Kynurenine: penetration to the brain, effect on brain tryptophan and 5-hydroxytryptamine metabolism and binding to plasma albumin

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The presence in brain of kynurenine, the first major metabolite of tryptophan on the pathway initiated by the liver enzyme tryptophan pyrrolase, has recently been reported (Joseph 1977, 1978; Gal & Sherman, 1978). Since an enzyme capable of forming kynurenine from tryptophan is present in brain (Gal, 1974; Hayaishi, 1976) it is of interest to study the penetration of kynurenine to the brain following peripheral administration. Peripheral administration of kynurenine has also been reported to reduce rat brain 5HT levels, perhaps via inhibition of tryptophan uptake (Green & Curzon, 1970).

(−)-Kynurenine sulphate (5 mg/kg i.p.) was administered to male Sprague-Dawley rats (weight 200–280 g). As shown in the table kynurenine levels were significantly elevated in plasma 30 min later, and in brain at 30, 60 and 120 min later. These results are in broad agreement with the less detailed findings reported in mice (Gould & Handley, 1978) and in rats (Gal, Young & Sherman, 1978) and confirm that kynurenine can penetrate to the brain following peripheral administration. Analysis of tryptophan, 5-hydroxytryptamine and 5-hydroxy-indoleacetic acid in the brains of the same animals revealed small but non-significant reductions in all three parameters only at 30 and 60 min post kynurenine which is not consistent with the findings of Green & Curzon (1970). Plasma tryptophan was also reduced although not significantly. Ultrafiltration of plasma samples by a technique developed from that of Bloxham, Hutson & Curzon (1977) indicated that tryptophan is not, as is frequently stated (e.g. Young & Sourkes, 1977; Green, 1978), the only amino acid to be bound to plasma albumin, since kynurenine was bound to a similar extent. Further data on this binding will be presented, and it is suggested that any effects of kynurenine on brain tryptophan metabolism might be mediated at least in part via effects on tryptophan binding to albumin since the latter is known to affect tryptophan availability to the brain (Young & Sourkes, 1977; Green, 1978).

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Table 1 The effect of (−)-kynurenine sulphate administration, i.p., on kynurenine in plasma and brain

Time after injection of (−)-kynurenine sulphate 5 mg/kg i.p.	*Kynurenine content*	
	Plasma (ng/ml)	*Brain (ng/g)*
0 (Control)	915 ± 318 (8)	78 ± 50 (8)
30 min	2394*** ± 737 (8) (262%)	323*** ± 140 (8) (413%)
60 min	1066 ± 561 (9) (117%)	247** ± 120 (9) (316%)
120 min	885 ± 596 (9) (97%)	173* ± 84 (9) (221%)

Results as mean ± s.d. (no. of animals) (% of control). Significantly different from control on 2-tailed '*t*' test. * $P < 0.02$. ** $P < 0.005$. *** $P < 0.001$.

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The uptake of kynurenine, a tryptophan metabolite, into mouse brain

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Kynurenine, a liver tryptophan metabolite, itself reduces brain tryptophan uptake (Green & Curzon, 1970). Since 5-HT synthesis depends on brain tryptophan levels (Carlsson & Lindqvist, 1978) kynurenine would be expected to reduce 5-HT turnover. This has been reported to occur 2 h after low (0.5 mg/kg) but not after higher (5–20 mg/kg) doses of (±)-kynurenine in the mouse (Gould & Handley, 1978). In order to investigate this anomaly, brain uptake of kynurenine has been examined.

(±)-Kynurenine (0.5–20 mg/kg) was injected intraperitoneally into male mice (BK/W, 23–27 g). Plasma and brain kynurenine was determined after Joseph, Baker & Lawson (1978). Doses are expressed as base equivalent.

Peak plasma kynurenine occurred at 30 min (table 1) and had returned to normal by 2 h except after 20 mg/kg when levels were still significantly raised at 2 h.

Brain kynurenine generally followed plasma kynurenine. The two values showed a strong linear correlation ($r = +0.969$, $P < 0.01$) and a rather constant proportion (about 25%) of plasma kynurenine entered brain. The process of entry could not be distinguished from passive diffusion. However during the secondary peaks 2 h after the two lower doses, the linear correlation no longer held and the brain/plasma ratio was much higher (42–48%). This probably represents slower, carrier-assisted uptake. It is likely that kynurenine, a neutral alpha amino-acid, would use the same carrier as tryptophan (see Christensen, 1975); accounting for its inhibition of tryptophan uptake.

The effects of the various doses on 5-HT turnover 2 h after kynurenine (Gould & Handley, 1978) were

Table 1 Plasma and brain kynurenine concentrations after injection of various doses of (±)-kynurenine

Pretreatment	*Time after injection (min)*	*Kynurenine (μg/ml ± s.e. mean)* *Plasma*	*Brain*
Saline		0.674 ± 0.020 (12)	0.166 ± 0.009 (22)
Kynurenine	30	0.869 ± 0.110 (5)*	0.217 ± 0.028 (7)*
(0.5 mg/kg i.p.)	60	0.733 ± 0.040 (6)	0.188 ± 0.024 (6)
	120	0.754 ± 0.095 (7)	0.314 ± 0.044 (10)**
Kynurenine	30	1.412 ± 0.131 (7)***	0.278 ± 0.025 (9)***
(5.0 mg/kg i.p.)	60	0.949 ± 0.080 (6)**	0.235 ± 0.026 (8)**
	120	0.641 ± 0.052 (10)	0.308 ± 0.020 (11)***
Kynurenine	30	3.416 ± 0.223 (6)***	0.865 ± 0.137 (6)***
(20.0 mg/kg i.p.)	60	1.503 ± 0.138 (5)***	0.512 ± 0.072 (6)***
	120	0.893 ± 0.130 (11)*	0.289 ± 0.033 (11)**

n of determinations given in brackets. Significance of increase above saline controls: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. Student's '*t*' test.