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Commentary

Conceptual Confluence: The Kynurenine Pathway as a Common Target for Ketamine and the Convergence of the Inflammation and Glutamate Hypotheses of Depression

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Two of the dominant theories regarding the development of depression and its response (or lack thereof) to conventional antidepressant therapies involve excessive activation of inflammatory pathways and alterations in glutamate metabolism. Increased inflammation has been demonstrated in a significant subset of depressed patients, and there appears to be a special relationship between inflammation and treatment resistance (Miller *et al*, 2009). Indeed, increased inflammatory markers prior to antidepressant treatment predict treatment non-response, and patients with treatment-resistant depression exhibit increased inflammatory markers. Moreover, clinical factors related to treatment non-response are associated with increased measures of inflammation, including anxiety disorders, childhood maltreatment, bipolar disorder, personality disorders, obesity, and medical illness. Alterations in glutamate metabolism have also been implicated in depression and treatment resistance (Sanacora *et al*, 2012). A number of studies using magnetic resonance spectroscopy have found alterations in glutamate and glutamate metabolite levels in multiple brain regions of depressed subjects. Moreover, loss of glial elements including astrocytes and oligodendrocytes as well as the transporters for excitatory amino acids, which are responsible for the reuptake and ultimate recycling of glutamate, are some of the most reliable changes found in postmortem brain tissue from depressed subjects. Probably, the most dramatic evidence of the glutamate hypothesis of depression and its role in treatment resistance is the profound and rapid response of treatment-resistant depressed patients to ketamine, an antagonist of the glutamate *N*-methyl-D-aspartate (NMDA) receptor. The effects of ketamine are believed in part to be related to activation of mTOR signaling and synaptic protein synthesis by brain-derived neurotrophic factor (BDNF), which is dependent upon glutamate stimulation of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors as a result of ketamine's antagonism of NMDA receptors (Duman *et al*, 2012).

Interestingly, inflammatory cytokines have been shown to interact with glutamate pathways in several important ways, including decreasing the expression of glutamate transporters on relevant glial elements and increasing the release of glutamate from astrocytes. Glutamate released by astrocytes has preferential access to extrasynaptic NMDA receptors, which have been shown to decrease BDNF and increase excitotoxicity (Miller *et al*, 2009). In addition, inflammatory cytokines including tumor necrosis factor (TNF) have been shown to reduce glutamine synthetase, which converts glutamate to glutamine, potentially leading to a build-up of intracellular and extracellular glutamate concentrations, which along with cytokine induction of nitrogen and oxygen free-radicals can lead to astrocyte death. Cytokines such as TNF can also reduce glutamate transporter expression on oligodendrocytes and in excess is directly toxic to these cells. These effects of inflammatory cytokines on glutamate metabolism, reuptake and release by astrocytes and oligodendrocytes, as well as the fundamental integrity (and survival) of these glial elements provide an intriguing intersection of the inflammation and glutamate hypotheses of depression and their relationship with treatment resistance.

In this issue of *Neuropsychopharmacology*, another example of how these pathways to pathology may synergize to sabotage the largely monoaminergic actions of conventional antidepressants is presented by Walker *et al* (2013), who also provide an intriguing remedy to this conspicuous conspiracy. These investigators offer compelling data that pretreatment with ketamine blocks the development of depressive-like behavior in mice as a result of administration of the potent inflammatory stimulus, lipopolysaccharide (LPS). Administration of LPS to rodents is one of the quintessential animal models of inflammation-induced depression. Surprisingly, ketamine had no effect on LPS-induced inflammatory activation in the brain. Interestingly,

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however, ketamine's proposed target was quinolinic acid. Quinolinic acid is a downstream product of the kynurenine pathway and has been shown to act as an agonist at the glycine-binding site of the NMDA receptor. LPS has been shown in a number of studies to activate the kynurenine pathway, as evidenced in this and other studies by LPS-induced increases in 3-hydroxykynurenine, 3-hydroxyanthranilic acid, as well as quinolinic acid, all of which are products of the metabolism of kynurenine in activated microglia. Of note, quinolinic acid has been shown to be increased in the cerebrospinal fluid of suicide victims (Erhardt *et al*, 2013), and increased immunoreactivity of quinolinic acid has been found in microglia in multiple brain regions of severely depressed patients including the subgenual cingulate cortex, a brain region well known to be implicated in treatment-resistant depression (Steiner *et al*, 2011). To further confirm that ketamine's effects were mediated by blocking the impact of quinolinic acid on the NMDA receptor, the AMPA receptor antagonist 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(f)quinoxaline-2,3-dione (NBQX) was administered in conjunction with ketamine. NBQX completely reversed the effects of ketamine on LPS-induced depressive-like behavior. Similar to LPS-induced activation of inflammatory pathways in the brain, ketamine had no effects on the production of quinolinic acid by LPS. Taken together, these results suggest that the kynurenine pathway in general and quinolinic acid in particular may represent another point of convergence of the impact of inflammation and glutamate pathways on the brain and behavior. Given the capacity of quinolinic acid to directly activate the NMDA receptor, quinolinic acid is uniquely poised to contribute to the mechanism by which activation of inflammatory pathways can impinge on glutamate signaling and its contribution to excitotoxicity and neuronal endangerment. By the same token, quinolinic acid and the kynurenine pathway become common targets for the effects of both inflammation and glutamate on synaptic integrity and mood regulation. Indeed, ketamine may be especially useful in depressed patients with increased inflammation before anti-inflammatory treatment strategies have taken hold. Conversely, anti-inflammatory treatments may be used for sustaining treatment responses in ketamine-treated depressed patients with increased inflammation. In either case, recognition of the points of convergence of the inflammation and glutamate hypotheses of depression and treatment resistance may lead to novel combinations of treatment approaches that borrow from overlapping and shared pathologies. One point of conceptual convergence in this regard is the kynurenine pathway.

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