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GENETIC AND ENVIRONMENTAL IMPACTS IN MAJOR DEPRESSIVE DISORDER ARE MEDIATED VIA KYNURENINE PATHWAY OF TRYPTOPHAN METABOLISM

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We were first to propose up-regulation of KYN pathway of TRY metabolism as an etiological factor in depression: “in depression metabolism of TRY is shunted away from serotonin production, and towards KYN production” since “activity of liver TRY-pyrrolase is stimulated by raised blood corticosteroids levels” (Lapin & Oxenkrug, Lancet, 1969). TRY-pyrrolase, i.e., tryptophan-2,3-dioxygenase (TDO) was the only known enzyme catalyzing TRY conversion into KYN. TDO is mostly located in liver and activated by cortisol and prolactin. Seven years later another enzyme catalyzing TRY conversion into KYN, indoleamine-2,3-dioxygenase (IDO), was discovered. IDO is located in microglia, astrocytes and macrophages, and transcriptionally induced by pro-inflammatory cytokines. Discovery of neurotropic activity of kynurenines suggested that upregulation of TRY - KYN pathway not only augments serotonin deficiency but also underlines depression-associated anxiety, psychosis and cognitive decline. Simultaneous presence of high promoters alleles of pro-inflammatory cytokines genes (IFNG and TNF-alpha) determines genetic predisposition to depression via up-regulation of IDO while impact of environmental stresses is mediated via hormonal activation of TDO. Potentiation of IFNG-induced up-regulation of IDO by stress hormones further underscores the importance TRY-KYN pathway as major meeting point of gene-environment interaction in depression and as a new target for pharmacological intervention.

https://doi.org/10.1016/S0924-9338(09)70899-5 Published online by Cambridge University Press