moreover, there is greater secretion of corticotrophin-releasing hormone (CRH) and impaired responsiveness to glucocorticoids [7]. The hypothalamic-pituitary-adernal (HPA) axis hyperactivity is present in around 50% of depressed patients (80% if severely depressed).

Decreased antioxidant concentration, and raised oxidative and nitrosative stress are major marker that are present in patients with major depression [8]. This is evidenced by reduced level of antioxidants such as vitamin C [9] vitamin E [10,11] and coenzyme Q10 [12] in plasma and by reduced antioxidant enzyme activity such as glutathione peroxidase [13]. These paucities in antioxidant defence system impaired the protection against reactive oxygen species (ROS), which lead to damaged fatty acids, proteins and DNA. In depression, there is rise in the lipid peroxidation levels, encompassing increase in malondialdehyde [14-16] and oxidative damage to DNA, characterized by increased levels of 8-hydroxy-2-deoxyguanosine [17]. Furthermore, elevated oxidative stress level in brain is reflective of neurotoxicity and neuronal death towards the progression of chronic stress-induced depressive disorders [18]. Nitric oxide (NO) is an important modulator of depression [19,20] because NO production is increased in depression. Moreover, In brain, No is an essential neurotransmitter that normalize depression, behavioral, cognitive and emotional processes [21]. In experimental animals, plasma nitrate levels have been increased significantly under stressful condition [22]. Psycho-social and physical stressors can inhibit the neurogenesis in various animal models and thus lead to decreased cell proliferation and survival [23]. The types of depression are depicted in Figure 1.
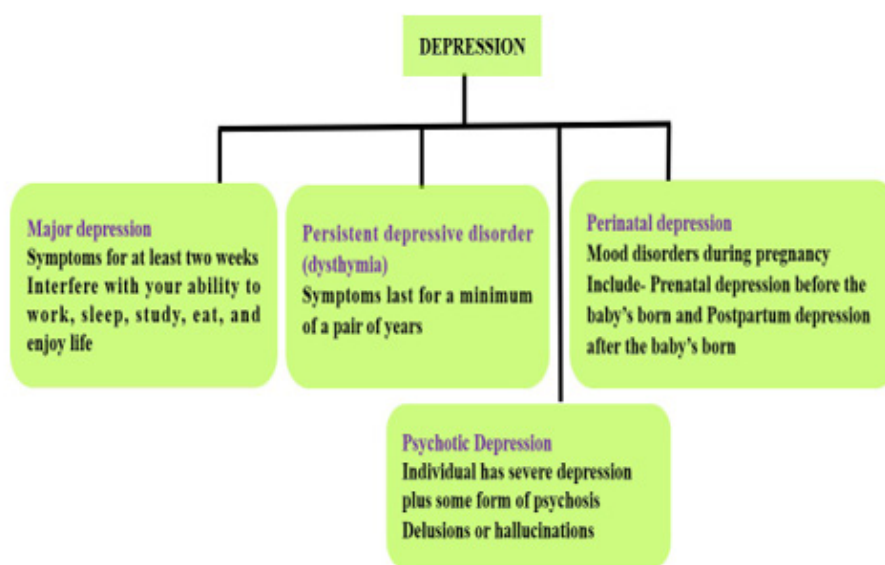

Figure 1: Types of depression.

Pathophysiological Hypotheses of Depression

Following neurotransmitters and receptor systems have been reported to be involved in pathophysiology of depression (Figure 2&3)
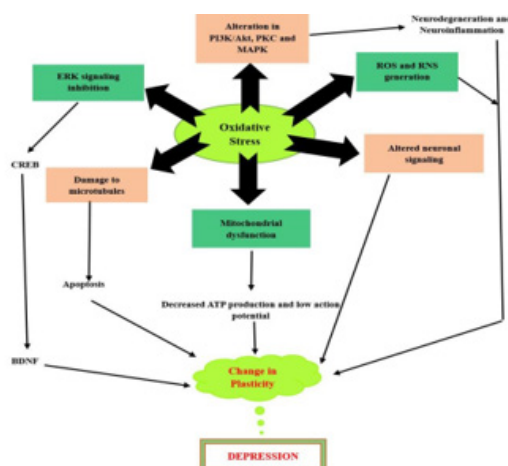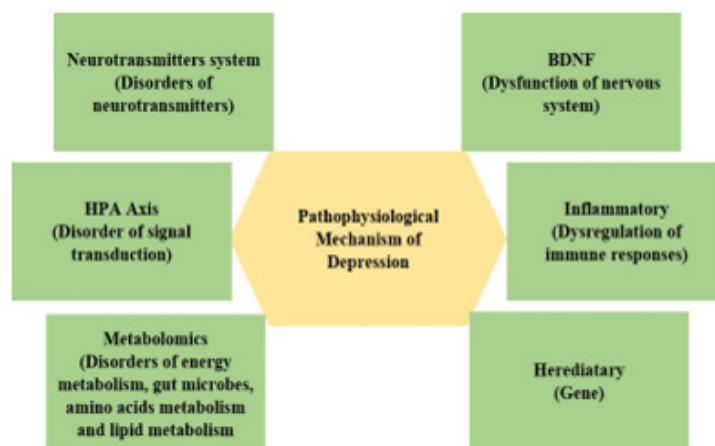

Figure 2: The different pathological mechanisms of depression.

Figure 3: The different pathological mechanisms of depression.

Role of monoaminergic system/ monoamine theory

Basic hypothesis of depression firstly described about the functional inadequacy of adrenergic neurotransmitters such as noradrenaline (NAdr), serotonin (5-HT) and dopamine (DA). Facts for this hypothesis obtained from the animal experiments and clinical studies, which depicted that the reserpine (an antihypertensive drug), a monoamine antagonist lead to the reduction of pre-synaptic stores of NAdr, DA and 5-HT, was used to treat things like high blood pressure, is rarely used at the present time due to the fact that depression is a common side effect. Thus, not solely monoamine agonists decrease depression, however monoamine antagonists (Reserpine) will induce depression [24]. The enzyme (monoamine oxidase) which plays an essential role in the malfunctioning and oxidation of monoamines like DA, NE and 5-HT. The monoamine oxidase A showing targeted preferred action on serotonin, and its an important target for screening antidepressant activity of monoamine oxidase inhibitors [24].

Neuronal framework of depression

Several reported literature provides the evidences of deformities in various parts of the brain that are the main driven force for controlling emotion, functions and reward outcomes. Post-mortem and neuroimaging examination have depicted the changes in morphology which is illustrated by reduced grey-matter volume and interstitial tissue density in the hippocampus and anterior cortex, which is the main focused region in animal analysis of depression. The decline in hippocampal operate, that is believed to possess a repressive result on the hypothalamic-pituitary- adrenal (HPA) axis, might probably be answerable for the hypercortisolemia seen in depression [25].

Serotonin hypothesis

Serotonin(5-hydroxy tryptamine), a monoamine with a large distribution throughout the CNS. It is concerned in physical activities like pain sensation, appetence regulation, aggression and mood. This terminology mainly based on the deficiency in 5-HT as the foremost cause of depression, which can be altered by antidepressants, which would bring back the actual functioning in the affected subjects. As approved by the post-mortem examination, neurochemical, genetic neuroimaging and pharmacological studies that a purposeful insufficiency in 5-HT neuronal firing within brain regions which is known to play role in controlling emotions have systematically been related to facet of the MDD pathophysiology. Moreover, subsequently SSRIs solely were seem to be efficient to treat the symptoms of depression. This fact more reinforced the involvement of 5-HT within the pathological process of the illness [26]. 5-HT is implicated in MDD, and the genesis of this disease may be linked to the dysfunctioning of 5-HT receptors [27]. It has been reported that 5-HT sensitivity (reduction of 5-HT/tryptophan), is more common in MDD patients [28]. Membrane transporters which help in translocation of 5-HT across the membrane are basically proteinaceous in nature and mostly targeted for the treatment of depression. These proteins help in the regulation of serotonergic transmission that are also associated with MDD.

Role of hypothalamic-pituitary-adrenal (HPA) axis system

The response systems for stress are mainly regulated by the HPA-axis. In the central nervous system when HPA-axis starts stimulation, than an individual's recognize the fearful and noxious stimulus (e.g., a traumatic episodes) from the surrounding [29]. Various researchers noted that the HPA-axis showing sensitivity towards psychological ans social stress agents, which is observed by alteration in cortisol levels which is accompanied with the increased risk of producing altered psychological symptoms in the affected population [29]. HPA- axis is activated in response to the traumatic episodes by a signal within the para-ventricular nucleus (PVN) of the hypothalamus. Neurons in the PVN synthesize and secrete corticotrophin-releasing hormone (CRH), which binds to specific receptors in the anterior pituitary. Then the anterior

pituitary specifically adrenal cortex stimulates the production and release of adrenocorticotropin hormone (ACTH) [30]. High cortisol or corticosterone levels may be the key factor in precipitating the symptoms of depression by impairing brain functions like neurogenesis, neuronal survival, neuronal excitability and plasticity (Figure 4) [31].

Figure 4: Stress and HPA axis. CRH: Corticotrophin-releasing hormone, ACTH: Adrenocorticotropin hormone

Role of neurotrophins

The most common and extensively dispersed neurotrophin is the brain-derived neurotrophic factors (BDNF) within the central nervous system. BDNF is liable for controlling cognitive functions, synaptic plasticity and neurogenesis, which is directly linked to the pathogenesis of depression [32,33]. There is decrease of brain BDNF levels in depression patients [34]. The raised BDNF levels improves depressive behaviors so that it is the area of interest for researchers for the antidepressant therapy [35].

Role of cytokines

Pro-inflammatory cytokines like interleukin (IL)-1β, IL-6, tumor necrosis factor á (TNF-α) and interferon-γ play an important role in pathophysiology of depression. Up-regulation of these pro-inflammatory cytokines were identified in depressed patients. Antidepressants decreased the levels of pro-inflammatory cytokines and improved symptoms of depression symptoms [36,37].

Role of Nrf-2 in depressive disorders

Nuclear factor (erythroid-derivative 2) is a transcription factor that plays a central role in cellular defense against oxidation and electrophilic insults. Nrf2, situated in the gene's promoter domain adhere to the antioxidant response elements (ARE) encodes several antioxidant and enzymes responsible for detoxification and stress-related responsive proteins. Interruption or failure of Nrf2 signaling pathway lead to the improved susceptibility towards the oxidative and electrophilic stresses and also injuries in the inflammatory tissues. Since Nrf2 has been recently described to play a crucial role in regulating inflammation, and inflammation has been related to depression. Furthermore, a relationship between Nrf2 and protective effects have also been described in the central nervous system (CNS) [38]. Nrf2 stimulates Heme oxygenase-1 (HMOX1, HO-1) and this enzyme catalyzes the breakdown of heme into biliverdin, carbon monoxide, and iron which is the beneficial aid for antidepressant action [39,40].
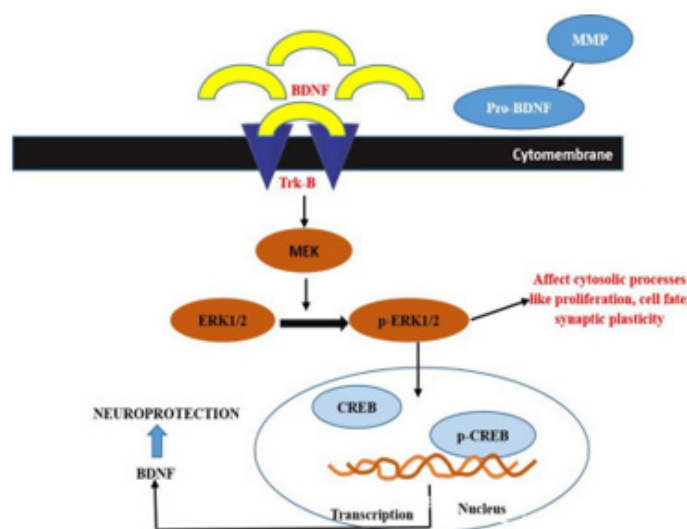
Involvement of Extracellular signal-regulated kinase (ERK) in depression

Table 1: Current therapeutic targets for depression [52].

S.No.	Therapeutic targets	Description
	1. Inflammatory pathway hypothesis:	
	Infliximab	TNF-α Antagonists
	Sirukumab	IL-6 Antagonists
	Acetylsalicylic acid	Irreversibly inhibits cyclooxgenase-1 and -2
	Celecoxib	COX-2 inhibitor
	Omega-3 polyunsaturated fatty acids	1. Natural anti-inflammatory agents
	Curcumin	Natural anti-inflammatory agents
	Doxycycline	Inflammatory mouse model, doxycycline reduces the incidence and severity of depressive-like behavior

	Minocycline	Minocycline exerts antidepressant action through its anti-inflammatory, antioxidant, anti-glutamatergic, and neuroprotective effects
	2. Oxidative and nitrostative stress hypothesis	
	N-acetyl cysteine	Act as a precursor of the antioxidant glutathione
	3. Hypothalamic-pituitary-adrenal (HPA) axis hypothesis	
	Metyrapone	Glucocorticoid (cortisol) synthesis inhibitor
	Ketoconazole	Glucocorticoid (cortisol) synthesis inhibitor
	Oxytocin	Act as a powerful suppressor of HPA axis activity
	Dehydroepiandrosterone	Endogenous steroid acting as a neurotrophin and is capable of binding NMDA, GAB-AA, and σ-1 receptors
	4. Glucose metabolism based hypothesis	
	Glucagon-like peptide-1	Delays gastric emptying and increases insulin sensitivity
	Gliptins	Inhibit dipeptidyl peptidase-4
	Pioglitazone	Insulin sensitizer, a PPAR-γ agonist
	5. Glutamatergic system hypothesis	
	Ketamine, Esketamine, Hydroxyketamine	Voltage-dependent NMDA antagonists
	Nitrous oxide	Noncompetetive NMDA receptor inhibitor
	Dextromethorphan	Nonselective, noncompetitive NMDA receptor antagonist
	Rapastinel, D-cycloserine	NMDA receptor glycine site partial agonist
	Sarcosine	Glycine transporter-I inhibitor that upregulates NMDA receptor function
	Riluzole	NMDA modulator
	6. Cholinergic system hypothesis	
	Scopolamine	Antimuscarinic, glutamatergic modulating effects
	Mecamylamine and Varenicline	Nicotinic acetylcholine receptors antagonists
	7. Other	
	Silexan	Extracted from lavender flowers, acts as voltage-operated calcium channel inhibitor, significantly reduce serotonin-1A binding potential in the brain, consequently increased extracellular serotonin levels. Also antagonistically bind the glutamate NMDA receptor

COX: Cyclooxygenase; IL-6: Interleukin-6; GABA-A: Gamma amino-butyric acid A; NMDA: N-methyl-D-aspartate; PPAR-γ: Peroxisome proliferator-activated receptor gamma; TNF-α: Tumor necrosis factor-alpha.

Figure 5: The ERK Signalling pathway involved in depression.

Mitogen-activated protein kinases (MAPKs) family consisting extracellular signal-regulated kinases (ERK1 and ERK2) [41], a downregulated target of BDNF, is stimulated by the binding of BDNF to tyrosine kinase receptor-B (Trk-B) in the Ras-dependent pathway. Moreover, this eventually leads to the phosphorylation of cAMP response element-binding protein (CREB) [42,43]. Various experimental studies have evidenced that the diminshed expression of ERK1/2 results in depressive behaviour in rodents [44,45]. Decreased ERK expression and activation have been found in the brain of suicidal persons with depression in autopsy [46]. Antidepressants can alleviate the altered effects of depression by the escalation in ERK1/2 [47] and p-ERK1/2 expression (Figure 5) [48-52].

Conclusion

In the present review we have described about the pathophysiological targets and targeted therapeutic for depression. There is an immense demand for a novel effective and efficacious therapeutic agents and therapeutic targets as the disease becoming very common in our all age groups. At present so many marketed formulation available but only few consumers getting a clinically significant benefits. Therefore we need to explore all the hypothesis deeply and try to understand the underlying mechanism in more possible ways.

Acknowledgement

Conflict of Interest

Authors declare no conflict of interest.

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