

Factors influencing effect of hydrocortisone on rat brain tryptophan metabolism

THE concentrations of rat brain 5-hydroxytryptamine (5-HT) and its metabolite 5-hydroxyindole acetic acid (5-HIAA) have been found to be decreased by injection of hydrocortisone¹⁻³ or other corticosteroids⁴. Benkert and Matussek⁵ did not, however, observe changes in 5-HT concentration at various times

this protocol we now find a fall of both total and free plasma tryptophan and a fall of tryptophan concentration in both liver and brain (Table 1). Brain 5-HT decreased but not significantly, while 5-HIAA was considerably and significantly lowered (Table 1).

● Brain tryptophan, 5-HT and 5-HIAA are all unaltered following hydrocortisone (5 mg kg⁻¹) administration to gerbils⁷. In these animals (unlike the rat) the hepatic enzyme tryptophan pyrrolase is not induced by hydrocortisone^{7,8}. This is consistent with an association between

liver homogenates after hydrocortisone treatment, and has now been demonstrated in the perfused liver. Thus, kynurenine production from tryptophan by isolated perfused rat liver preparations is much lower in older animals both before and after hydrocortisone (5 mg kg⁻¹) pretreatment 3 h previously (Table 2).

Thus we have shown that hydrocortisone can alter tryptophan metabolism both peripherally and in the brain and confirm that changes are consistent with decreased brain 5-HT synthesis. These changes are,

Table 1 Effect of hydrocortisone on tryptophan metabolism in rats

Injected	Plasma tryptophan (µg ml ⁻¹)		Tissue tryptophan (µg g ⁻¹)		Brain 5-hydroxyindoles (µg g ⁻¹ wet weight)	
	Total	Free	Liver	Brain	5-HT	5-HIAA
Saline	27.04 ± 2.05	3.92 ± 0.84	4.89 ± 0.51	2.04 ± 0.19	0.45 ± 0.05	0.87 ± 0.12
Hydrocortisone	22.77 ± 3.38*	1.84 ± 0.51†	3.66 ± 0.35†	1.45 ± 0.09‡	0.38 ± 0.05	0.51 ± 0.06‡

Male Sprague-Dawley rats (Anglia Laboratory Animals, Alconbury) 35 d old were used. Animals were killed 6 h after injection. Plasma tryptophan was measured as described previously¹⁰, tissue tryptophan by the method of Denckla and Dewey¹¹ and brain 5-HT and 5-HIAA by the method of Curzon and Green¹². Results expressed as mean ± s.d. of six observations. Different from saline injected controls.

* $P < 0.05$.

† $P < 0.01$.

‡ $P < 0.001$.

Table 2 Influence of age on effect of hydrocortisone on kynurenine production by isolated perfused rat liver

Age (d)	Injected	Hepatic kynurenine production (µg ⁻¹ g ⁻¹ h ⁻¹)
35	Saline	35 ± 5(4)
	Hydrocortisone	139 ± 32(4)*
100	Saline	22 ± 8(4)†
	Hydrocortisone	65 ± 31(5)*‡

Livers were perfused by the method of Hems *et al.*¹³ with a semi-synthetic medium¹⁴ containing tryptophan (1.0 mM). Rats were injected with hydrocortisone (5 mg kg⁻¹) or saline 3 h before the start of the liver perfusion. Results expressed as mean ± 1 s.d. with number of observations in brackets.

* Different from saline-injected control rats of same age $P < 0.01$.

† Different from saline-injected 35-d rats $P < 0.05$.

‡ Different from hydrocortisone-injected 35 d rats $P < 0.01$.

after injecting hydrocortisone acetate. More recently, Hillier *et al.*⁶ reported no change of 5-HT but a rise of 5-HIAA 3 h after hydrocortisone (15 mg kg⁻¹ intraperitoneally). The latter authors also found no change in serum total tryptophan and an increase in free serum tryptophan at this time. The following observations may clarify these contradictory findings.

● Using the hydrocortisone dose of Hillier *et al.*⁶ of 15 mg kg⁻¹, we confirm that there is no change in total plasma tryptophan 3 h after injection of the steroid, but also found no alteration in free tryptophan. In the original work however^{1,2} 5 mg kg⁻¹ hydrocortisone (as the sodium succinate derivative) was injected intraperitoneally and brain 5-HT and 5-HIAA determinations were made 6 h later, at which time the decrease in both compounds was maximal. Using

the increased hepatic pyrrolase activity in rats following hydrocortisone² and the changes in tryptophan metabolism now reported.

● Other factors may also be important when studying the effects of hydrocortisone on tryptophan metabolism. The time courses of hydrocortisone actions depend on the form in which it is injected. Hydrocortisone sodium succinate leads to more rapid changes of pyrrolase activity than the less water soluble hydrocortisone acetate or free steroid⁹.

● The age of the animals is also important. Older animals (100 days or more) do not exhibit the brain 5-hydroxyindole changes or the large hepatic pyrrolase induction shown by younger rats (35 days; 120 g) following the same hydrocortisone dose per kg body weight⁹. This smaller increase of pyrrolase activity in older animals was previously demonstrated by measuring enzyme activity in

however, dependent on several factors; times of observation, age of animals and the hydrocortisone preparation used. Though it would be rash to extrapolate too readily from acute pharmacological experiments to a chronic illness such as endogenous depression, the possibility exists that similar changes have significant roles in the aetiology of psychiatric disorders in some subjects^{1,2} or, indeed, in the 5-HT metabolism of normal subjects in certain circumstances.

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