BIOCHEMICAL EVIDENCES FOR INTERACTION PHENOMENA BETWEEN NORADRENERGIC AND SEROTONINERGIC SYSTEMS IN THE CAT BRAIN

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RECENTLY, functional interactions between monoaminergic systems were suggested to explain some aspects of the sleep-waking cycle regulation (JOUVET, 1971; JOUVET and PUJOL, 1972). Indirect evidence for a noradrenergic control of serotonin (5-HT) synthesis was previously obtained in the cat PETITJEAN and JOUVET, 1970 and in the rat (BLONDAUX *et al.*, 1973; JOHNSON *et al.*,1972; JUGE *et al.*, 1972). In this paper we describe two experimental models of reciprocal biochemical mechanisms of regulation between some noradrenergic and serotoninergic neurons.

In a first experimental situation an inactivation of dorsal noradrenergic pathways was obtained by bilateral coagulation of the initial part of the bundle at the level of the ponto-mesencephalic junction. 48-Hours later, a global study of the rate of synthesis of 5-HT was performed in different brain areas by following the initial accumulation of ^{3}H-5HT and ^{3}H-5-hydroxy indole acetic acid (5-HIAA) endogeneously synthetised from exogenous ^{3}H-Tryptophan (Trp) (1 Ci/mM The Radiochemical Centre, Amersham) injected intravenously (1·5 mCi) 20 min before sacrifice. An important and significant increase of the *in vivo* conversion index of Trp was observed in the raphe region as well as in the cortex (Fig. 1) and in other areas of projection of the serotoninergic system (e.g. in the thalamus, mesencephalon or medulla oblongata).

A reciprocal interaction between the two aminergic systems was found by studying the effect of inactivation of the anterior part of the raphe system upon the rate of disappearance of Norepinephrine (NE) after blockade of its synthesis by alpha-methyl-*p*-Tyrosine (AMPT 2000 mg/kg i.p. 8 hr before the sacrifice). 48 Hours after coagulation of the raphe dorsalis and the raphe centralis nuclei the following observations were made:

(1) The destruction of the anterior part of the raphe system did not change the NE concentrations measured in the different brain structures examined 48 hr after the lesion.

(2) At this time, 8 hr after administration of AMPT, the NE concentrations measured in the cortex and cerebellum (Fig. 1) were significantly lower as compared to control animals. The rate of disappearance of NE was also higher in the mesencephalon but not in the other areas of the brain.

These results show that the surgical inactivation of the anterior raphe system induces a significant increase of NE turnover at the level of dorsal noradrenergic bundle terminals. Our observation of activation of both cortical and cerebellar terminals agrees with the increase in green fluorescence observed by Olson and

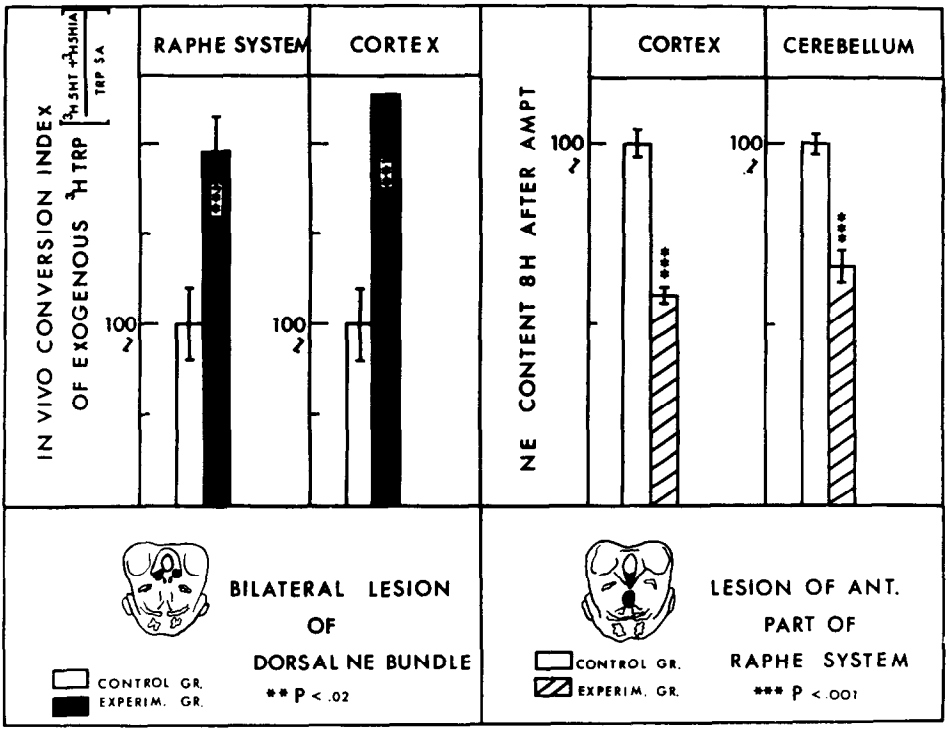

FIG. 1.—Biochemical interaction between serotonergic and dorsal ascending noradrenergic systems. In the left part of the figure results obtained 48 hr after bilateral coagulation of the dorsal noradrenergic bundles are represented The rate of synthesis of 5-HT was estimated by following the initial accumulation of ^{3}H-5HT and ^{3}H-5HIAA endogenously synthetised from ^{3}H-Trp and measuring the conversion index of Trp by the ratio:

$$\frac{^3\text{H-5HT} + ^3\text{H-5HIAA}}{\text{Trp S. A.}}$$

Results for the experimental group (black bars) are expressed as a percentage of the mean value for the control group (white bars) ± S.E.M. (5 determinations). *P*-values were calculated by a "t" test. The right part of the figure shows NE concentrations in the cortex and cerebellum of control cats (white bars) and raphe destroyed cats (hatched bars) 8 hr after blockade of NE synthesis by AMPT (200 mg/kg i.p.). Results are expressed as described above.

Fuxe in the cerebellum after lesion of dorsal noradrenergic pathway in the rat (OLSON and FUXE, 1971).

These facts strongly suggest the existence of interaction phenomena between the 5HT-containing neurons of the raphe system and the dorsal noradrenergic neurons. Anatomical demonstrations of these interconnections as well as their biochemical mechanisms remain to be elucidated.

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