Table 1 shows that animals treated with the narcotic antagonist cyprenorphine (CYP) had reduced brain concentration of [^{3}H]-ET. After the injection of 20 μg/kg [^{3}H]-ET, brain levels in CYP pretreated animals were reduced to a different extent depending on the dose ratio [^{3}H]-ET/CYP (expt. II). Such a different degree of reduction in [^{3}H]-ET levels was consistent with the effectiveness of the antagonism (partial or complete inhibition of catatonia) elicited by CYP. The comparison of the results obtained with the dose of CYP constant (e.g. 100 μg/kg, expt. I and II) and changing the amount of [^{3}H]-ET injected, did not indicate a relation between the dose ratio [^{3}H]-ET/CYP and the degree of reduction of [^{3}H]-ET levels.

The brain/plasma ratio of [^{3}H]-ET was approximately the same (about 4 : 1) irrespective of whether 0.2, 2 or 20 μg/kg [^{3}H]-ET had been injected; after 20 μg/kg this ratio was determined up to 3 hours. Fifteen minutes after injection the distribution of [^{3}H]-ET determined in the brainstem, hemispheres, and cerebellum was uneven; they presented concentrations in decreasing order, the one of cerebellum being about one-third that of the brainstem. Similar ratios between the concentrations in these brain regions were found regardless of the dose of [^{3}H]-ET injected (0.2, 2 or 20 μg/kg). Pretreatment with CYP prior to the administration of 20 μg/kg [^{3}H]-ET resulted in the similar reduction of [^{3}H]-ET levels in all brain regions except the cerebellum; [^{3}H]-ET in the spinal cord was also reduced. Other antagonists (i.e. nalorphine and naloxone) were also effective in reducing [^{3}H]-ET brain levels, while no such reduction could be evidenced with agonists (i.e. morphine and heroin) using several dose schedules and experimental conditions.

In view of the latter finding, the reduction in brain etorphine levels by opiate antagonists that we have reported cannot be at present regarded as the result of displacement of etorphine from specific mutual binding sites and therefore its nature remains to be determined.

[^{3}H]-etorphine was kindly provided by Reckitt & Colman, Hull, England.

Reference

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Effect of growth hormone deficiency on brain serotonin metabolism

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In recent years considerable evidence has been accumulated for the participation of brain serotonin (5-HT) in the neurohormonal control of anterior pituitary function; less attention has been paid to the effects of hormones on central 5-HT metabolism. Such an aspect has been considered in this investigation which has explored the possibility that plasma levels of circulating hormones may influence brain 5-HT metabolism.

In Sprague-Dawley female rats, hypophysectomized (hypox) two weeks before, brain tryptophan (TP) and 5-hydroxyindolacetic acid (5-HIAA) were significantly higher than in age-matched intact controls: (TP 6.9 ± 0.3 vs 3.4 ± 0.2 μg/g; 5-HIAA 0.65 ± 0.02 vs 0.39 ± 0.01 μg/g, respectively). Brain 5-HT levels were practically unchanged.

Since no change in tryptophan hydroxylase activity has been reported following hypophysectomy, the present results on 5-HT metabolism in hypox rats, could be explained by an increased TP availability in brain serotoninergic neurones.

Among the several physiological factors whose lack could be responsible for the effect present after pituitary ablation, growth hormone (GH) deserves particular attention. It is known in fact that GH has a profound effect on amino acid disposition.

Treatment of hypox rats with bovine GH (NIH B-17, 1 mg i.p. daily x 7 days), reduced considerably brain TP and 5-HIAA (TP 4.9 ± 0.2 vs 7.1 ± 0.3 μg/g; 5-HIAA 0.54 ± 0.03 vs 0.64 ± 0.01 μg/g, respectively) and did not modify 5-HT levels.

These results suggest that GH deficiency could be responsible at least in part for the altered 5-HT metabolism present in hypox rats.

Consistent with this view are the findings that in mature female dwarf mice (dw/dw) of Snell-Bag strain, which are selectively deficient in GH, brain

TP and 5-HIAA were markedly higher than in age-matched heterozygote mice (dw/+) (TP 6.40 ± 0.33 vs 4.20 ± 0.21 μg/g; 5-HIAA 0.65 ± 0.03 vs 0.33 ± 0.02 μg/g, respectively). Similar to hypox rats, a GH replacement therapy (200 μg i.p. daily for one week) significantly decreased brain TP and 5-HIAA in dwarf mice (TP 6.40 ± 0.3 vs 5.5 ± 0.2 μg/g; 5-HIAA 0.65 ± 0.03 vs 0.57 ± 0.014 μg/g, respectively).

The present findings support the possibility that fluctuations in some essential plasma constituents as a result of hormonal inputs may influence brain TP availability thus altering brain 5-HT metabolism.

Catecholaminergic control of Thyroid Stimulating Hormone (TSH) and Adrenocorticotrophic Hormone (ACTH) secretion

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The possibility that central monoaminergic system(s) may take part in controlling secretion of the anterior pituitary hormones has often been suggested (Ganong, 1972). While experimental evidence supports the existence of a central noradrenergic system tonically inhibiting secretion of corticotrophin releasing factor (Scapagnini & Preziosi, 1973), little data is available concerning the role played by central monoamines upon secretion of thyroid releasing hormone (Kotani, Onaya & Yamada, 1973).

In our study, the effect of pretreating rats with α-methyl-*p*-tyrosine (α-MpT), a catecholamine synthesis inhibitor capable of depleting brain catecholamines, was examined with respect to secretion of adrenocorticotrophic hormone (ACTH) and thyroid stimulating hormone (TSH) under basal and cold-stress conditions. Male rats, 200-220 g, were given α-MpT (250 mg/kg, i.p.), 1 h before and in some rats followed by L-Dopa (100 mg/kg i.p.) 45 min before cold stress (exposure to 4°C for 2 h), the latter ostensibly to enhance ACTH and TSH secretion; control rats were given an equivalent volume of saline, i.p. The rats were then decapitated and trunk blood collected for subsequent radioimmunological determination of ACTH (Vague, Oliver, Jaquet & Vague, 1971) and TSH (Jaquet, Franchimont, Rinaldi, Sainty, Codaccioni & Vague, 1971).

Results shown in Table 1 indicate that pretreatment of rats with α-MpT significantly enhanced ACTH secretion both in normal and cold-stressed rats. Concurrent administration of L-Dopa, a catecholamine precursor, reduces this effect in normal rats. TSH secretion was reduced following α-MpT, but only significantly so in the cold-stressed rats.

Our results are compatible with brain catecholamines influencing in an opposite way secretion of ACTH and TSH.

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Table 1

Treatment	*Plasma ACTH*	*Plasma TSH*
Saline	33.6 ± 6.1(10)	4.5 ± 1.3(10)
α-MpT	155.4 ± 16.9(5)*	3.4 ± 0.3(6)
α-MpT + L-Dopa	66.8 ± 9.5(6)*(a)	–
Saline + Cold stress (C.S.) 2 h	89.5 ± 10.9(10)*	18.8 ± 1.8(9)*
α-MpT + C.S.	125.7 ± 11.7(10)**	8.0 ± 1.0(9)***

ACTH and TSH are expressed respectively in pg/ml and uU/ml.
The values shown are means ± s.e. The figures within brackets show the number of rats. Asterisks represent statistical significant differences between mean values of ACTH and TSH for saline treated rats and those given α-MpT, α-MpT + L-Dopa with or without cold-stress (* $P < 0.01$ in comparison to saline treated rats: (a) $P < 0.01$ in comparison to α-MpT treated rats; ** $P < 0.05$ in comparison to cold-stress treated rats; *** $P < 0.01$ in comparison to cold-stress treated rats).