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HOT TOPICS

Novel approaches to estimate prefrontal synaptic strength in vivo in humans: of relevance to depression, schizophrenia, and ketamine

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Synaptic strength, defined as the magnitude of the postsynaptic response to a presynaptic action potential, is essential in the creation and adaptation of brain networks and plays a critical role in mental health and illnesses. Converging preclinical evidence indicate loss of glutamatergic synaptic strength in various paradigms of chronic stress and depression. A major challenge in the field is to implement a reliable approach to estimate overall glutamatergic synaptic strength within a brain region in vivo in humans to determine its role in the pathophysiology and treatment of depression and other neuropsychiatric disorders.

Dynamic carbon-13 magnetic resonance spectroscopy (^{13}C MRS) is a unique imaging technique that can provide estimates of two measures directly related to glutamatergic synaptic strength: (1) the rate of glutamate neurotransmission cycling (V_{Cycle}) and (2) the rate of neuronal oxidative energy production (V_{TCAn}) [1]. Considering the tight coupling between synaptic signaling and brain energetics [1], the ratio of V_{TCAn}/V_{Cycle}, which is Energy Per Cycle (EPC), was proposed as a putative biomarker of glutamatergic synaptic strength [2]. Notably, EPC is highly conserved across species and is very stable in differing mental state from fully awake to fully anesthetized [1]. To our surprise, approximately a decade ago, we found a remarkable 26% reduction in cortical EPC in patients with major depressive disorder (MDD) compared to healthy controls, consistent with preclinical evidence of reduced synaptic strength in depression pathology [2].

Ketamine, an N-methyl-D-aspartate receptors (NMDAR) antagonist, is known to both block NMDAR transmission and paradoxically increase presynaptic glutamate release [3]. Thus, ketamine administration offers a distinctive paradigm of pharmacologically induced transient reduction in glutamatergic synaptic strength. Preclinical ^{13}C MRS studies support the presence of ketamine-induced reduction in glutamatergic synaptic strength [4]. To extend these preclinical findings to humans, we investigated the effects of subanesthetic ketamine on prefrontal ^{13}C enrichment during ^{13}C-glucose infusion in healthy and MDD participants [5]. Immediately following ketamine administration, we found a significant reduction in glutamatergic synaptic strength, as estimated by EPC [5]. These transient effects of ketamine on prefrontal glutamate neurotransmission are believed to induce prefrontal synaptic growth and rapid acting antidepressant effects 24 h posttreatment [3, 6]. Intriguingly, the magnitude of ketamine-induced reduction in prefrontal EPC during infusion was significantly associated with the psychomimetic effects of the drug, a human paradigm to recapitulate core symptoms of psychosis [5]. The latter finding suggested that psychosis pathology in schizophrenia may not necessarily be solely related to disruption in glutamate release, but rather a loss of communication fidelity between presynaptic signaling and postsynaptic activation [5].

Together, these data underscore the essential role of prefrontal synaptic strength in the pathology of psychiatric disorders. The evidence also demonstrates the robustness and utility of EPC, measured by ^{13}C MRS, as valid biomarker of glutamatergic synaptic strength. Future studies will determine the pattern of EPC disruption across disorders and its response to rapid acting antidepressants, such as ketamine.

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COMPETING INTERESTS

CGA has served as a consultant, speaker and/or on advisory boards for Genentech, Janssen, Psilocybin Labs, Lundbeck, Guidepoint, and FSV7, and as editor of *Chronic Stress* for Sage Publications, Inc. He also filed a patent for using mTORC1 inhibitors to augment the effects of antidepressants (Aug 20, 2018). GFM lists patent application U.S. patent number 10,770,276 for techniques of mass spectrometry for isotopomer analysis and related systems and methods. He reports payments of less than $10,000 per year from Merck & Co., Sumitomo Dainippon Pharma Co., and UCB Pharma.

ADDITIONAL INFORMATION

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