

Tryptophan Pathway Depletion and Hyperactivity of the HPA Axis in Major Depressive Disorder

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Hypothesised aetiologies of Major Depressive Disorder (MDD) include Kynurenine Pathway (KP) induction and hyperactivity of the hypothalamic pituitary adrenal axis (HPAA). Metabolism of tryptophan into kynurenine is one proposed mechanism of serotonin depletion in MDD. Kynurenine production is induced via tryptophan 2,3-dioxygenase (TDO), which is activated by HPAA activity including increases in cortisol. In this study, the possible relationship between depressive symptoms, tryptophan depletion, and cortisol activity will be investigated in MDD.

Saliva samples collected from patients with first presentation MDD (n=55) and healthy controls (n=49) were analysed by LCMS to capture the Cortisol Awakening Response (CAR) which is an established measure of HPAA activity. Blood samples were collected and High Performance Liquid Chromatography (HPLC) was performed on plasma to determine concentrations of several Tryptophan Pathway metabolites. Several rating scales were utilised to assess mood, suicidality, and sleep.

An independent t-test revealed that depressed patients had significantly lower levels of both Tryptophan (8322.7 vs. 9889.7; $p=0.001$) and Kynurenine (667.3 vs. 824.6; $p=0.001$) than healthy controls. The depressed group also exhibited an altered CAR, with a significantly higher cortisol concentration at wakening (10.95 nMol/L vs 7.33 nMol/L; $p=0.041$). Additionally, the slope of the regression line through the log transformed CAR data was significantly lower in depressed patients than controls (0.0016 vs. -0.0011, $p=0.024$). A Pearson's correlation revealed a significant relationship between Tryptophan and HAM-D Score ($r=-0.344$, $p=0.003$), Kynurenine and HAM-D score ($r=-0.310$, $p=0.008$) wakening cortisol and HAM-D ($r=0.245$, $p=0.038$), and between Kynurenine and wakening cortisol ($r=-0.319$, $p=0.029$). These results indicate that Kynurenine is depleted in conjunction with Tryptophan, and KP induction is not evident despite HPAA hyperactivity.