Glutamatergic Synapse: A Promising Target to Treat Major Depressive Disorder (MDD)

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ABSTRACT

After few decades, mono-amine hypothesis could grab the attention of millions with the captivating evidence that, prevailing changes in the areas of brain with complex networks of cognitive and emotional behaviors for long time witnessing mood and anxiety disorders. Major Depressive Disorder (MDD) encompasses a large number of psychological illness include, loss of interest, mood disturbance, loss of appetite, insomnia, feeling of fatigue and decreased concentration and standing as the major illness worldwide. Later on, a wealth of data from experimental models started exploring on the environmental factors enhancing the stress which enhances some powerful exerts and induces limbic remodeling or the reduction of synapses pivoted by “Glutamatergic Synapse”. As the majority of neurons in the brain circuits use glutamate as neurotransmitter, it should be recognized that the glutamatergic system is the primary key for the pathophysiology, potentially addressing the therapeutic action of antidepressant drugs.

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A radical shift from the monoamine hypothesis to neuroplasticity hypothesis supported by glutamate signaling visualizes a considerable advancement in the technology, which drives to look into new hypothesis and therapies. Our work, displays an extensive analysis of Glutamate signaling pathway and the enthralling genes involved in it. In addition, the role of glutamate receptors and the inhibitory pathway GABA was elucidated for the convoluting cause of MDD. We propose a hypothesis to bridge the gap between the failure of existing drug therapies based on mono amine theory and the discovery of biomarker based on the glutamate signaling to bring out novel advancements in the pharmacology for the treatment of MDD.

Keywords: Mono amine hypothesis, Glutamatergic synapse, neuroplasticity, MDD, GABA,.

INTRODUCTION

Depression is an extensive chronic medical illness that can affect thoughts, mood, and physical health. It is characterized by disturbing mood, lack of endurance, anxiety, sadness, insomnia, and an inability to enjoy life. However a lot of displeased outcomes were observed by the patients diagnosed with depression. It is a common cause of death and morbidity, but the biological bases of the insufficiencies in emotional and intellectual processing remain incompletely understood. Current antidepressant therapies are effective in only some patients and act slowly**.** Stress and depression are associated with neuronal atrophy, characterized by loss of synaptic connections in key cortical and limbic brain regions implicated in depression. This is thought to occur in part via decreased expression and function of growth factors, such as brain-derived neurotrophic factor (BDNF), in the prefrontal cortex (PFC) and hippocampus [1].

Major Depressive Disorder (MDD):

Major depressive disorder (MDD) is a severe, debilitating medical illness that affects millions of individuals worldwide. This mental disorder is caused by the combination of genetic, environmental, and psychological factors. A total of 16.6% of the U.S. population and 350 million people worldwide have been victimized under this disorder which further, is a growing problem. It was originally predicted by World Health Organization (WHO), that this will be the second leading cause of disability worldwide by 2020 [2].

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Due to the worldwide impact of MDD, it is important to understand this disease in a greater extent. Recent studies have largely focused on identifying mechanisms and cellular targets that may explain the etiology of MDD and provide novel substrates for development of more effective and faster-acting therapeutic agents. The hippocampus shows a high degree of functional and structural plasticity in response to many types of stimuli including stress [3]. The hippocampus is considered as one of the main limbic structure concerned with the MDD. Brain imaging and post-mortem studies provide evidence of changes in cellular building and/or morphology within this brain region, including decrease in hippocampal volume in MDD patients, deterioration of hippocampal pyramidal neurons and decreased neuropil.

Preclinical studies show that exposure to either acute or chronic stressor decreases adult neurogenesis in the sub granular zone of dentate gyrus (DG) and causes atrophy of dendritic structures of pyramidal neurons [4]. The ratio of occurrence of MDD in adult men and women is approximately 1:2. Medical proof supports a shielding effect of androgens against depressive disorders. Decreased level of androgen in adult men is associated with increase in dominance of depressive disorders, and improvement appears in the hypo gonadal male patients when they are subjected to androgen replacement therapy [5]. Although most glutamate-related modifications seem to be brain region-dependent and to some extent unpredictable, but there is an outcome which shows the down regulation of glial glutamate transporters in a very consistent manner. These membrane proteins are situated mainly in the astrocytes surrounding the synaptic cleft and establish a pivotal element on the regulation of glutamatergic neurotransmission. Moreover, the reports concerning with the down regulation of glutamate transporters in MDD indicate that other components of the glial compartment may be compromised as well [6].

Over the years, a number of genes have been identified which are associated with MDD. However, in many cases, the role of these genes and their relationship in the origin and development of MDD remains uncertain. Under these conditions, the systems biology focuses on the function correlation and interaction of the candidate genes in the framework of MDD which will provide useful information on discovering the molecular mechanisms in relation to the disease [7].

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Present pharmacological treatments for MDD are often insufficient for many patients, the next generation of treatments needs to be more effective, rapid acting and better tolerated than currently available medications. Proven evidences are there that shows, the glutamatergic system holds potential in developing the next generation of novel and mechanistically distinct agents for the treatment of MDD [8].

Biomarker for MDD:

A biomarker is a characteristic feature that can be extensively used for the identification or creating differences between the normal and pathogenic process. A biomarker for MDD can be used for diagnosis, forecasting causes which may be environmental or genetic, identification of those factors which are at risk on major extant, and development of the next generation treatments. Structural and diffusion-weighted magnetic resonance imaging (MRI) are the type of Neuro- imaging techniques are thought to be the biomarkers for the MDD. In structural MRI (sMRI), a comparison was made between the depressed person and a healthy individual. There are other imaging techniques like fMRI and phMRI which broadens the understanding of glutamate site of

action mechanisms, treatments and effects. These two techniques are governed by the change in the amount of blood oxygenation level–dependent (BOLD) signal. A variant of magnetic resonance techniques, named magnetic resonance spectroscopy (^{1}H MRS) is also considered to assess the functioning of brain chemistry. At low concentration Glutamate and Glutamine are also detectable by MRS. A non-invasive nuclear medicine imaging technique named Positron emission tomography (PET) is also acceptable to study the CNS functioning. Due to its slower temporal resolution and low spatial resolution (2–6 mm) it is less effective. To improve this limitation, PET can be combined with other imaging techniques and built into the same machinery, for example single photon emission computed tomography (SPECT), which provides 3-D images that can be used, among other peculiarities [9].

Some studies showed common volumetric differences in cortical gray matter regions. In a person with MDD it is frequently observed that several regions of the brain including hippocampus, basal ganglia, orbitofrontal cortex, and prefrontal cortex have smaller volumes.

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Due to increase in advancement in neurobiology here we are aiming to indicate the genetic, molecular, and neuroimaging studies that are significant for assessment and treatment selection of this disorder. In 1990s, the glutamate hypothesis of depression was proposed, when antagonists of the N-methyl- D-aspartate (NMDA) receptor (an ionotropic glutamate receptor), were reported to shows anti- depressant like behavior of action in mice. Variations in glutamatergic neurotransmission are associated with the pathophysiology of depression, and the glutamatergic system represents a treatment target for depression [10]. Therefore, we conducted a systematic review and meta- analysis to compare the levels of specific regional glutamatergic neuro metabolites in a comprehensive fashion, including the most recent studies on the topic.

GENES OF GLUTAMATE SYNAPSE ENRICHING MDD

Glutamate is the powerful excitatory neurotransmitter in the central nervous system (CNS) of mammals. Glutamate is majorly fundamental to brain bioenergetics and metabolism. Glutamate is derived from both neuronal / glial pathways and as well as Tricarboxylic acid cycle (TCA) [11]. Glutamate signalling starts with the production of glutamate in the cytoplasm of glutamatergic neurons. Thereafter, this glutamate is pumped into synaptic vesicles of the neuron terminals. Once the informative signalling pathway passes from other neurons, it leads to the stimulatory action and induces the various signalling pathways along with glutamate pathway. This increases the levels of glutamate in the synaptic cleft and later on detected by glutamate receptors. EAATs remove the further accumulation of glutamate in the regions of synaptic cleft. A set of genes (ADCY3, ADCY9, GRIK, etc.,) were identified which are involved in the glutamate signalling pathway from the inception of glutamate synthesis in the cytoplasm of neurons till the release into the synaptic cleft [12]. Their respective location was mentioned in the tabular format to elucidate the importance of each gene.

A comprehensive map was generated using a data visualisation tool to demonstrate the synapse pathway of glutamate and its interaction with genes. Genes play a major role in the regulation of pathways by regulating its function and signaling roles. Cell designer is a software based data visualization tool to bridge the gap between the raw data. It gives a detailed, comprehensive, easily consumable map.

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It is structural diagram editor to draw biological networks and gene-regulatory mechanisms. Networks are designed using graphical notation and are stored in the database using Systems Biological Markup Language (SMBL). These networks are able to link with simulation and analysis packages using Systems Biological Workbench (SBW). Using this Cell Designer, one can browse and modify existing SBML models with references to existing databases, simulate and view the dynamics through an intuitive graphical interface.

The constructive insight from various research papers were taken from using resources like, PubMed, NCBI, Google Scholar etc., to obtain a set of promising information for the further analysis of this meaningful study. The list of important genes were taken to construct the diagrammatic part of the respective study, which brought up the detailed correlations between the genes and the signaling pathway molecules. Also, this study piqued our interest to look towards the direction of the underlying ineffectiveness of inbuilt various other signaling pathways in combating with such neuro-psychiatric disorders.

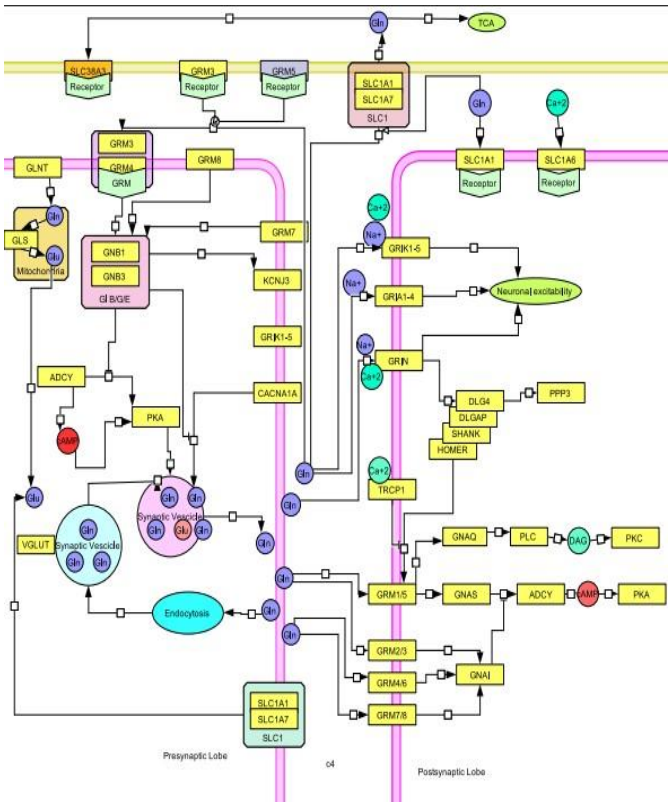

Fig 1.1 A comprehensive map of Gene interactions in Glutamate synapse

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S. No	GENESYMBOL	GENE NAME	LOCATION	EXPRESSION
1.	ADCY3	Adenylate cyclase 3	2p23.3	Ubiquitous expression in placenta and ovary
2.	ADCY9	adenylate cyclase 9	16p13.3	Ubiquitous expression in thyroid, lung
3.	ADCY6	adenylate cyclase 6	12q13.12	Ubiquitous expression in fat, heart
4.	ITPR1	inositol 1,4,5-trisphosphate receptor type 1	3p26.1	Ubiquitous expression in thyroid, brain
5.	PLD1	phospholipase D1	3q26.31	Ubiquitous expression in gall bladder, duodenum
6.	GNB1	G protein subunit beta 1	1p36.33	Ubiquitous expression in brain, small intestine
7.	GNB3	G protein subunit beta 3	12p13.31	Ubiquitous expression in ovary, heart
8.	HOMER1	homer scaffold protein 1	5q14.1	Broad expression in brain, thyroid.
9.	CACNA1A	calcium voltage-gated channel subunit alpha1 A	19p13.13	Biased expression in brain, stomach
10.	CACNA1C	calcium voltage-gated channel subunit alpha1 C	12p13.33	Broad expression in endometrium, heart
11.	CACNA1D	calcium voltage-gated channel subunit alpha1 D	3p21.1	Broad expression in adrenal gland, lung
12.	GRIA1	glutamate ionotropic receptor AMPA type subunit 1	5q33.2	Biased expression in brain and lung

13.	GRIA2	glutamate ionotropic receptor AMPA type subunit 2	4q32.1	Restricted expression towards brain
14.	GRIA4	glutamate ionotropic receptor AMPA type subunit 4	11q22.3	Biased expression in brain, adrenal gland
15.	GRIK1	glutamate ionotropic receptor kainate type subunit 1	21q21.3	Biased expression in adrenal gland, brain
16.	GRIK4	glutamate ionotropic receptor kainate type subunit 4	11q23.3	Biased expression in brain, ovary
17.	GRIN2A	glutamate ionotropic	16p13.2	Biased expression in brain, heart

Table1.1: List of Genes involved in Glutamate Signaling

RECEPTORS INVOLVED IN GLUTAMATE SIGNALLING

Then Glutamate is transported by vesicular glutamate transporters (vGLuTs) after packaged into synaptic vesicles. Being an excitatory neurotransmitter glutamate can excite nerve cells to their death by process called “excitotoixicity “. Glutamate has two broad classes of receptors: ionotropic receptor and metabotropic receptor [11]. Glutamate and its receptor play an important role in pathophysiology of major depression disorder (MDD). The detailed classification as follows:

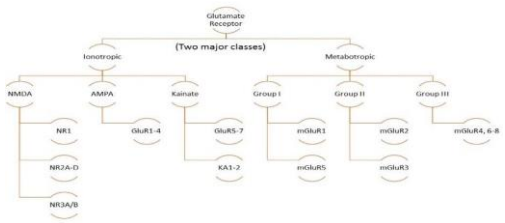

Fig 1.2: Glutamate receptors

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Two major classes of Glutamate receptor: ionotropic receptor and metabotropic receptor. Further ionotropic receptor is divided into three subclasses: 1) NMDA 2) AMPA 3) kainate. Ionotropic receptors leads to influx of ions like calcium ions and sodium ions. Metabotropic receptor is further classified into three subclasses: 1) Group I 2) Group II 3) Group III. Metabotropic receptors belongs to family of G – protein coupled receptors (GPCRs).

Release of Glutamate into synaptic cleft leads to influx of calcium ions [13].The Glutamate then binds to cognate receptors on Postsynaptic membrane. Ionotropic receptors leads to influx of calcium ions and sodium ions from extracellular space. Ionotropic receptors have three major subclasses: a) NMDA b) AMPA c) kainate. NMDA receptor have subunits: NR1, NR2A-D, NR3A/B and NMDA receptor form heterotetramic complexes and shown high calcium permeability. Activation of synaptic NMDA receptors promotes cell survival, On the other hand, overstimulation of extra synaptic NMDA receptors due to increased Glutamate induce cellular death [14].AMPA receptor has subunit : GluR1-4 and AMPA receptor forms heterotetramic complex and has low to moderate calcium permeability. Kainate have subunits: GluR5-7, KA1-2 and kainate receptor forms homotetrameric or heterotetramic complex and shown low calcium permeability. Metabotropic receptors belongs to family of G protein coupled receptor and have three subclasses: Group l, Group ll and Group III. Group I metabotropic receptor have two subunits- mGluR1, mGluR5 and Group I metabotropic receptor establish homodimeric complex and located post-synaptically. Group II metabotropic receptor have two subunits: mGluR2, mGluR3 and Group II metabotropic receptor forms homodimeric complex and located mainly pre-synaptically and Group III metabotropic receptor has subunits: mGluR4, 6-8 and Group III receptors forms homodimeric complex and located mostly pre-synaptically. Activation of NMDA receptor leads to delayed and longed excitation with the help of calcium ion influx. AMPA / kainate receptor activates due to sodium ion influx.

Pathophysiology of glutamate receptors in MDD: Alterations in Glutamate level in brain tissue, plasma, serum, Cerebrospinal fluid and alterations in activities of Glutamate receptors plays an important role in pathophysiology of various mood disorders and major depression disorder. Findings of many studies have shown the increased Glutamate level in plasma of depressed patients compared to control ones [15].

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Depressed patients have elevated Glutamate level in plasma [16]. Recent study revealed the elevation of Glutamate levels of postmortem dorsolateral

prefrontal cortex tissue in bipolar individuals [17]. Activation of extra synaptic NMDA receptors leads to cell death or cellular toxicity [18]. These studies have shown the alterations in Glutamate level and activities of Glutamate receptors linked with pathophysiology of major depression disorder.

Currently available medications based on monoamine hypothesis alleviate symptoms of depression but many patients do not fully respond and many take several weeks and many trials to achieve response, and monoamine hypothesis have limited understanding of pathophysiology of depression. Alterations of Glutamate level in brain tissue, plasma, serum and cerebrospinal fluid and alterations in activities of Glutamate receptors in depressed patients acts as biomarker of depression and provides complete understanding of pathophysiology of major depression disorder.

POTENT INHIBITOR OF GLUTAMATE SYNAPSE – GABA

GABA: Gamma immune butyric acid is the most prevalent inhibitory neural transmitter in central nervous system of human body. GABA is generated from glutamine, a vital amino acid in the brain. There is a promising evidence that the inhibitory GABA and excitatory glutamate system are necessary for sufficient response to stress [19]. The Hypothalamus, pituitary and adrenal axis activity is modulated by GABAergic and glutamatergic brain circuits. In case of anxiety, overactive fear circuits are centered on the amygdala (fear center). GABA neurons gets connected to amygdala, which is called synapse. The brain has an elaborate structure designed to isolate and protect it against invading toxins, chemicals and potentially harmful substances. This mechanism of self-protection is called the blood-brain barrier [20]. GABA is inhibitory, when GABA is released and binds to the post synaptic receptors, it inhibits the amygdala and slows down the hyperactivity of amygdala and reduce anxiety. According to studies, GABA shortage may be embraced in mood disorders like depression and by increasing the synapse that uses GABA as its neurotransmitter, neurotransmission may use an antidepressant effect and a mood stabilizing effect [19,20].

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Pathway

GABA gets associated with the amygdala and communicates via the synapse. In GABA neuron, there are GABA neurotransmitters in the vesicles. These vesicles release their contents into the synapse and binds to the receptors which opens up an ion channel and lets chloride ion to enter into it. This inhibits the neurotransmission post synaptically and therefore reduces hyperactivity of amygdala. GABA is reabsorbed and recycled by Gamma ray uptake pump such as serotonin uptake pump [21]. There are also some oral supplements when you take it, they block the reuptake of GABA and thereby increases the GABA concentration in the synaptic pathway and therefore more binding and opening which increases the inhibition and decrease in anxiety [22]. GABA on a concluding note acts as a balancing tool of brain's synaptic system.

For restoring the equilibrium after shrewd or acute stress, GABAergic and glutamatergic neurotransmission is crucial [23]. The synaptic receptors are saturated by GABA once it gets released from the synaptic vesicle and it activates them within 1 millisecond. In stress situations, the GABA levels in the plasma and CSF is increased. The GABA receptor functioning gets affected by the stressors. GABA level directly influences the severity of depression [24]. The timings of synaptic inhibition is controlled by $GABA_A$ receptor subunits. There is low level of GABA receptor subunits in the suicidal MDD brains. MDD, being a biochemically heterogenous illness in which CRH, 5-HT and GABA act together to influence depressive disorders. GABA processes may be therapeutically affected by SSRI treatments. The association pathway of GABA and Glutamate in the complex brain circuits are explained below:

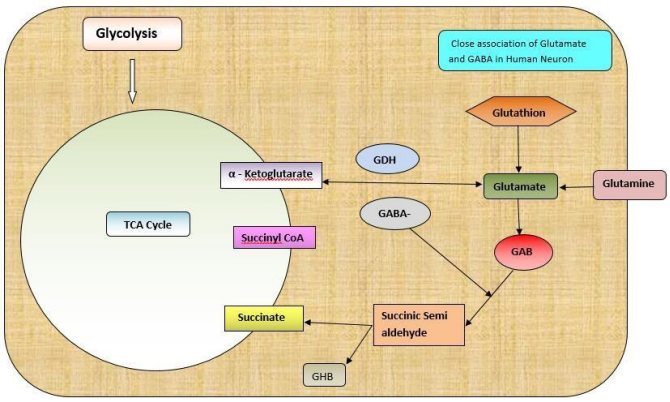

Fig1.3: Close associations of GABA and Glutamate in Neurons of Human

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DRUG THERAPY

For the treatment of major depressive disorders, monoaminergic-targeted drugs have prompted great advances in the development. Most of the patients do not respond to the drugs properly as they have delayed clinical effect [25]. In the research of the neurobiology of depression, Ketamine played the role of introductory agent. The Ketamine brought the new wave of studies regarding the development of new and more effective antidepressant drugs and comprehension of the neurobiology of the depression. The different targets of glutamatergic system and neurobiological pathways are confirmed by Ketamine. The ketamine produces a remarkable rapid onset antidepressant effect hours or days in contrast to the delayed onset of current antidepressant drugs is confirmed by abundant clinical data. For the treatment of depressive illness, the discovery of ketamine's rapid onset antidepressant effect is a game changer [26].

Ketamine: -

Ketamine is N-Methyl-D-Aspartate receptor and is known to rapidly reduce suicidal ideation (SI) and depressive symptoms in patients with major depressive disorder. It exerts antidepressant effects and enhances descending inhibiting serotoninergic pathways. It is a racemic mixture comprising of (S)-Ketamine or (esketamine) and (R)-Ketamine or (arketamine). (S)-Ketamine has higher affinity for N-Methyl-D-Aspartate than (R)-Ketamine, so Esketamine was developed as an antidepressant. It was approved by Food and drug administration on 5th March 2019 [27].

Structure: -

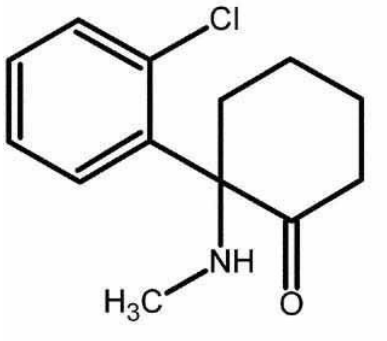

Fig1.4: Structure of Ketamine ($C_{13}H_{16}ClNO$**)**

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Pharmacodynamics

Ketamine rapidly reduces the depression and suicidal thoughts within 1 day and up to 1 week significantly on clinician administration. Numerous routes of administration has been investigated. For the ease of use and high accessibility, the oral ketamine is being administered. Intravenous

(IV) has rapid antidepressant effects but poor accessibility of route IV [28]. Intravenous routes are most commonly employed but the safety and efficacy have been described by the other routes of administration i.e. oral, intranasal, subcutaneous, sublingual and intramuscular routes. Ketamine is mostly administered in the dose of 0.5 mg/kg. Some patients who respond to the low doses may require 0.1 mg/kg dose. The safety and the efficacy of ketamine dose have been demonstrated in the sessions ranging between 2 to 100 minutes but it is conventionally administered across 40 minutes [29]

Mechanism of action

Ketamine as an antidepressant includes synaptic or GluN2B- selective extra – synaptic N-Methyl- D-Aspartate receptor (NMDAR) inhibition, inhibition of NMDAR – dependent burst firing of lateral habenula neurons, inhibition of NMDARs localized on GABAergic interneurons and the role of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor. Ketamine's downstream mechanisms regulates the synaptic plasticity, including brain derived neurotrophic factor (BDNF), mechanistic target of rapamycin (mTOR), glycogen synthase kinase-3 (GSK-3) and eukaryotic elongation factor 2(eEF2). The ketamine's (R)-ketamine enantiomer and hydroxynorketamine (HNK) metabolites, (2R,6R)-HNK does not involve the mechanisms of direct inhibition of the NMDAR. The ketamine's action may act in the complementary manner to exert acute changes in synaptic plasticity, leading to the strengthening of excitatory synapses, which are necessary for antidepressant behavioral actions [30].

Absorption and role of elimination

The absorption of ketamine is very rapid and the bioavailability is 93%. Only 17% of administered drug is absorbed after the first pass of the metabolism. It presents the distribution half life of 1.95 minutes. The levels of the Cmax reach at the peak of 0.75mcg/ml in plasma and 0.2 mcg/ml in the cerebrospinal fluid.

Pharmacokinetic studies have resulted in 85-95% of the administered dose in the urine is recovered in the form of metabolites. The other routes of elimination of ketamine are bile and faeces. The resultant recovery is distributed by 91% of the administered dose in urine and 3% in the faeces, when the drug is administered intravenously.

Being a chronic condition that affects 5.1% of men and 8.1% of women during their life time, 121 million people around the world currently suffer from major depressive disorder. Over a third of the patients suffering from major depressive disorder fail to respond to two or more antidepressant treatments [31]. There are lot many drugs related to major depressive disorder like Fluoxetine, Citalopram, Sertraline, Ketamine, Dextromethorphan but all of these are not related to glutamatergic pathway except Ketamine. For the treatment of MDD, the glutamatergic system has emerged as a novel pathway with the focus on producing both rapid and sustained antidepressant effects. Dextromethorphan is considered as noncompetitive N-Methyl-D-Aspartate receptor antagonist that have antidepressant like effects. The rapid and sustained antidepressant like effects have not been evaluated [32]. The research is going on to the development of easy to administer drug given to NMDAR antagonists without the risk of brain toxicity and which is related to glutamatergic system.

CONCLUDING REMARKS

MDD is a severe psychiatric illness that affects the lives and functioning of millions of people worldwide. Compelling evidence suggests that, cellular resilience and neuroplasticity take part in the expression of affective illness [33]. This provides a credible role for implicating glutamatergic system dysregulation in the pathophysiology of MDD. The reviewed data here explains that, MDD is associated with abnormal functioning of the glutamatergic synapse and it’s signaling. A continued collaboration between preclinical studies and clinical study can fetch good results to omit the extent of these abnormalities.

A decent clinical study added with brain imaging report analysis targeting glutamatergic synapse of reasonable sampling sizes paves way to lead this review to promising research finding. The role of ketamine, targeting glutamate pathway in the treatment of MDD leads to the new revolution in the pharmacodynamics and the mode of action of the drugs.

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