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Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: Evidence for an immune-modulated glutamatergic neurotransmission?

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Abstract

Background: Immune dysfunction, including monocytosis and increased blood levels of interleukin-1, interleukin-6 and tumour necrosis factor α has been observed during acute episodes of major depression. These peripheral immune processes may be accompanied by microglial activation in subregions of the anterior cingulate cortex where depression-associated alterations of glutamatergic neurotransmission have been described.

Methods: Microglial immunoreactivity of the N-methyl-D-aspartate (NMDA) glutamate receptor agonist quinolinic acid (QUIN) in the subgenual anterior cingulate cortex (sACC), anterior midcingulate cortex (aMCC) and pregenual anterior cingulate cortex (pACC) of 12 acutely depressed suicidal patients (major depressive disorder/MDD, n = 7; bipolar disorder/BD, n = 5) was analyzed using immunohistochemistry and compared with its expression in 10 healthy control subjects.

Results: Depressed patients had a significantly increased density of QUIN-positive cells in the sACC ($P = 0.003$) and the aMCC ($P = 0.015$) compared to controls. In contrast, counts of QUIN-positive cells in the pACC did not differ between the groups ($P = 0.558$). Post-hoc tests showed that significant findings were attributed to MDD and were absent in BD.

Conclusions: These results add a novel link to the immune hypothesis of depression by providing evidence for an upregulation of microglial QUIN in brain regions known to be responsive to infusion of NMDA antagonists such as ketamine. Further work in this area could lead to a greater understanding of the pathophysiology of depressive disorders and pave the way for novel NMDA receptor therapies or immune-modulating strategies.