# Dose-dependent dual action of kynurenine, a tryptophan metabolite, on the turnover of 5-hydroxytryptamine

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The major metabolic route for tryptophan is via the kynurenine pathway initiated by tryptophan pyrrolase. The activity of this enzyme may be increased in depressive illness (e.g. Cazzullo, Mangoni & Mascherpa, 1966). This could be secondary to an induction of pyrrolase by cortisol (Thomson & Mikuta, 1954) since elevated plasma cortisol levels have been found in depressive illness (e.g. Sachar, Hellman, Roffwang, Halpern, Fukushima & Gallagher, 1973). Both cortisol (Curzon & Green, 1968) and (−)-kynurenine itself (Green & Curzon, 1970) reduced brain 5-hydroxytryptamine (5-HT) levels and synthesis, possibly by diversion of tryptophan into the kynurenine pathway or by reducing brain tryptophan uptake (Green & Curzon, 1970). However, (±)-kynurenine (5 mg/kg) decreased central 5-HT activity as shown by a decreased head twitch response to 5-hydroxytryptophan (5-HTP), while 0.5 mg/kg caused a marked increase (Handley & Miskin, 1977). To investigate the possible mechanisms of this effect the same doses of kynurenine were used and changes in plasma and brain kynurenine levels and in 5-HT turnover were determined.

Male Bk/W mice housed under a natural light cycle were used and all experiments performed between 1400–1700 h to minimize the effect of diurnal 5-HT variation.

5-HT turnover was measured by monoamine oxidase inhibition by pargyline (75 mg/kg) and by inhibition of 5-hydroxyindoleacetic acid (5-HIAA) efflux with probenecid (200 mg/kg) (Morot-Gaudry, Hamon, Bourgoin, Ley & Glowinski, 1974).

5-HT and 5-HIAA were assayed in brain (Joseph & Baker, 1976) and kynurenine was assayed in brain and plasma by an adaptation of the method of Joseph (1977).

Two hours after pretreatment with (±)-kynurenine (0.5 mg/kg or 5 mg/kg) there was no significant change in plasma kynurenine levels whereas brain kynurenine had increased by 94 and 86% respectively. Brain 5-HT and 5-HIAA did not change after either dose, 0.5 mg/kg significantly decreased ($P = 0.02$, probenecid method) brain 5-HT turnover rate whereas 5 mg/kg had no effect.

Thus (±)-kynurenine was distributed into brain from plasma such that after 2 h plasma levels were normal. It is unlikely that 5-HT synthesis inhibition by kynurenine could be due to competition with tryptophan for uptake, since it did not occur at the higher dose. That kynurenine does not inhibit 5-HTP decarboxylase was shown by Curzon & Green (1970) and supported by the observation that kynurenine had the same effect on the head twitch response whether intraperitoneal 5-HTP or intracerebral 5-HT was used (Handley & Miskin, 1977).

The dual effect of kynurenine on the 5-HT and 5-HTP head twitch was reflected by a dual effect of the two doses on brain 5-HT turnover.

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