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Interleukin-1β: A New Regulator of the Kynurenine Pathway Affecting Human Hippocampal Neurogenesis

Patricia A Zunszain[1], Christoph Anacker[1], Annamaria Cattaneo[2], Shanas Choudhury[1], Ksenia Musaelyan[1], Aye Mu Myint[3], Sandrine Thuret[4], Jack Price[4] and Carmine M Pariante*,[1]

[1]Section of Perinatal Psychiatry and Stress, Psychiatry and Immunology (SPI-lab), Department of Psychological Medicine, Institute of Psychiatry, King's College London, London, UK; [2]Biology and Genetic Division, Department of Biomedical Sciences and Biotechnology, University of Brescia, Brescia, Italy; [3]Psychiatric Hospital, Ludwig-Maximilian University, Munich, Germany; [4]Centre for the Cellular Basis of Behaviour (CCBB), Institute of Psychiatry, King's College London, London, UK

Increased inflammation and reduced neurogenesis have been associated with the pathophysiology of major depression. Here, we show for the first time how IL-1β, a pro-inflammatory cytokine shown to be increased in depressed patients, decreases neurogenesis in human hippocampal progenitor cells. IL-1β was detrimental to neurogenesis, as shown by a decrease in the number of doublecortin-positive neuroblasts (−28%), and mature, microtubule-associated protein-2-positive neurons (−36%). Analysis of the enzymes that regulate the kynurenine pathway showed that IL-1β induced an upregulation of transcripts for indolamine-2,3-dioxygenase (IDO), kynurenine 3-monooxygenase (KMO), and kynureninase (42-, 12- and 30-fold increase, respectively, under differentiating conditions), the enzymes involved in the neurotoxic arm of the kynurenine pathway. Moreover, treatment with IL-1β resulted in an increase in kynurenine, the catabolic product of IDO-induced tryptophan metabolism. Interestingly, co-treatment with the KMO inhibitor Ro 61-8048 reversed the detrimental effects of IL-1β on neurogenesis. These observations indicate that IL-1β has a critical role in regulating neurogenesis whereas affecting the availability of tryptophan and the production of enzymes conducive to toxic metabolites. Our results suggest that inhibition of the kynurenine pathway may provide a new therapy to revert inflammatory-induced reduction in neurogenesis.
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