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Role of calcium, glutamate and NMDA in major depression and therapeutic application

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ABSTRACT

Major depression is a common, recurrent mental illness that affects millions of people worldwide. Recently, a unique fast neuroprotective and antidepressant treatment effect has been observed by ketamine, which acts via the glutamatergic system. Hence, a steady accumulation of evidence supporting a role for the excitatory amino acid neurotransmitter (EAA) glutamate in the treatment of depression has been observed in the last years. Emerging evidence indicates that *N*-methyl-D-aspartate (NMDA), group 1 metabotropic glutamate receptor antagonists and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) agonists have antidepressant properties. Indeed, treatment with NMDA receptor antagonists has shown the ability to sprout new synaptic connections and reverse stress-induced neuronal changes. Based on glutamatergic signaling, a number of therapeutic drugs might gain interest in the future. Several compounds such as ketamine, memantine, amantadine, tianeptine, pioglitazone, riluzole, lamotrigine, AZD6765, magnesium, zinc, guanosine, adenosine aniracetam, traxoprodil (CP-101,606), MK-0657, GLYX-13, NRX-1047, Ro25-6981, LY392098, LY341495, D-cycloserine, D-serine, dextromethorphan, sarcosine, scopolamine, pomaglumetad methionil, LY2140023, LY404039, MGS0039, MPEP, 1-aminocyclopropanecarboxylic acid, all of which target this system, have already been brought up, some of them recently. Drugs targeting the glutamatergic system might open up a promising new territory for the development of drugs to meet the needs of patients with major depression.

1. Background

Depression presents with loss of interest, depressed mood, loss of drive and pleasure, feelings of guilt, poor concentration, low self-esteem, sleep disturbances and increased or decreased appetite. Depression can become chronic or recurrent and lead to substantial impairments in an individual's ability to take care of his or her everyday responsibilities. At its worst, depression can lead to suicide, a tragic fatality associated with the loss of about 850,000 lives every year. According to the World Health Organization, depression is the leading cause of disability as measured by disability adjusted live years. In this paper, an attempt is made to overview a glutamatergic concept of the disease and search for perspectives on antidepressant treatment strategies based on glutamatergic neurotransmission.

A paradigm shift from a monoamine hypothesis of depression to a neuroplasticity hypothesis represents a substantial advancement in the working hypothesis that drives research for new therapies of depressive patients. Stress and depression are associated with neuronal atrophy and decreased synaptic connections in the prefrontal cortex, limbic brain regions and hippocampus. Normally, synapses of glutamate terminals are maintained and regulated by circuit activity and function, including activity-dependent release of brain-derived neurotrophic factor (BDNF) and downstream signaling pathways. Stress leads to decreased expression and release of BDNF as well as increased levels of adrenal glucocorticoids. These stress-induced effects are comparable with long-term depression.

Accumulating evidence suggests that the glutamatergic system plays an important role in this process and in the neurobiology and treatment of depression. Excitatory amino acid (EAA) and monoamine neurotransmission are extensively colocalized in brain nuclei relevant for depressive psychopathology such as the locus caeruleus and dorsal raphe. Rapid-acting antidepressants, notably ketamine, cause a burst of glutamate resulting in an increase in synaptogenesis that has been compared with long-term potentiation. The increase in glutamate is thought to occur via blockade of *N*-methyl-D-aspartate (NMDA)

Abbreviations: N-methyl-D-aspartate, (NMDA); gamma-aminobutyric acid, (GABA); brain-derived neurotrophic factor, (BDNF); excitatory amino acid transporters, (EAAT); long-term potentiation, (LTP); calmodulin-dependent protein kinase II, (CaMKII); glycogen synthase kinase, (GSK3); phosphoinositol-dependent kinase 3, (PI3K); NMDA receptor subtype 2B, (NR2B).

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receptors located on inhibitory gamma-aminobutyric acid (GABA)-ergic neurons, resulting in disinhibition of glutamate transmission. The burst of glutamate increases BDNF release and causes the synthesis of synaptic proteins required for new spine synapse formation. These new connections allow for proper circuit activity and normal control of mood and emotion. Indeed, the non-competitive NMDA receptor antagonist ketamine and other glutamatergic drugs are considered as one of the most attractive candidates for an innovative fast antidepressant treatment (Fig. 1).

2. Glutamate

Glutamate is the primary excitatory neurotransmitter in the brain (Kornmeier and Sosic-Vasic, 2012). Glutamate is found in substantially higher concentrations than monoamines and in more than 80% of neurons, cementing its role as a major excitatory synaptic neurotransmitter. Accumulating evidence shows that glutamate plays a key role in regulating neuroplasticity, learning and memory. Indeed, the balance of glutamate with the major inhibitory neurotransmitter GABA is essential for the physiological homeostasis in the CNS (Sanacora et al., 2008). It has been indicated that glutamatergic neurons and synapses by far outnumber all other neurotransmitter systems in the brain with the only exception of the GABAergic system (Sanacora et al., 2012). Whereas glutamate is necessary for the normal development of dendritic branching, excessive glutamatergic neurotransmission, however, causes dendritic retraction and loss of spines. These changes would effectively limit the number of exposed glutamate receptors and as a result, drugs thought to reduce glutamatergic neurotransmission may prevent dendritic retraction and protect brain synapses.

Moreover, studies observed abnormalities of the glutamate clearance at the synaptic space and a modulation of astrocytic energy metabolism involving glutamate (John et al., 2012). In this context, significant differences in the methylation patterns specific to astrocytic dysfunction associated with depressive psychopathology have been published recently (Nagy et al., 2014).

Changes in glutamate levels have been noted in plasma (Küçükibrahimoğlu et al., 2009; Mitani et al., 2006), cerebrospinal fluid (Frye et al., 2007; Levine et al., 2000) and brain tissue (Hashimoto et al., 2007) of individuals with mood disorders, as well as in suicide victims (Bernstein et al., 2013). A recent review of the magnetic resonance spectroscopy (MRS) literature in mood disorders found reduced glutamate and glutamine levels in the anterior cingulate cortex, left dorsolateral prefrontal cortex, dorsomedial prefrontal cortex, ventromedial prefrontal cortex, amygdala and hippocampus of major depressive patients (Jun et al., 2007). The deficits of glutamatergic metabolism have been found to be related to the aberrant neuronal activation patterns of the anterior cingulum in depression (Walter et al., 2009).

In bipolar patients, glutamate and glutamine levels have been found elevated in the grey matter areas of the anterior cingulate cortex, medial prefrontal cortex, dorsolateral prefrontal cortex, parieto-occipital cortex, occipital cortex, insula and hippocampus (Jun et al., 2007).

3. The glutamate–glutamine cycle

Glutamate is readily formed in neurons from glutamine synthesized in astrocytes, released into the extracellular space and taken up by neurons (McKenna, 2007). However, the glutamate–glutamine cycle is not a stoichiometric cycle but rather an open pathway that interfaces with many other metabolic pathways to varying extents depending on cellular requirements and priorities (McKenna, 2007). Multiple subcellular compartments of glutamate are located within both neurons and astrocytes, and glutamate can be derived from other amino acids and many energy substrates, including glucose, lactate and 3-hydroxybutyrate (McKenna, 2007). A disruption of glutamate–glutamine cycle significantly impacts on suicidal behavior (Bernstein et al., 2013).

4. Glutamate receptors

Glutamate acts on three key cell compartments: presynaptic neurons, postsynaptic neurons and glia. This “tripartite glutamatergic synapse” functions in the uptake, release and inactivation of glutamate. Glutamate is cleared from the extracellular space by high-affinity excitatory amino acid transporters (EAATs), which are located on neighboring glial cells

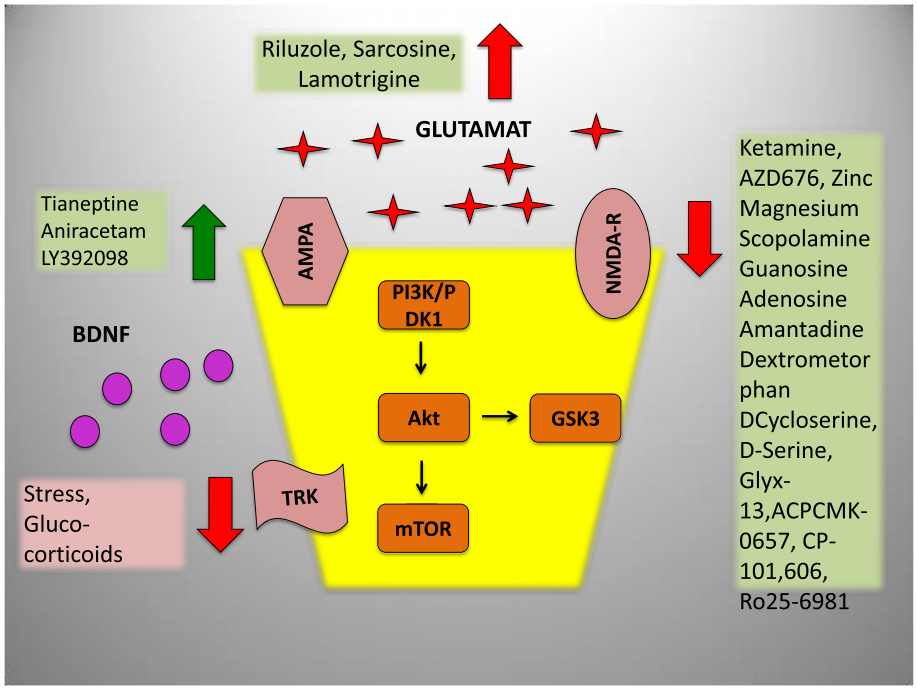

Fig. 1. Different medications targeting the glutamatergic system and their postulated mechanism via AMPA and NMDA receptor and on intracellular relevant signaling cascades.