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Chronic Stress in a Rat Model of Depression Disturbs the Glutamine–Glutamate–GABA Cycle in the Striatum, Hippocampus, and Cerebellum [Letter]

Anuj Babber, Anuradha Sharma

Department of Molecular Biology and Genetic Engineering, School of Biosciences and Bioengineering, Lovely Professional University, Phagwara, Punjab, India

Correspondence: Anuradha Sharma, Email s.anuradha21@ymail.com

Dear editor

Clinical depression or major depressive disorder (MDD) is a common and serious mental health issue. Being the most prevalent type of depression globally, it affects approximately 6.7% of the population annually, and 16.6% will experience it at least once in their lifetime.

MDD, characterized by persistent low mood and lack of excitement for two weeks or more, involves changes in the brain's neurochemical environment, particularly in neurotransmitters like serotonin, dopamine, and norepinephrine in the central nervous system. Current hypothesis states that low neurotransmitter levels in the synaptic cleft aids depressive behaviour. Most antidepressant drugs are designed as monoamine therapies to maintain the neurotransmitter levels in the synaptic cleft.[1]

Recent studies highlighted the role of GABA (an inhibitory neurotransmitter) and glutamate (an excitatory neurotransmitter) in depression. Glutamate, one of the brain's most abundant neurotransmitters, excites neurons and starts a signalling cascade involving many neurotransmitters.[1] It is an important component for functions in the brain, such as plasticity, neurogenesis, long term potentiation (LTP), and neural network formation. However, precise regulation of glutamate release with respect to time and amount is essential, as excessive amounts in the synaptic cleft can be toxic, resulting in cell death (excitotoxicity).[2] Appropriate glutamate regulation and related functions involve different receptors, transporters and transporting vesicles for glutamate and any variations in their expression levels can drastically affect brain functioning.

Excitatory amino acid transporters (EAATs) are the proteins transporting extra glutamate from the synaptic cleft to astrocytes. There are five types of EAATs discovered that are present in different brain regions. In depression studies, glutamate levels and expression levels of these EAATs have shown inconclusive results. Zhao et al found that EAAT levels differed by brain region and differed between suicidal and non-suicidal MDD patients, with decreased levels in non-suicidal and increased levels in suicidal patients. These studies were performed on the postmortem brains of MDD patients.[1]

A study using gas chromatography/mass spectrometry (GC/MS) to detect metabolite changes in the striatal, hippocampal, and cerebral tissues of chronic unpredictable mild stress (CUMS) rats found a significant decrease in L-glutamine levels, a key neurotransmission pathway component. The same study also found a significant decrease in GLT1 (SLC1A2) gene expression, which encodes EAAT 2, while also observing the mRNA expression of different genes.[3] Contrarily, Brown et al reported a 46% increase in GLT (SLC1A2) in the anterior cingulate cortex (ACC) of the postmortem brains of humans.[4]

Another study by Robert and James (2002) explored the EAAT 1–4 mRNA expression levels in patients with schizophrenia, bipolar disorder and MDD, finding only EAAT 4 levels significantly decreased as compared to the control group while other EAAT levels were similar to the control groups.[5]

The current literature review shows a huge uncertainty in EAAT's expression levels during depression, in studies mainly performed on animal models or the postmortem brains of humans. Given this limitation, it is now eminently

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necessary to investigate the levels of EAATs during depression in living models. For example, invitro studies can be performed on neuronal cell cultures in which depression like conditions can be induced.

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Disclosure

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