Glutamate: The Master Neurotransmitter and Its Implications in Chronic Stress and Mood Disorders

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This brief review article makes the argument that glutamate is deserving of its well-established attention within the neuroscience literature and that many directions of important research have yet to be explored. Glutamate is an excitatory neurotransmitter with several types of receptors found throughout the central nervous system (CNS), and its metabolism is important to maintaining optimal levels within the extracellular space. As such, it is important to memory, cognition, and mood regulation. The mechanisms by which chronic stress and mood disorders affect the glutamatergic system and neuroplasticity are outlined. Several implications for potential pharmacologic and non-pharmacologic interventions are discussed.

Keywords: glutamate, neuroplasticity, GABA, NMDA—receptor, long-term potentiation

THE POPULARITY OF GLUTAMATE

Until early 1980s (Fonnum, 1984) glutamate has often been mentioned only as a sidenote to the more well-known neurotransmitters such as serotonin and norepinephrine. Like the shy kid who suddenly became visible with a new haircut, glutamate has taken the neuroscience literature by storm. This brief review article will explain why glutamate is deserving of this newfound attention and may well be the master neurotransmitter responsible for shaping the entire brain.

FUNCTIONS AND MECHANISMS OF GLUTAMATE

Storage and Transmission

Over the past three decades, researchers have learned that glutamate is the major excitatory neurotransmitter of the healthy mammalian brain, as the most profuse free amino acid that happens to sit at the intersection between several metabolic pathways (Watkins and Jane, 2006; Zhou and Danbolt, 2014). Glutamate is stored in synaptic vesicles of nerve terminals until it is released by exocytosis into the extracellular fluid, where it can quickly become highly concentrated (Zhou and Danbolt, 2014). Additionally, micromolar concentrations of basal extracellular glutamate, originating from non-vesicular release from the cystine-glutamate antiporter, continue to circulate in the space outside the synaptic cleft (Baker et al., 2002). Maintaining optimal levels in this space is essential, as low levels can deplete energy whereas excess levels can lead to cell death (Zhou and Danbolt, 2014).
Astrocytes play a major role in facilitating excess glutamate removal from extracellular space which is re-uptaken by glutamate transporters (Mahmoud et al., 2019) while receptor proteins at the surface of cells detect glutamate in the extracellular fluid and receive it (Zhou and Danbolt, 2014).

Most cells in the central nervous system (CNS) express at least one type of glutamate receptor. These include the ionotropic N-methyl-D-aspartate (NMDA), AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid), and kainate receptors, which mediate fast excitatory transmission; this in addition to the family of eight metabotropic glutamate receptors (mGluR1-8), which are located pre-, post-, and extrasynaptically throughout the CNS (Watkins and Jane, 2006; Reznikov et al., 2011; Zhou and Danbolt, 2014). The complex and widespread mechanisms of transmission means that there is almost unlimited potential for research on each class of glutamate receptors (i.e., ionotropic and metabotropic) and their subunits (Watkins and Jane, 2006; Traynelis et al., 2010; Niciu et al., 2012).

Neuroplasticity

As a neurostimulator, there is strong support for a role for glutamate in a variety of neuroplasticity mechanisms including long-term potentiation (LTP), long-term depression (LTD), regulation of spine density, and synaptic reorganization (Reznikov et al., 2011; Lüscher and Malenka, 2012). As a result, glutamate is now known to be exceptionally important in cognition, learning and mood, all areas in which neuroplasticity is essential to adapting to environmental stressors (Reznikov et al., 2011). LTP in several structures of the CNS employs NMDA and AMPA glutamate receptors to strengthen synaptic connections, necessary for learning and memory (Lynch, 2004; Sah et al., 2008). Morphologic adaptation is necessary for the regulation of mood and cognition (Reznikov et al., 2011).

However, chronic stress can lead to malfunctioning of the glutamate system and reduced neuroplasticity. In the hippocampus, chronic stress leads to increased glutamate release, impaired LTP, atrophy of the apical dendrites, and learning and memory deficits (Reznikov et al., 2011). In the prefrontal cortex, chronic stress leads to decreased glutamate release, impaired LTP, reduced dendritic spines, and impaired attention (Reznikov et al., 2011). In the amygdala, chronic stress leads to decreased glutamate release, impaired or enhanced LTP, dendritic hypertrophy, increased dendritic spines, and anxiety (Reznikov et al., 2011). Guo et al. (2020) have suggested that the negative impact of stress may be due to activation of the microglial cells, which trigger neuroinflammation, affecting both intracellular and extracellular signaling pathways. Furthermore, stress is also known to increase LTD while decreasing LTP (Wong et al., 2007; Reznikov et al., 2011). In LTD every single area of glutamate expression from release to glial cells is altered (Sanacora et al., 2012) and this can also be seen at the level of blood levels. A meta-analysis from Inoshita et al. (2018) showed that blood glutamate levels were significantly higher in Major Depressive Disorder (MDD) patients than controls. Excessive amounts of glutamate linked to neurodegenerative diseases, cancers, and tumors expansion, were also found to increase production of microglial proinflammatory cytokines IL-6, TNF-α, IL-1β (Blaylock, 2013), leading to CNS inflammation and ultimately to loss of neuronal plasticity.

**PO tential for future treatment**

**Antidepressant Medications**

Glutamate system dysfunction has been implicated in several pre-clinical and clinical studies of mood disorders. MDD, a severe psychiatric disorder predicted number one mood disorder by 2030 by World Health Organisation WHO (Bains and Abdijadid, 2021) is characterized by consistent episodes of depression and anhedonia.

Glutamate reductions have been noted in several neural areas of patients with MDD (Arnone et al., 2015), while mixed results were found with bipolar disorder (BD) (Gigante et al., 2012; Chitty et al., 2013), a similarly severe psychiatric condition characterized by episodes of depressive moods alternating with periods of abnormally elevated moods (Li et al., 2019). Additionally, several glutamate related genes alterations (i.e., GRIA3, GRIK2, GRIK4, and GRM7) linked to AMPA and Kainate receptors have been implicated in mood disorders and suicide ideation (Sequeira et al., 2009; de Sousa et al., 2017). Several glutamatergic agents have been demonstrated to effectively decrease depressive symptoms in people with MDD and BD (Henter et al., 2018).

Among the most studied is ketamine, which rapidly achieves its antidepressant effects with long-lasting effects of a small dose in even treatment resistant MDD and BD (Kantrowitz et al., 2015; Newport et al., 2015; Mandal et al., 2019). Although the mechanisms of ketamine’s actions are still not understood, preclinical studies in mice suggest that its antidepressant effects may be produced by the metabolite (2R,6R)-hydroxynorketamine (HNK) that increases AMPA receptor activation (Zanos et al., 2016). Intravenous esketamine, an S(+) enantiomer of ketamine with a high affinity for NMDA receptors, was found to have a rapid and robust antidepressant effect within 2 h in several large randomized controlled trials (RCT) of people with MDD (Singh et al., 2016), and has now been approved within the US for intranasal administration for people with high risk of suicide (Henter et al., 2018). Also, results from a meta-analysis, with 10 trials included (Wilkinson et al., 2018) showed that one single infusion of IV Ketamine reduced suicidal ideation within 1 day.

Two NMDA receptor antagonists, specific for NR2B subunit, were recently tested for MDD. While CP-101,606 (traxoprodil) was effective but was halted due to cardiovascular toxicity, MK-0657 (CERC-301) had no significant side effects but had mixed outcomes (Henter et al., 2018). Rapastinel, a glycine analog and therefore a NMDA agonist, has shown high efficacy in clinical trials for MDD (Donello et al., 2019) as well as increased synaptic neuroplasticity detectable in only hours from administration (Preskorn et al., 2015; Moskal et al., 2017; Vassilescu et al., 2017; Donello et al., 2019). Despite its initial promising results, in 2019 the company Allergan announced that Rapastinel has failed to differentiate from placebo and has not been approved for...
the adjunctive treatment of MDD (AbbVie News Centre, 2019). Preliminary results show that sarcosine, a glycine transporter-I inhibitor that potentiates NMDA function, was more effective than citalopram, with no significant side effects (Huang et al., 2013). 4-CI-KYN (AV-101), a blocker of the glycine binding site on NMDA receptor, was highly effective in animal studies and is now being tested in clinical trials for MDD (Zanos et al., 2015). Additionally, there are agents that target the mGluRs, but none have been demonstrated to achieve a strong anti-depressive effect (Henter et al., 2018). Thus, the mechanisms and effectiveness of several glutamnergic agents require further study.

Natural Boosts for Everyday Functioning

Another reason to get glutamate into the public eye is that with minimal knowledge of its mechanisms, there are many natural ways the lay public can boost their overall health and well-being. Physical exercise and mindfulness exercises have both been demonstrated to be powerful modulators of non-pharmaceutical glutamate and GABA interventions.

Physical exercise leads to increase levels of both glutamate and GABA (Maddock et al., 2016), resulting in participants feeling energized and focused while also experiencing psychological calm. In adult rats, running has been demonstrated to stimulate neurogenesis and increase the gene expression levels of the NR2B subunit of the NDMA receptor in the dentate gyrus, leading to enhanced learning, memory, and mood functioning (Vivar and van Praag, 2017). In humans, three different experiments show that vigorous physical activity results increased content of glutamate and GABA in the visual and anterior cingulate cortices in comparison with sedentary activity (Maddock et al., 2016). Levels rose approximately 5 percent and persisted for at least 30 min post-exercise. Additionally, participants who had higher resting glutamate levels in the exercise in the previous week also had higher resting glutamate levels.

Mindfulness has a strong impact on brain glutamate and GABA levels observed in the brains of people who practice meditation (e.g., Zen Meditation, Transcendental Meditation, Buddhist Meditation; Fayed et al., 2013; Venditti et al., 2020). A cross-sectional study comparing the brains of meditators from a Zen Buddhist monastery with healthy non-meditators showed differences on glutamate levels in the left thalamus, which may indicate a higher level of efficiency of glutamate metabolism in this area in the case of meditators (Fayed et al., 2013). The Zen meditators also had high myo-inositol concentrations in the posterior cingulate, which may indicate higher levels of glial and microglial activation. The exact mechanisms by which glutamate may modulate the effects of mindfulness still must be explored.

CONCLUSION

This brief review has highlighted the widespread impact of glutamate throughout the brain and its implications for brain health. Glutamate is essential for maintenance of ideal energy levels, necessary for most CNS functions, and neuroplasticity, which is critical for adaptation to changes in the environment. Rather than being delegated as a sidenote as in the past, glutamate is deserving of a main focus in future neuroscience research and clinical studies. Additionally, efforts should be made to educate the lay public as to the importance of glutamate to everyday functioning and how to maintain healthy levels for increased resiliency in times of stress.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of Interest: MP is the Director at In Cognition UK, private clinic and sole author to the presented research. This research has been conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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