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ROLE OF TRYPTOPHAN-KYNURENINE PATHWAY IN DEPRESSION: PSYCHOPATHOLOGICAL ASPECT

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It was reported that cytokines such as IFN-γ reduce the synthesis of 5-HT by stimulating the activity of indoleamine 2,3 dioxygenase (IDO) enzyme which degrades tryptophan to kynurenine. Kynurenine is further metabolized to kynurenic acid (KYNA), 3-hydroxykynurenine (3OHK) and quinolinic acid (QA) by kynurenine aminotransferase (KAT), kynurenine 3-monooxygenase (KMO) and kynureninase. Both KMO and kynureninase are also shown to be activated by IFNγ. The 3OHK is neurotoxic apoptotic while QA is the excitotoxic N-methyl-D-aspartate (NMDA) receptor agonist. Conversely KYNA is an antagonist of all three ionotropic excitatory amino acid receptors and considered neuroprotective. In the brain, tryptophan catabolism occurs in the astrocytes and. The astrocytes are shown to produce mainly KYNA whereas microglia and macrophages produced mainly 3OHK and QA. The astrocytes have been demonstrated to metabolise the QA produced by the neighbouring microglia.
Tryptophan breakdown has been found to be increased but KYNA, the neuroprotective metabolite is decreased in both blood and cerebrospinal fluid of the patients with major depression compared to healthy controls. Moreover, the ratio between KYNA and 3OHK showed significant correlation with response to treatment. These findings lead to the hypothesis an imbalance neuroprotection-neurodegener-ation in terms of kynurenine metabolites and their immunological and biochemical interactions in the brain might further induce the apoptosis of the neuroprotective astrocytes and the vulnerability to stress is thereby enhanced.

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