Neuroscience and Psychiatry

Why Hippocampal Glutamate Levels Are Elevated in Schizophrenia

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Recently completed genetic studies,[1,2] the largest and most comprehensive of their kind, help resolve schizophrenia's complex pathobiology. With a preponderance of implicated genes localizing to hippocampal glutamatergic neurons, in particular pathogenic loss-of-function mutations in subunits of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) glutamate receptors, the genetics inform the disorder's anatomy and its pathophysiology.

Functional and structural magnetic resonance imaging (MRI) anatomically concords with the genetics, localizing the hippocampus and its CA1 subdivision as the brain region affected first and foremost in schizophrenia.[3] The pathophysiology of the disordered hippocampus emerges from functional imaging[3,4] and magnetic resonance spectroscopy (MRS).[5] Collectively, the disordered hippocampus is characterized by abnormal increases in glutamate levels, hyperactivity, and atrophy.[6]

Clinically, schizophrenia is characterized by both positive symptoms (ie, psychosis) and negative symptoms (ie, cognitive deficits). Support that the hippocampal pathophysiological state is linked to glutamate receptor loss of function on the one hand, and can drive schizophrenia's symptoms on the other, is provided by medical conditions that phenocopy schizophrenia's symptoms[3]: paraneoplastic limbic encephalitis caused by antibodies directed against either the hippocampal-enriched AMPA or NMDA receptors; neurotoxic syndromes induced by an overdose of drugs that inhibit the hippocampal-enriched NMDA receptors; and seizures that localize to and emanate from the hippocampus. Helping to mechanistically explain this clinical phenocopy and how it links to schizophrenia's genetic triggers, inhibiting hippocampal glutamate receptors in mice causes hippocampal glutamate elevation, hyperactivity, and atrophy.[7] Hippocampal hyperactivity can drive striatal dopamine release via monosynaptic connections with the striatum, explaining positive symptoms, and hippocampal atrophy can partly explain the disorder's negative symptoms.[7] An integration is now possible, connecting the disorder's genetic triggers, to its pathophysiological state, through its defining symptoms (**Figure**).

Since the elevations in synaptic glutamate initiate this series of events, what is the precise cause? One hypothesis, articulated over a decade ago, is that there is a redistribution of synaptic glutamate, whereby presynaptic neurons release more glutamate into the synaptic cleft. This hypothesis was the basis for developing drugs that decrease presynaptic glutamate release, but when tested in clinical trials they failed to confer clinical benefit.

The redistribution of glutamate was hypothesized before a reliable increase in MRS-detected hippocampal glutamate was observed. MRS can only detect a net increase in total synaptic glutamate levels, not its redistribution to the synaptic cleft. We accordingly hypothesize that disruptions to the glutamate metabolic cycle are the more plausible mechanism for hippocampal glutamate elevations. This biological pathway, alternatively called the glutamate-glutamine cycle, is the key regulator of total synaptic glutamate levels whose enzymatic steps are distributed across different synaptic cells (Figure).

Besides its plausibility, empirical evidence supports the hypothesis. Starting with indirect evidence, glutamate receptor inhibition has been found to disrupt the pathway and leads to glutamate elevations, more so in the hippocampus than other neocortical regions.[8] The fact that the hippocampus appears to be differentially vulnerable to pathway disruptions is supported by studies in patients with epilepsy and mouse models that show that, when the pathway's enzymes are defective, it is hippocampal glutamate and its activity that is most reliably affected.[9,10]

Directly linking the pathway to schizophrenia, a gene expression study of the CA1 hippocampal region, harvested post mortem from patients with schizophrenia, identified deficiencies in glutamate dehydrogenase 1 (GLUD1).[9] GLUD1 is a key enzyme in the pathway (Figure), producing glutamate in the synapse's astrocyte. Inducing GLUD1 deficiency in mice phenocopies the disorder's pathophysiological state, causing increased hippocampal glutamate and its activity,[9] and leads to hippocampal atrophy and associated cognitive deficits.

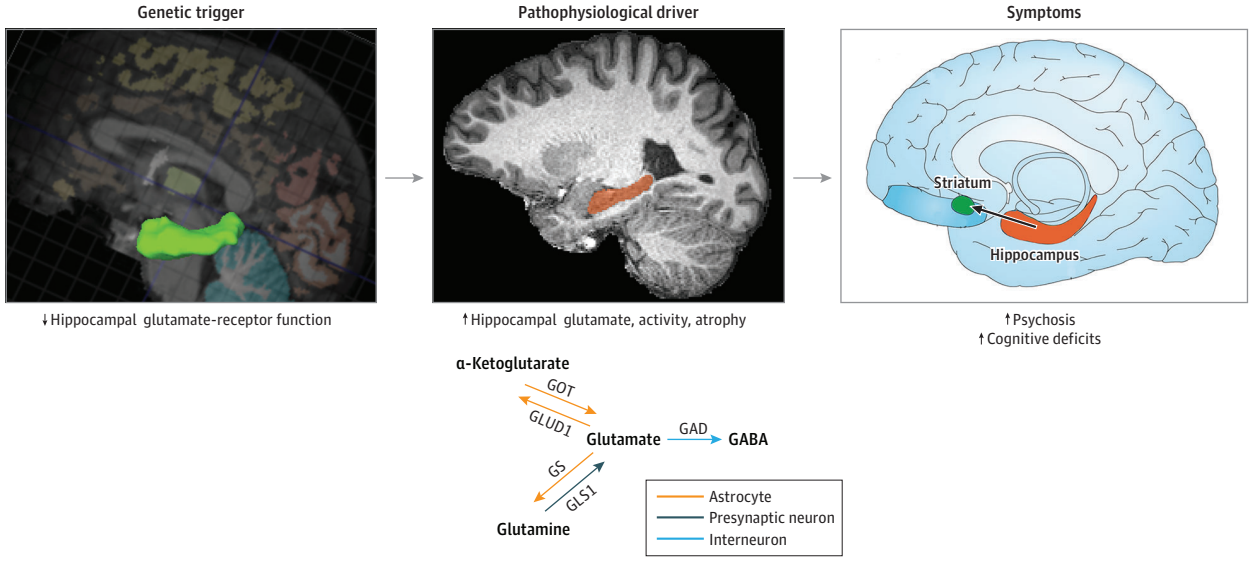
Informatively, mouse models with deficiencies in glutaminase 1 (GLS1), a pathway enzyme that catabolizes glutamate in the presynaptic neuron (Figure), show an inverse effect on hippocampal glutamate and its activity and have been shown to manifest a schizophrenia-resilient phenotype.[10] The mice are resilient to amphetamine-induced hyperactivity and downstream striatal dopamine release, the opposite of what is observed in patients, and potentiates hippocampal-dependent cognitive function.

Acute application of pharmacological inhibitors of NMDA receptors has often been used as a schizophrenia model when trying to understand the disorder's pathobiology. Models can offer practical advantages, but if possible, testing a hypothesis in the actual disorder is obviously always better. Relying on advancements in MRS, it is now possible to directly test the hypothesis in the hippocampus of patients. Since schizophrenia progresses over time, the hypothesis is best tested in patients in the prodromal stages of the disorder.

Carbon 13–labeled (^{13}C) MRS in combination with stable ^{13}C isotopically labeled substrates is in principle the ideal approach, as it can measure the actual rates of the pathway's enzymatic steps. However, it is limited by technical complexity and availability. Proton MRS is the more standard, widely available, and easily deployed approach. But only with recent pulse sequence advancements has it become possible to reliably measure multiple key pathway metabolites—notably, glutamate, glutamine, and γ-aminobutyric acid. These co-measurements are sufficient to establish an MRS signature of pathway disruption.

Besides clarifying the fundamental pathobiology of schizophrenia, validating the hypothesis will guide new therapeutic strategies. An MRS signature of pathway disruption can be used in future clinical trials as a biomarker for enrolling patients and even as a biomarker of target engagement.

Figure. Hippocampal Glutamate in the Pathogenesis of Schizophrenia



Loss of function of hippocampal-enriched glutamate receptors act as genetic triggers (left panel, highlighting the hippocampus in green from the Allen Human Brain Atlas). A reduction in glutamate receptor function can increase hippocampal glutamate levels, activity, and atrophy, a pathophysiological state that characterizes the disorder (middle panel, adapted from Provenzano et al[6]). Hippocampal hyperactivity can drive striatal dopamine release, leading to psychotic symptoms, and hippocampal atrophy can lead to cognitive deficits (right panel, modified from Small et al[3]). GABA indicates γ-aminobutyric acid; GAD, glutamic acid decarboxylase; GLS1, glutaminase 1; GLUD1, glutamate dehydrogenase 1; GOT, glutamate-oxaloacetate transaminase; and GS, glutamine synthetase.

In particular, it is notable that inhibiting GLS1 in mice safely reduces hippocampal glutamate and its activity. Indeed, there is a class of GLS1-inhibiting drugs that have been developed for cancer that have proven to safely reduce glutamate. By design, this class does not readily cross the blood-brain barrier but they can be used as a starting point to design or find GLS1 inhibitors that do.

In summary, future MRS studies can be used to test the hypothesis for why glutamate is abnormally elevated in the hippocampus of patients with schizophrenia and related disorders. More importantly, an MRS signature of pathway dysfunction can be used to accelerate the discovery of clinically meaningful interventions for one of the most devastating lifelong brain disorders that strikes in young adolescence.

ARTICLE INFORMATION

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