frontiers in Human Neuroscience

MINI REVIEW
published: 29 October 2021
doi: 10.3389/fnhum.2021.722323

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

*Mia Michaela Pal**

In Cognition UK, Church Lawton, United Kingdom

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

OPEN ACCESS

Edited by:
Arturo Ortega,
Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Mexico

Reviewed by:
Zila Martinez-Lozada,
Children's Hospital of Philadelphia, United States
Axel Hutt,
Inria Nancy - Grand-Est Research Centre, France

***Correspondence:**
Mia Michaela Pal
contact@purplestarcoaching.com;
contact@in-cognition.co.uk

Specialty section:
This article was submitted to Brain Health and Clinical Neuroscience, a section of the journal Frontiers in Human Neuroscience

Received: *08 June 2021*
Accepted: *13 September 2021*
Published: *29 October 2021*

Citation:
Pal MM (2021) Glutamate: The Master Neurotransmitter and Its Implications in Chronic Stress and Mood Disorders. Front. Hum. Neurosci. 15:722323. doi: 10.3389/fnhum.2021.722323

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 extra-synaptically 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.

POTENTIAL 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; Vasilescu 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-Cl-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 glutaminergic 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 levels of 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 Mediation, 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.

REFERENCES

AbbVie News Centre (2019). *Allergan Announces Phase 3 Results for Rapastinel as an Adjunctive Treatment of Major Depressive Disorder (MDD)*. Lake Bluff, ILL: AbbVie News Center.

Arnone, D., Mumuni, A. N., Jauhar, S., Condon, B., and Cavanagh, J. (2015). Indirect evidence of selective glial involvement in glutamate-based mechanisms of mood regulation in depression: meta-analysis of absolute prefrontal neuro-metabolic concentrations. *Eur. Neuropsychopharmacol.* 25, 1109–1117. doi: 10.1016/j.euroneuro.2015.04.016

Bains, N., and Abdijadid, S. (2021). "Major depressive disorder," in *StatPearls* (Treasure Island, FL: StatPearls Publishing).

Baker, D. A., Xi, Z. X., Shen, H., Swanson, C. J., and Kalivas, P. W. (2002). The origin and neuronal function of in vivo nonsynaptic glutamate. *J. Neurosci.* 22, 9134–9141. doi: 10.1523/jneurosci.22-20-09134.2002

Blaylock, R. L. (2013). Immunoexcitatory mechanisms in glioma proliferation, invasion and occasional metastasis. *Surg. Neurol. Int.* 4:15. doi: 10.4103/2152-7806.106577

Chitty, K. M., Lagopoulos, J., Lee, R. S., Hickie, I. B., and Hermens, D. F. (2013). A systematic review and meta-analysis of proton magnetic resonance spectroscopy and mismatch negativity in bipolar disorder. *Eur. Neuropsychopharmacol.* 23, 1348–1363. doi: 10.1016/j.euroneuro.2013.07.007

de Sousa, R. T., Loch, A. A., Carvalho, A. F., Brunoni, A. R., Haddad, M. R., Henter, I. D., et al. (2017). Genetic studies on the tripartite glutamate synapse in the pathophysiology and therapeutics of mood disorders. *Neuropsychopharmacology* 42, 787–800. doi: 10.1038/npp.2016.149

Donello, J. E., Banerjee, P., Li, Y. X., Guo, Y. X., Yoshitake, T., Zhang, X. L., et al. (2019). Positive N-Methyl-D-Aspartate receptor modulation by rapastinel promotes rapid and sustained antidepressant- like effects. *Int. J. Neuropsychopharmacol.* 22, 247–259. doi: 10.1093/ijnp/pyy101

Fayed, N., Lopez Del, Hoyo, Y., Andres, E., Serrano-Blanco, A., Bellón, J., et al. (2013). Brain changes in long-term zen meditators using proton magnetic resonance spectroscopy and diffusion tensor imaging: a controlled study. *PLoS One* 8:e58476. doi: 10.1371/journal.pone.0058476

Fonnum, F. (1984). Glutamate: a neurotransmitter in mammalian brain. *J. Neurochem.* 42, 1–11. doi: 10.1111/j.1471-4159.1984.tb09689.x

Gigante, A. D., Bond, D. J., Lafer, B., Lam, R. W., Young, L. T., and Yatham, L. N. (2012). Brain glutamate levels measured by magnetic resonance spectroscopy in patients with bipolar disorder: a meta-analysis. *Bipolar Disord.* 14, 478–487. doi: 10.1111/j.1399-5618.2012.01033.x

Guo, X., Rao, Y., Mao, R., Cui, L., and Fang, Y. (2020). Common cellular and molecular mechanisms and interactions between microglial activation and aberrant neuroplasticity in depression. *Neuropharmacology* 181:108336. doi: 10.1016/j.neuropharm.2020.108336

Henter, I. D., de Sousa, R. T., and Zarate, C. A. Jr. (2018). Glutamatergic modulators in depression. *Harv. Rev. Psychiatry* 26, 307–319. doi: 10.1097/HRP.0000000000000183

Huang, C. C., Wei, I. H., Huang, C. L., Chen, K. T., Tsai, M. H., Tsai, P., et al. (2013). Inhibition of glycine transporter-I as a novel mechanism for the treatment of depression. *Biol. Psychiatry* 74, 734–741. doi: 10.1016/j.biopsych.2013.02.020

Inoshita, M., Umehara, H., Watanabe, S. Y., Nakataki, M., Kinoshita, M., Tomioka, Y., et al. (2018). Elevated peripheral blood glutamate levels in major depressive disorder. *Neuropsychiatric Dis. Treatment* 14, 945–953. doi: 10.2147/NDT.S159855

Kantrowitz, J. T., Halberstam, B., and Gangwisch, J. (2015). Single-dose ketamine followed by daily D-Cycloserine in treatment-resistant bipolar depression. *J. Clin. Psychiatry* 76, 737–738. doi: 10.4088/JCP.14l09527

Li, C. T., Yang, K. C., and Lin, W. C. (2019). Glutamatergic dysfunction and glutamatergic compounds for major psychiatric disorders: evidence from clinical neuroimaging studies. *Front. Psychiatry* 9:767. doi: 10.3389/fpsyt.2018.00767

Lüscher, C., and Malenka, R. C. (2012). NMDA receptor-dependent long-term potentiation and long-term depression (LTP/LTD). *Cold Spring Harb. Perspect. Biol.* 4:a005710. doi: 10.1101/cshperspect.a005710

Lynch, M. A. (2004). Long-term potentiation and memory. *Physiol. Rev.* 84, 87–136.

Maddock, R. J., Casazza, G. A., Fernandez, D. H., and Maddock, M. I. (2016). Acute modulation of cortical glutamate and GABA content by physical activity. *J. Neurosci.* 36, 2449–2457. doi: 10.1523/JNEUROSCI.3455-15.2016

Mahmoud, S., Gharagozloo, M., Simard, C., and Gris, D. (2019). Astrocytes maintain glutamate homeostasis in the CNS by controlling the balance between glutamate uptake and release. *Cells* 8:184. doi: 10.3390/cells8020184

Mandal, S., Sinha, V. K., and Goyal, N. (2019). Efficacy of ketamine therapy in the treatment of depression. *Ind. J. Psychiatry* 61, 480–485.

Moskal, J. R., Burch, R., Burgdorf, J. S., Kroes, R. A., Stanton, P. K., Disterhoft, J. F., et al. (2014). GLYX-13, an NMDA receptor glycine site functional partial agonist enhances cognition and produces antidepressant effects without the psychotomimetic side effects of NMDA receptor antagonists. *Expert Opin. Investig. Drugs* 23, 243–254. doi: 10.1517/13543784.2014.852536

Moskal, J. R., Burgdorf, J. S., Stanton, P. K., Kroes, R. A., Disterhoft, J. F., Burch, R. M., et al. (2017). The development of rapastinel (Formerly GLYX-13); a rapid acting and long lasting antidepressant. *Curr. Neuropharmacol.* 15, 47–56. doi: 10.2174/1570159x14666160321122703

Newport, D. J., Carpenter, L. L., McDonald, W. M., Potash, J. B., Tohen, M., Nemeroff, C. B., et al. (2015). Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. *Am. J. Psychiatry* 172, 950–966. doi: 10.1176/appi.ajp.2015.15040465

Niciu, M. J., Kelmendi, B., and Sanacora, G. (2012). Overview of glutamatergic neurotransmission in the nervous system. *Pharmacol. Biochem. Behav.* 100, 656–664. doi: 10.1016/j.pbb.2011.08.008

Preskorn, S., Macaluso, M., Zammit, G., Moskal, J. R., Burch, R. M., and Glyx-13 Clinical Study Group. (2015). Randomized proof of concept trial of GLYX-13, an N-methyl- D-aspartate receptor glycine site partial agonist, in major depressive disorder nonresponsive to a previous antidepressant agent. *J. Psychiatric Practice* 21, 140–149. doi: 10.1097/01.pra.0000462606.17725.93

Reznikov, L. R., Fadel, J. R., and Reagan, L. P. (2011). "Glutamate-mediated neuroplasticity deficits in mood disorders," in *Neuroplasticity*, eds J. A. Costa, E. Silva, J. P. Macher, and J. P. Olié (Tarporley: Springer).

Sah, P., Westbrook, R. F., and Luthi, A. (2008). Fear conditioning and long-term potentiation in the amygdala: what really is the connection? *Ann. N. Y. Acad. Sci.* 1129, 88–95.

Sanacora, G., Treccani, G., and Popoli, M. (2012). Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. *Neuropharmacology* 62, 63–77. doi: 10.1016/j.neuropharm.2011.07.036

Sequeira, A., Mamdani, F., Ernst, C., Vawter, M. P., Bunney, W. E., Lebel, V., et al. (2009). Global brain gene expression analysis links glutamatergic and GABAergic alterations to suicide and major depression. *PLoS One* 4:e6585. doi: 10.1371/journal.pone.0006585

Singh, J. B., Fedgchin, M., Daly, E., Xi, L., Melman, C., De Bruecker, G., et al. (2016). Intravenous esketamine in adult treatment-resistant depression: a double-blind, double-randomization, bo-controlled study. *Biol. Psychiatry* 80, 424–431. doi: 10.1016/j.biopsych.2015.10.018

Traynelis, S. F., Wollmuth, L. P., McBain, C. J., Menniti, F. S., Vance, K., Ogden, K. K., et al. (2010). Glutamate receptor ion channels: structure, regulation, and function. *Pharmacol. Rev.* 62, 405–496. doi: 10.1124/pr.109.002451

Vasilescu, A. N., Schweinfurth, N., Borgwardt, S., Gass, P., Lang, U. E., Inta, D., et al. (2017). Modulation of the activity of N-methyl-d-aspartate receptors as a novel treatment option for depression: current clinical evidence and therapeutic potential of rapastinel (GLYX-13). *Neuropsychiatric Dis. Treatment* 13, 973–980. doi: 10.2147/NDT.S119004

Venditti, S., Verdone, L., Reale, A., Vetriani, V., Caserta, M., and Zampieri, M. (2020). Molecules of silence: effects of meditation on gene expression and epigenetics. *Front. Psychol.* 11:1767. doi: 10.3389/fpsyg.2020.01767

Vivar, C., and van Praag, H. (2017). Running changes the brain: the long and the short of it. *Physiology* 32, 410–424. doi: 10.1152/physiol.00017.2017

Watkins, J. C., and Jane, D. E. (2006). The glutamate story. *Br. J. Pharmacol.* 147(Suppl. 1), 100–108. doi: 10.1038/sj.bjp.0706444

Wilkinson, S. T., Ballard, E. D., Bloch, M. H., Mathew, S. J., Murrough, J. W., Feder, A., et al. (2018). The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta- analysis. *Am. J. Psychiatry* 175, 150–158. doi: 10.1176/appi.ajp.2017.17040472

Wong, T. P., Howland, J. G., Robillard, J. M., Ge, Y., Yu, W., Titterness, A. K., et al. (2007). Hippocampal long-term depression mediates acute stress- induced spatial memory retrieval impairment. *Proc. Natl. Acad. Sci. U. S. A.* 104, 11471–11476. doi: 10.1073/pnas.0702308104

Zanos, P., Moaddel, R., Morris, P. J., Georgiou, P., Fischell, J., Elmer, G. I., et al. (2016). NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature* 533, 481–486. doi: 10.1038/nature17998

Zanos, P., Piantadosi, S. C., Wu, H. Q., Pribut, H. J., Dell, M. J., Can, A., et al. (2015). The prodrug 4-chlorokynurenine causes ketamine-like antidepressant effects, but not side effects, by NMDA/glycineB-site inhibition. *J. Pharmacol. Exp. Therapeut.* 355, 76–85. doi: 10.1124/jpet.115.225664

Zhou, Y., and Danbolt, N. C. (2014). Glutamate as a neurotransmitter in the healthy brain. *J. Neural. Transm.* 121, 799–817.

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.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.