

Inflammation, Cytokines and Glutamate

A New Pathway to Depression

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Recent years have witnessed the evolution of the concept of inflammation from a vague descriptor of ill health to a fundamental disease process that links major depressive disorder to such diverse conditions as diabetes, cardiovascular disease and dementia. Meta-analyses of studies on community and clinical samples have revealed that the plasma levels of inflammatory markers including IL-6, IL-1, TNF- α and C-reactive protein (CRP) are significantly elevated in major depressive disorder (MDD) (Maes et al., 2010). Elevated levels of these cytokines are particularly prevalent in depression with a late life onset (Alexopoulos & Morimoto, 2011).

The occurrence of depression in the elderly is often the harbinger for Alzheimer's dementia, a condition associated with marked increase in brain inflammation. Obesity is also associated with elevated inflammatory markers and type II diabetes. The prevalence of major depressive disorder is significantly increased in type II diabetes and is associated with increased risk for diabetic complications including vascular disease and blindness. The risk for depression is significantly increased with myocardial infarction, a disorder also associated with elevated plasma cytokines and CRP. The co-occurrence of depression with myocardial infarction is a robust predictor of subsequent death. MDD with elevated plasma cytokines that occurs in these various medical illnesses is often poorly responsive to treatment with serotonin specific reuptake inhibitors (SSRIs). An important question concerns the direction of causality between inflammation and depression. Recent clinical studies strongly suggest that inflammation is the causal factor (Capuron et al., 2009). Chronic viral hepatitis C is now treated with a combination of interferon- α (IFN- α) and riboflavin. IFN- α is a cytokine of the early immune system, which

induces the cellular release of other proinflammatory mediators such as IL-6. A significant proportion of patients treated with IFN- α develop major depressive disorder, and their cerebral spinal fluid levels of IL-6 correlate with depression symptoms.

What are the neurochemical processes that bridge the gap between elevated inflammatory markers in plasma and depression? Studies by Maes et al., (2010) indicate that proinflammatory cytokines induce indole amine 2,3-dioxygenase (IDO), which catabolizes tryptophan into the kynurenine pathway. Elevated IDO reduces plasma tryptophan levels, which ultimately attenuates the synthesis of serotonin in brain because tryptophan hydroxylase is not saturated by tryptophan. Of perhaps greater significance are the downstream metabolites of tryptophan, kynurenine and quinolinic acid. Kynurenine has anxiogenic effects, whereas quinolinic acid, an NMDA receptor agonist, has prodepressive effects and at high concentrations has excitotoxic effects.

The potential role of excessive NMDA receptor agonism by quinolinic acid as an alternative pathway to depression has received clinical support from recent studies with the NMDA receptor antagonist ketamine (Diazgranados et al., 2010). In placebo-controlled trials a single dose of ketamine produced a rapid and persistent antidepressant effect lasting up to 10 days in patients selected for being poorly responsive to SSRI treatment. Li et al., (2010) have developed the evidence that the acute NMDA receptor blockade activates the mammalian target of the rapamycin (mTOR) pathway via rebound AMPA receptors activation, thereby promoting synaptogenesis in the prefrontal cortex (Li et al., 2010). Regardless of the precise mechanisms, this robust therapeutic effect of ketamine in cases of major depression unresponsive to traditional antidepressant treatment (approximately 50% of MDD patients are unresponsive) suggests the existence of a distinct pathophysiology for depression involving glutamatergic mechanisms and

unrelated to the classical biogenic amine hypothesis.

References

Alexopoulos, G. S., & Morimoto, S. S. (2011). The inflammation hypothesis in geriatric depression. *International Journal of Geriatric Psychiatry*, (Epub ahead of print).

Capuron, L., Fornwalt, F. B., Knight, B. T., Harvey, P. D., Ninan, P. T., & Miller, A. H. (2009). Does cytokine-induced depression differ from idiopathic major depression in medically healthy individuals? *Journal of Affective Disorders*, *119*, 181–185.

Diazgranados, N., Ibrahim, L., Brutsche, N. E., Newberg, A., Kronstein, P., Khalife, S., et al. (2010). A. Jr. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Archives of General Psychiatry*, *67*, 793–802.

Li, N., Lee, B., Liu, R. J., Banasr, M., Dwyer, J. M., Iwata, M., et al. (2010). mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*, *329*, 959–964.

Maes, M., Leonard, B. E., Myint, A. M., Kubera, M., & Verkerk, R. (2010). The new ‘5-HT’ hypothesis of depression: Cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression.

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