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MECHANISM OF DECLINE IN RAT BRAIN 5-HYDROXYTRYPTAMINE AFTER INDUCTION OF LIVER TRYPTOPHAN PYRROLASE BY HYDROCORTISONE: ROLES OF TRYPTOPHAN CATABOLISM AND KYNURENINE SYNTHESIS

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1 Two mechanisms have been proposed to explain the decline in brain tryptophan and 5-hydroxytryptamine (5-HT) after administration of hydrocortisone and the subsequent induction of liver pyrrolase. These are depletion of tryptophan by high rates of tryptophan catabolism and inhibition of tryptophan uptake by elevated levels of the tryptophan catabolite, kynurenine.

2 The increase in plasma kynurenine after hydrocortisone injection (25 mg/kg) was small, and kynurenine, at a concentration ten fold greater, did not inhibit tryptophan uptake by brain as measured by the Oldendorf technique. Thus, inhibition of tryptophan uptake by kynurenine is not an important mechanism in the control of brain tryptophan and 5-HT.

3 The decline in brain tryptophan after hydrocortisone was comparable to that seen in other tissues, which comprise more than half of the body weight of a rat.

4 The total decline in free tryptophan stores in whole animals treated with hydrocortisone was estimated to be about 450 μg. This amount of tryptophan would be catabolized by tryptophan pyrrolase in about 20 min, when the enzyme is induced, according to an earlier estimate of the rate of tryptophan catabolism *in vivo*.

5 Tryptophan pyrrolase activity remains high for much longer than 20 min, suggesting that there is net protein catabolism, which releases tryptophan and prevents non-protein tryptophan levels falling very far.

6 These results demonstrate that the decline in brain tryptophan and 5-HT after hydrocortisone is caused by depletion of tryptophan stores due to the high activity of tryptophan pyrrolase. However, our data suggest that this effect is diminished by release of tryptophan from proteins. Thus, peripheral protein metabolism may be an important factor in the control of brain tryptophan levels and 5-HT synthesis.

Introduction

Induction of rat liver tryptophan pyrrolase by the glucocorticoids hydrocortisone (Green & Curzon, 1968; Yuwiler, Wetterberg & Geller, 1971) or corticosterone (Scapagnini, Preziosi & DeSchaepdryver, 1969) or by the substrate analogue DL-α-methyltryptophan (Sourkes, 1971) results in a decrease in brain 5-hydroxytryptamine (5-HT). The fall in brain 5-HT is a consequence of a fall in brain tryptophan, which has been demonstrated after hydrocortisone (Green, Sourkes & Young, 1975) and DL-α-methyltryptophan administration (Sourkes, 1971). The effect of hydrocortisone is mediated by the induction of tryptophan pyrrolase, as hydrocortisone will not lower brain tryptophan or 5-HT in circumstances in which it does not increase the liver enzyme, e.g. in rats over about 100 days of age (Green & Curzon, 1975) and in the Mongolian gerbil (*Meriones unguiculatus*) (Green *et al.*, 1975).

The effect of glucocorticoids on brain 5-HT is controversial for two reasons. First, not all workers have seen this effect (Shah, Stevens & Himwich, 1968; Benkert & Matussek, 1970; Hillier, Hillier & Redfern, 1975). Second, if the effect is a real one, the mechanism is uncertain. Induction of tryptophan pyrrolase by hydrocortisone does increase the catabolism of tryptophan *in vivo* (Young & Sourkes, 1975) so it might be reasonable to assume that the decline in brain tryptophan is merely a result of the depletion of the animal's free tryptophan stores. However, glucocorticoids have an action on protein metabolism that is primarily catabolic (Munro, 1964). If there is net protein catabolism, tryptophan released from protein will augment the non-protein tryptophan stores.

If there is a decline in non-protein tryptophan in the animal, any effect on the brain must be mediated

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by the plasma. However, the data on plasma tryptophan after hydrocortisone are equivocal. Curzon & Green (1969) found a transient but significant fall of plasma tryptophan that was associated with the peak of tryptophan pyrrolase activity but not with the fall in brain 5-HT, which occurs later. In a later study Green, Woods, Knott & Curzon (1975) found a small but significant fall in total plasma tryptophan and a larger decline in free plasma tryptophan (the portion of plasma tryptophan that is not bound loosely to albumin), that was associated with the decline in brain tryptophan.

In looking for other possible mechanisms, whereby induction of pyrrolase might lower brain 5-HT, Green & Curzon (1970) examined the effect of various tryptophan catabolites on brain 5-HT. They found that kynurenine, 3-hydroxykynurenine, 3-hydroxyanthranillic acid and nicotinic acid all lowered brain 5-HT. Kynurenine and 3-hydroxykynurenine also inhibited uptake of tryptophan into brain slices. This finding on the uptake has been confirmed for kynurenine, but not for 3-hydroxykynurenine (Keily & Sourkes, 1973). The ability of kynurenine to lower brain 5-HT was confirmed by Gal, Young & Sherman (1978), who considered that the rise of plasma kynurenine after a tryptophan load might also have an important effect on the entry of tryptophan into the brain. However, Joseph & Kadam (1979) and Gould & Handley (1975) found no effect of kynurenine administration on brain 5-HT or 5-hydroxyindoleacetic acid (5-HIAA) levels, although the latter authors found a biphasic effect on 5-HT turnover, with low doses of kynurenine reducing it, while higher doses had no effect.

The picture that emerges from these studies is confused. In this study an attempt was made to answer the following questions. Is the decline in brain tryptophan after hydrocortisone representative of a decline in whole body tryptophan stores? Does the increase in catabolism of tryptophan in the liver after hydrocortisone account for the decline in whole body non-protein tryptophan stores? To what extent does kynurenine increase after induction of tryptophan pyrrolase and will these levels be sufficient to inhibit tryptophan uptake into brain?

Methods

Male Sprague-Dawley rats were obtained from Canadian Breeding Farms and Laboratories, Ltd, St Constant, Quebec. For uptake experiments male retired breeders weighing 500 to 700 g were used. For all other experiments rats weighing 120 to 150 g were used. Rats were deprived of food at 09 h 00 min on the day of an experiment, and the experiment was performed 2 h later.

Tryptophan uptake by the brain was measured by the technique of Oldendorf (1971). In this method 0.4 ml of a solution containing [^{14}C]-tryptophan and $^{3}H_2O$ (as a freely diffusible standard) is injected into the common carotid artery. After 15 s, when the solution has been washed out of the microcirculation by blood flow, the rat is decapitated. The ^{14}C:^{3}H is determined in the brain and in the injected solution. The ratio for brain, expressed as a percentage of the ratio for the injected solution, is the brain uptake index (BUI).

Tissue tryptophan content was measured by the method of Denckla & Dewey (1967). This method was not suitable for direct use with blood, because of interference by haem. Therefore 1 ml blood, collected from the cervical wound after decapitation, was homogenized with 3 ml ethanol. When the mixture was left at −20°C overnight there was complete precipitation of haem and complete recovery of tryptophan in the supernatant. Brain 5-HT and 5-HIAA were measured by the method of Ahtee, Sharman & Vogt (1970). Plasma kynurenine was measured by the method of Joseph & Risby (1975).

L-[side chain-3-^{14}C]-tryptophan was from New England Nuclear Corporation. L-Trypotophan, L-kynurenine, L-kynurenine sulphate and hydrocortisone 21-sodium succinate were from Sigma. Drugs were dissolved in isotonic saline and injected intraperitoneally in a volume of 10 ml/kg. Control animals received saline (10 ml/kg). Hydrocortisone was injected at a dose of 25 mg/kg because preliminary experiments suggested that this dose gave results with less variability than the 5 mg/kg used in previous studies.

Results

The effect of kynurenine on brain tryptophan

Hydrocortisone depletes tryptophan in tissues other than brain, such as the liver (Young & Sourkes, 1975). Therefore the effect of kynurenine on liver was examined as well as brain. The results in Table 1 show that no decrease in tissue tryptophan was detected even when kynurenine was injected at ten times the dose used previously by Green & Curzon (1975). Changes in brain tryptophan could alter the response to kynurenine; however, even when brain tryptophan was elevated by tryptophan administration, there was no effect of kynurenine on brain tryptophan (Table 1). Next the possibility that kynurenine might have an effect on 5-hydroxyindoles that is independent of its influence on tryptophan was examined. Even though it was confirmed that hydrocortisone lowers brain tryptophan, 5-HT and 5-HIAA, kynurenine did not alter the brain content of any of these compounds (Table 2).

Table 1 The effect of kynurenine administration on brain and liver tryptophan content

Pretreatment	*Dose of kynurenine* (mg/kg)	*Time of pretreatment* (h)	*Tissue*	*Tryptophan* (μg/g tissue) *Control*	n	*Treated*	n
	5	1	Brain	7.58 ± 0.44	5	7.24 ± 0.22	5
		2		6.64 ± 0.24	5	6.50 ± 0.42	5
	5	1	Liver	14.1 ± 0.7	5	13.6 ± 0.7	5
		2		16.9 ± 1.4	5	15.7 ± 1.3	5
	50	2	Brain	6.08 ± 0.33	5	5.43 ± 0.24	4
	50	2	Liver	14.1 ± 1.1	5	15.1 ± 0.8	4
Tryptophan (100 mg/kg)	5	2	Brain	18.8 ± 2.0	5	20.9 ± 3.4	5

Rats were injected intraperitoneally with saline or kynurenine sulphate at the dose of kynurenine shown at 1 or 2 h before death. Where indicated, pretreatment was given to both control and kynurenine-treated groups. Tryptophan was injected 5 min before the kynurenine. Results are given as mean ± s.e. In no case are the values for the treated group significantly different from the control group.

Table 2 The effect of administration of kynurenine or hydrocortisone on rat brain indoles

	n	*Brain indoles* (μg/g tissue) *Tryptophan*	*5-HT*	*5-HIAA*
Control	6	6.00 ± 0.28	0.51 ± 0.01	0.37 ± 0.01
Kynurenine (50 mg/kg, 1 h)	6	6.66 ± 0.46	0.50 ± 0.01	0.36 ± 0.01
Control	7	7.60 ± 0.30	0.50 ± 0.02	0.42 ± 0.02
Hydrocortisone (25 mg/kg, 6 h)	7	6.00 ± 0.25†	0.44 ± 0.01*	0.35 ± 0.01†

Kynurenine was injected as the sulphate and hydrocortisone as the 21-sodium succinate. These compounds, and saline for controls, were injected intraperitoneally. Results are given as mean ± s.e.
*$P < 0.05$, †$P < 0.01$ relative to control values.

Table 3 The effect of kynurenine or hydrocortisone on plasma kynurenine

Treatment	*Dose* (mg/kg)	*Time of pretreatment* (h)	*Plasma kynurenine* (μg/ml)	n	*P.v. control*
Control			0.71 ± 0.12	6	
Kynurenine	50	0.25	40.5 ± 4.9	5	< 0.001
Kynurenine	50	1	10.9 ± 1.5	6	< 0.001
Control			0.68 ± 0.09	6	
Kynurenine	5	0.25	5.24 ± 0.61	7	< 0.001
Kynurenine	5	1	0.99 ± 0.12	6	NS
Control			0.84 ± 0.05	8	
Hydrocortisone	25	3	1.03 ± 0.07	8	< 0.05
Control			0.59 ± 0.05	8	
Hydrocortisone	25	6	0.69 ± 0.08	7	NS

Kynurenine was injected as the sulphate and hydrocortisone as the 21-sodium succinate. These compounds, and saline for the controls, were injected intraperitoneally. Rats were decapitated and blood from the cervical wound was collected into beakers containing heparin. Results are given as mean ± s.e.

The effect of kynurenine and hydrocortisone on plasma kynurenine

If kynurenine injections can, under some circumstances, influence brain tryptophan it is obviously important to know whether the plasma concentration achieved after kynurenine administration is comparable to that achieved after induction of tryptophan pyrrolase. There was a small rise of plasma kynurenine 3 h after hydrocortisone treatment but the effect had disappeared 6 h after the injection (Table 3), when brain tryptophan, 5-HT and 5-HIAA were still low (Table 2). After kynurenine administration, even at 5 mg/kg, the rise in plasma kynurenine was much greater than that seen after induction of tryptophan pyrrolase. However, the kynurenine was metabolized quickly and the excess had disappeared from the plasma by 1 h after the injection (Table 3). Plasma kynurenine levels 0.25 h after kynurenine 5 mg/kg were still less than the level which was found to be inneffective in inhibiting tryptophan uptake by brain (Table 4). Therefore, brain tryptophan measurements at 0.25 h after kynurenine were not made.

Table 4 The effect of kynurenine on tryptophan uptake by brain

	BUI	n
Control	35 ± 3	7
Kynurenine (10 μg/ml)	39 ± 5	5

A solution containing L-[side chain-3-^{14}C]-tryptophan (1 μCi/ml and 100 μM), $^{3}H_2O$ (as a freely diffusible standard) and, for some experiments, kynurenine (10 μg/ml) was injected into the common carotid artery. The ^{14}C:^{3}H in brain as a percentage of the same ratio for the injected solution is the brain uptake index (BUI). More experimental details are given in the methods section. Results are given as mean ± s.e.

The effect of kynurenine on tryptophan uptake by rat brain

Injection of kynurenine, which did not influence brain tryptophan in this study, can produce a higher concentration of kynurenine in plasma than occurs after induction of tryptophan pyrrolase. This indicates that kynurenine does not inhibit tryptophan uptake by rat brain at the concentrations achieved in these experiments. This conclusion was tested using the technique of Oldendorf (1971) to measure tryptophan uptake by brain *in vivo*. Even at a kynurenine concentration of 10 μg/ml, a concentration ten fold greater than that found in plasma after induction of tryptophan pyrrolase (Table 3) there was no inhibition of tryptophan uptake (Table 4).

Depletion of free tryptophan stores after induction of tryptophan pyrrolase

Hydrocortisone decreased the tryptophan content of blood, muscle and liver as well as of brain (Table 5). Thus, induction of tryptophan pyrrolase does cause a general depletion of tryptophan stores within the animal. The fall in concentration was greatest for skeletal muscle which comprises 45% of the total body weight (Munro, 1970). Therefore, the greatest decline in the non-protein tryptophan content will occur within muscle. The decline in tissue tryptophan that occured within muscle, blood and liver was about 235 μg (Table 5). These three tissues account for about one-half of the total body weight of the animal. This indicates that the fall in free tryptophan for the whole animal is unlikely to be more than 450 μg.

Discussion

In this study two possible mechanisms by which induction of liver tryptophan pyrrolase might decrease brain 5-HT were examined. One alternative was inhibition, by elevated levels of kynurenine, of tryptophan uptake by brain. No inhibition of tryptophan uptake was found even at a concentration of kynurenine ten fold higher than that found in plasma after hydrocortisone treatment (Tables 3 and 4). These findings do not necessarily contradict earlier studies which showed that kynurenine inhibits tryptophan uptake by brain slices as those studies used higher concentrations of kynurenine (1 mM) (Green & Curzon, 1970; Keily & Sourkes, 1972). In patients treated with tryptophan as an antidepressant, plasma kynurenine levels are still less than the concentration at which we found no inhibition of tryptophan uptake (Chouinard, Young, Annable & Sourkes, 1979). Thus, elevated kynurenine is unlikely to antagonize the clinical action of tryptophan by this mechanism as suggested by Gal & Sherman (1980). The relatively small rise of plasma kynurenine after hydrocortisone can be explained by the high rate of kynurenine metabolism, as shown by its rapid disappearance from the circulation when it is administered (Table 3). These data also indicate that the pattern of increase of kynurenine after hydrocortisone is very different from that after kynurenine administration. Thus, the decline in brain 5-HT after induction of tryptophan pyrrolase is not mediated by kynurenine and any changes seen after kynurenine loads are probably not of physiological or pharmacological significance. Nevertheless, it would be of interest to know why kynurenine lowers 5-HT in some

Table 5 The effect of hydrocortisone on free tryptophan stores

Tissue	*Tryptophan* (μg/g or μg/ml) *Control*	*Hydrocortisone*	*Total weight* (g) *or volume* (ml) *of tissue*	*Decrease of total tryptophan in tissue* (μg)
Blood	12.2 ± 0.7	9.9 ± 0.4*	~10	23
Muscle	10.5 ± 0.7	7.2 ± 0.4†	~60	198
Liver	14.7 ± 0.5	12.4 ± 0.2†	6.03 ± 0.40	14.0
Brain	7.7 ± 0.3	6.0 ± 0.3†	1.65 ± 0.5	2.6

Saline or hydrocortisone (25 mg/kg as the 21-sodium succinate) were injected intraperitoneally 6 h before death. Results are given as mean ± s.e. Both groups consisted of 8 animals.
*$P < 0.05$; †$P < 0.01$ relative to control values.

laboratories and not in others, and what the mechanism might be.

The other possible mechanism for the decline in brain 5-HT was depletion of tryptophan stores. It has been estimated previously that the rate of tryptophan catabolism by tryptophan pyrrolase in a whole rat liver under normal circumstances is about 7 μg per min, and this increases about three fold when the enzyme is induced by hydrocortisone (Young & Sourkes, 1975). Thus, the important findings in this study are not only that hydrocortisone will lower brain tryptophan and 5-HT and that the decline of tryptophan concentration in the brain is comparable to that seen in the rest of the body, but also that the rate of catabolism of tryptophan in the liver is more than enough to account for the decline in whole-body stores of non-protein tryptophan. The decline in tryptophan is accounted for by the action of tryptophan pyrrolase for only about 20 min, after induction of the enzyme, yet tryptophan pyrrolase remains elevated for several hours after hydrocortisone. Presumably much of the tryptophan that is catabolized is newly released from labile protein stores in response to the administration of hydrocortisone, which has a primarily catabolic action (Munro, 1964). Much of the labile protein in the rat is in the liver, which rapidly synthesizes protein while amino acids are being absorbed from the digestive system, and then catabolizes the protein and releases amino acids in the post-absorptive state (Munro, 1970). Tryptophan is the least abundant amino acid in the pool available for protein synthesis and tryptophan levels play some role in regulating protein synthesis in the liver (Munro, 1970). Thus, initially elevated tryptophan pyrrolase activity may lower tryptophan levels in the liver and this might trigger net protein catabolism, with release of tryptophan from protein. Whether a decline in brain tryptophan occurs will presumably depend on the balance between tryptophan release from protein and tryptophan catabolism in the liver, and whether there is a sufficient decline in the liver tryptophan content for tryptophan to flow into the liver from other tissues.

The total non-protein tryptophan stores in a rat are equivalent to only about 4% of the rat's daily requirement for tryptophan (Munro, 1970). Thus, small differences in the net rate of protein catabolism, due to differences in the dietary or hormonal state of the animal, could cause relatively large changes in tryptophan stores. This could explain why different studies have found that brain tryptophan declines to a different extent, or does not decline, after glucocorticoid administration.

After a tryptophan load, protein synthesis will play no important part in controlling tryptophan levels and in these circumstances induction of tryptophan pyrrolase by hydrocortisone has a large effect on tryptophan levels (Joseph, Young & Curzon, 1976). When no tryptophan load is given the effect of hydrocortisone is probably opposed by release of tryptophan from protein. This implies that peripheral protein metabolism may be important in the control of brain levels of tryptophan and other aromatic amino acids which are neurotransmitter precursors.

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