Novel Antidepressant Agents: A Review on Mechanism and Biological Targeting Process.

SHIVANI DIXIT[1], PRIYANKA THAKUR[2], SHAGUN[3], SAKSHI SHARMA[4], AKASHDEEP SINGH[5]

Abstract*— Depression is a complex and multifactorial disease, and the development of novel antidepressant agents has been a significant challenge. Recently, several novel antidepressant agents have been discovered, offering new hope for the treatment of Depression. This review aims to provide a comprehensive overview of the mechanisms and biological targeting processes of these novel agents. We conducted a systematic review of the literature, including preclinical and clinical studies, to identify the key mechanisms and biological targets involved in the antidepressant activity of these novel agents. Our analysis reveals that these agents target a range of biological processes, including neurotransmitter modulation, neuroinflammation, and neuroplasticity.

Indexed Terms- Novel antidepressants, Mechanism of action, Biological targeting, Neurotransmitter modulation, Neuroinflammation, Mono Amine Oxidase Inhibitors.

I. INTRODUCTION

Depression is defined by a brain illness and wide variety of symptoms that are related to change in cognitive, psychomotor and affective functions[1].They feel apathetic, hollow, and lifeless; men in particular may even feel restless and aggressive. If depression is not addressed, it can become more and more incapacitating, regardless of how you experience it[2]. Nowadays, lifestyle modifications are showing equal efficacy in treating mild to moderate forms of depression as medicine.

Sadness, loss of interest or pleasure, guilt or low self-worth, interrupted sleep or food, fatigue, and difficulty concentrating are all signs of depression, a common mental illness.It is more than just brought on by life's challenges and disappointments[3]. Depression can exhaust or deplete you, making it difficult for you to work, learn, eat, sleep, and enjoy life. A severe illness with significant clinical and sociological implications is major depression[4] . The first biochemical theory of depression was proposed in the 1950s with the development of antidepressant medications, indicating that central monoaminergic function impairment was the primary cause of the illness[5]. The development of novel antidepressant medications and fundamental studies in many areas of neuroscience, including genetics, have completely changed our knowledge of the mechanisms underlying depression and medication effect[6]. The failure to respond appropriately to stress or other aversive stimuli may be the cause of depression, and antidepressants may work by either resolving this dysfunction or by directly eliciting the proper adaptive responses[7].

II. VARIOUS MECHANISMS INVOLVED IN THE DEPRESSION

Various neurotransmitters played totally different and necessary role in depression amongst them serotonin/5-Hydroxy tryptamine (5-HT), Gamma Amino Butyric Acid (GABA), Benzodiazapine receptor,nor-epinephrine/nor-adrenaline (NE/NA) and plenty of others like have additionally been joined to depressive disorders[8].It is estimated that genes contribute 30% to 50% to the development of an anxiety disorders.Conversaly development of an anxiety disorders due to non-genetic factors is approximately 50%to 70%.Hence it is necessary to study the mechanism of action[9].

There are a number of theories being discussed at the moment about depression, and the most frequently recognized ones are included here :

2.1 The monoamine hypothesis: The insufficient activity of monoamine neurotransmitters has been observed in the central and peripheral nervous systems of patients with depression[10]. In order to control mood, several antidepressants raise the amount of monoamine neurotransmitters in the synaptic cleft of neurons through a number of mechanisms, including as blocking serotonin and norepinephrine reuptake, serotonin reuptake, and norepinephrine reuptake[11].

2.2 The hypothalamic–pituitary–adrenal (HPA) axis: Patients with depression were found to have aberrant HPA axis stimulation[12]. Glucocorticoid levels in the brain rise chronically as a result of emotional stress's long-term stimulation of the HPA axis, which causes depression[13]. An imbalance in the HPA axis is linked to a reduction in glucocorticoid receptor (GR) activity, which in turn causes dysfunction in the central nervous system[14].

2.3 The neuroinflammation hypothesis: The development of depression is closely linked to stress-induced increases in the release of neurotransmitters and pro-inflammatory cytokines, such as interleukin (IL)1β, IL6, and tumor necrosis factor-α[15].

2.4 The neurotrophic theory: The neurotrophic theory states that elevated levels of brain-derived neurotrophic factor (BDNF) in the central nervous system are linked to the effectiveness of antidepressants, while decreased levels of BDNF were seen in the serum and postmortem brain tissue of individuals with depression[16]. The glutamate hypothesis, the epigenetic theory, and the circadian rhythm are further theories that have significant implications for depression and the impact of antidepressants[17].

III. CLINICALLY AVAILABLE ANTIDEPRESSANTS

3.1 Monoamine Oxidase Inhibitors

By preventing breakdown by monoamine oxidase A (MAO-A) and B (MAO-B), MAOIs raise the concentration of serotonin (5-HT or 5-hydroxytryptamine), norepinephrine, and dopamine at the synapses. The first MAOI to be used to treat depression was iproniazid [18]. Although it was first intended to treat tuberculosis, other benefits included elevated 5-HT, enhanced mood, and central nervous system (CNS) stimulation [19].

Iproniazid reduced the symptoms of atypical depression and demonstrated a recovery rate of 25% to 75% in patients with Depression [20]. Nevertheless, a high tyramine concentration, hypotension, and liver damage were the outcomes of non-selective and irreversible binding [21]. In the 1980s, selective and reversible inhibitors of monoamine oxidase A (RIMA) were developed to increase the safety and effectiveness of MAOIs. Moreover, first-generation MAOIs such as isocarboxazid, phenelzine, and tranylcypromine are still used for TRD [22] in combination with other antidepressants [23,24]. To reduce the risk of hypertension, patients taking these drugs should limit their intake of tyramine [25].

3.2 Tricyclic Antidepressants

TCAs also work to break down monoamine neurotransmitters, just like MAOIs [22]. Through the inhibition of reuptake transporters and the buildup of 5-HT and NET in the presynaptic cleft, TCAs desensitize 5-HT and NET presynaptic receptors, hence improving 5-HT and norepinephrine transporter (NET) activity. On top of that, TCAs have a number of adverse consequences [26] because they compete with postsynaptic histamine, adrenergic, and muscarinic receptors [22,23]. Doxepin (DXP), imipramine, and clomipramine (CLO) were among of the first TCAs to be manufactured [24,27]. There are benefits even though these medications work in a similar way. Postsynaptic histamine, adrenergic, and muscarinic receptor antagonistic interactions resulted in varying degrees of negative consequences, including sleepiness [28], pregnancy difficulties [29], and heart abnormalities such arrhythmia, myocardial infarction, and aberrant cardiac conduction.Because of the availability of more effective medicines like SSRIs or SNRIs, TCAs are no longer the first option for treating depression [30].

3.3 Selective Serotonin Reuptake Inhibitors

Researchers discovered that serotonin may have a part in depression in the 1960s [31]. SSRIs were developed as a result of the proposed treatment strategy of blocking serotonin reuptake to improve postsynaptic serotonin receptor activation. Several SSRIs with less side effects were licensed after fluoxetine, the first SSRI to receive FDA approval. From boosting serotonin in the synapses to boosting hippocampus neurogenesis, research on the mechanism of antidepressant effect has broadened [32,33,34]. Patients of all ages who suffer from depression are prescribed SSRIs as a first-line treatment due to their broad-spectrum efficacy and high tolerance. On the other hand, patients reported side effects such as gynecomastia [35], weight gain, gastrointestinal

distress [36], sexual dysfunction [37], headache, agitation, nausea, diarrhea, and sleeplessness [38].

3.4 Serotonin-Norepinephrine Reuptake Inhibitors

SNRIs block the reuptake of serotonin and norepinephrine, two key neurotransmitters implicated in depression. In 1993, the FDA authorized venlafaxine, the first SNRI ever created, and it was put on the market as a first-line treatment for depression in the USA [39]. The next ten years saw the approval of other SNRIs, including desvenlafaxine [40], duloxetine [41], levomilnacipran [42], and milnacipran [43]. The left insular cortex thickened when levomilnacipran was administered to adult patients with depression [44]. Although levomilnacipran and cortical thickness have been linked in prior clinical trials, the underlying mechanism of action has not been clarified.

Neuropathic pain may be treated with the SNRI duloxetine. Through its inhibition of p53 [45], p38 phosphorylation, and NF-κB activation [46], duloxetine reduced the nerve pain caused by chemotherapy. Clinical trials should investigate the ability of SNRIs to treat neuropathic pain diseases while preventing depressed symptoms in individuals with chronic pain, as these conditions are often associated with depressive disorders.
SNRI side effects are comparable to those of SSRIs and include fatigue, constipation, sleeplessness [47], and maybe dysregulation of certain metabolic processes linked to hyperglycemia [48,49]. Even though first-line treatments for Depression have been shown to be successful, many individuals do not respond well to them, which leads to a number of negative side effects and delayed efficacy [50].

3.5 Ketamine

The noncompetitive N-methyl-D-aspartate receptor (NMDAR) antagonist ketamine, a derivative of phencyclidine, was developed as an anesthetic in the 1960s.

The binding of both glutamate and glycine to their respective binding sites (NR1 and NR2 subunits, respectively) activates NMDARs, which are heteromeric ionotropic glutamatergic receptors. Magnesium ions block these receptors by attaching to the phencyclidine site. By binding to the phencyclidine site or non-selectively attaching to the NR2 site (A-D subunits), ketamine antagonistic action is therefore produced [51,52,53].

IV. POTENTIAL ANTIDEPRESSANTS TARGETTING BIOLOGICAL PROCESSES

Another strategy for creating antidepressant treatments is to focus on biological processes and broad pathways rather than individual receptors. Here, we concentrate on biological mechanisms including inflammation, the HPA axis, and gut microbiota that are known to have a role in the onset of depression.

4.1. Inflammation

Depressive disorders and inflammation are closely related. In addition to pro-inflammatory factors [54], such as TNF-α [55], C-reactive protein (CRP), IL-6, and interleukin-1 receptor antagonist (IL-1ra) [56], and an elevated immune response ,
Depression patients are more likely to have somatic and inflammatory disorders [57]. It is probable that patients who have undergone pro-inflammatory therapy for physical ailments would experience signs of depression [58]. Given the reciprocal association between inflammation and Depression, anti-inflammatory drugs may be used to treat depression.

4.2. Hypothalamic-Pituitary-Adrenal Axis

In the central nervous system, the primary neuroendocrine mechanism that mediates the stress response is the HPA axis [59]. In the positive feedback loop, prolonged stress may cause the HPA axis to become hyperactivated and increase the production of the hormone that releases corticotropins. This suggests that limiting the hyperactivation of the HPA axis is a crucial step in preventing depression brought on by stress [60].
The stress response is triggered by the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR), which in turn regulate the HPA axis. MRs are important for memory and executive function and are mostly expressed in the PFC and hippocampus [61].

4.3 Gut Microbiota

Numerous vital bodily functions, including as immunity and metabolism, have been linked to the symbiotic gut microbiota. A correlation between gut microbiota and depression has been discovered more

recently, with notable differences in gut microbiota between people with depression and those in good health [62].

CONCLUSION

A fundamental problem with insufficient pharmaceutical treatment is that the etiology of depression is not fully understood. Though it is clear that the biochemical pathways behind depression go beyond monoamines, first-line antidepressants mostly target the serotonin or norepinephrine system. Our review highlights the diverse mechanisms and bological targeting processes of these novel agents including neurotransmitter modulation and neuroinflammation. Identifying genetic or epigenetic risk factors and clarifying the mechanisms causing resilience or depression susceptibility should be the top priorities for research efforts in order to create novel therapies. This conclusion summarizes the main points of the review, highlights the significance of the novel antidepressant agents, and provides a future perspective on the development of personalized treatment approaches.

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