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Control of ACTH- and MSH-secretion by catecholaminergic neurones in the tuber cinereum

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Ever since it has been recognized that the control of pituitary functions can be localized within the basal part of the hypothalamus, a good deal of experimental work on the regulation of the secretion of pituitary hormones has been focused upon the neuronal systems which can be found in this area of the brain stem.

Initially, much attention has been paid to a neuronal system which at that time (some twenty years ago) was the only well-recognized and circumscript system in the hypothalamus, the supraoptic-neurohypophysial tract. It consists of big cell bodies in the supraoptic and paraventricular nuclei, sending their axons to the posterior lobe of the pituitary, and it is supposed to elaborate the posterior lobe hormones, the octapeptides vasopressin and oxytocin, by way of a neurosecretory process. The neurosecretory material within these nerve cells could be visualized by several histochemical staining procedures. This system was first considered as the source of hypothalamic factors controlling the anterior lobe as well, but it appeared soon that this was not the case. It was then taken as a model for possible other neurosecretory systems within the hypothalamus, which could be specifically involved in the regulation of anterior lobe secretions. A line of thinking was developed, in which smaller neurosecretory cells (aptly called parvicellular systems) were supposed to produce the respective releasing or inhibiting factors for the different adenohypophysial hormones. These factors were thought to be peptides, mainly because of the analogy with the magnocellular system.

Unfortunately, up to now, it has not been possible to identify these systems by histochemical or other procedures, and it also proved very difficult to isolate and identify their products. At present, only a TSH-releasing factor (TRF) has been characterized chemically. In fact, it has not been demonstrated that such small neurosecretory or peptidergic hypothalamic neurons exist, but it would be difficult to propose other alternatives.

More recently, however, more interest was drawn to a third category of hypothalamic nerve systems, which have in common synaptic transmission

by acetylcholine or a number of monoamines, notably noradrenaline, dopamine or serotonin. Our knowledge about such monoaminergic neurons increased rapidly during the last few years, as a result of intensive pharmacological research on psychoactive drugs, and not in the least by the development of the specific histochemical fluorescence method.

From recent research it became clear that the activity of these monoaminergic systems correlates with changes in pituitary function, suggesting that they may be involved in some way in the control of the endocrine system. Since at the same time an important role of these neuronal systems in the regulation of vegetative and emotional processes (like sleep, food and water intake, temperature, sexual performance, mood and drive) was demonstrated, a provocative link could be made between neuroendocrine and behavioral patterns, which may render us a promising breakthrough in the field of psychosomatics.

We have been interested since many years in the control of the pituitary-adrenal system. The adrenal cortex produces a number of steroids, which production is regulated by ACTH from the anterior pituitary. The secretion of ACTH is supposed to be controlled by a still hypothetical releasing factor (CRF) from the hypothalamus, and the production of CRF should be influenced by neural and humoral stimuli, which convey a certain type of messages (generally concerning disturbances of the homeostatic regulations of the body) to the CRF-neurons.

An obvious assumption would be that neural stimuli reach these CRF-neurons by synaptic transmission, and this transmission could be of cholinergic, adrenergic or other aminergic character. Are such systems involved in the excitation or inhibition of CRF-neurons?

Earlier work with lesions and electrical stimulation suggested that structures activating the pituitary-adrenal system were situated in the anterior and tuberal region of the hypothalamus. In this respect it is interesting to note that according to the Swiss tradition of the work of Hess a balance system may exist in the hypothalamus, in which the anterior part would represent a trophotropic area and the posterior part an ergotropic area. These areas more or less coincide with respectively a parasympathetic and a sympathetic division of autonomic functions. In view of this, we have studied the effects of hypothalamic lesions destroying either the anterior or the posterior hypothalamus, and we found that anterior lesions inhibited the pituitary-adrenal response to stress, and that posterior lesions facilitated this response (Fig. 1, from SMELIK 1959). This would indicate that the posterior hypothalamus may exert an inhibitory influence on the secretion of ACTH.

Other lines of evidence also pointed into the direction of a central adrenergic inhibitory system for ACTH secretion. The hypersecretion of ACTH, induced by the administration of reserpine, has been interpreted in this way (WESTERMANN et al. 1962; MARKS et al. 1970; see also GOLD and GANONG 1967). In contrast, other drugs inhibiting monoamine synthesis did not

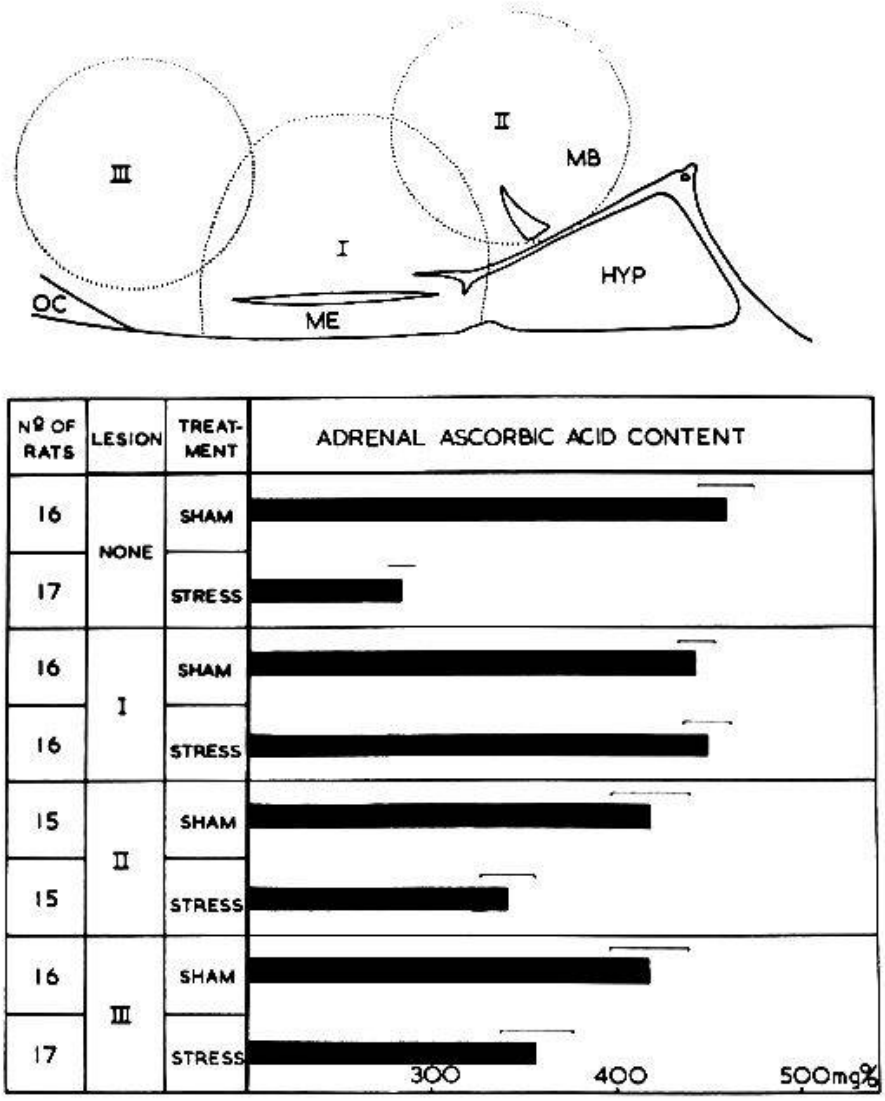

Fig. 1. Effect of three different hypothalamic lesions destroying either the anterior, posterior or tuberal region, on the adrenal ascorbic acid depletion following unilateral adrenalectomy. LA = left adrenal; RA = right adrenal, removed 1 h after LA.

affect ACTH secretion in response to stress (HIRSCH and MOORE 1968; DE SCHAEPDRIJVER et al. 1969; MARKS et al. 1970).

If drugs like reserpine would stimulate ACTH secretion by depletion of monoaminergic neural systems within the tuberal part of the hypothalamus, then the reserpine-induced hypersecretion of ACTH would be prevented by elimination of these systems. In order to obtain a specific and localized functional elimination of these nerves, we implanted reserpine in this region and checked the effectiveness of the implant by the disappearance of fluorescent material. Fig. 2 shows that in such animals, the usual rise in ACTH secretion after systemic reserpine administration remained present (SMELIK 1967).

On the other hand, central administration of carbachol has been reported to enhance ACTH secretion (KRIEGER and KRIEGER 1967; ENDRÖCZI et al. 1963; MARKS et al. 1970). Implants of atropine into the anterior part of the hypothalamus (Fig. 3) readily blocks the pituitary-adrenal response to

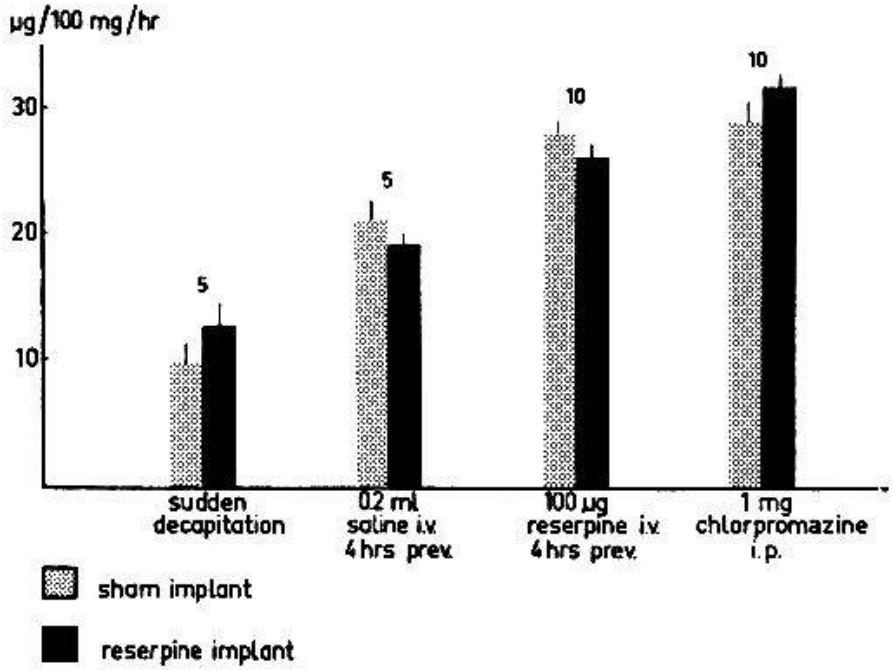

Fig. 2. *In vitro* corticosteroid production in response to intravenous injection of reserpine or chlorpromazine in rats, sham-implanted or implanted with 2 µg of reserpine into the tuberal part of the hypothalamus 2 days previously.

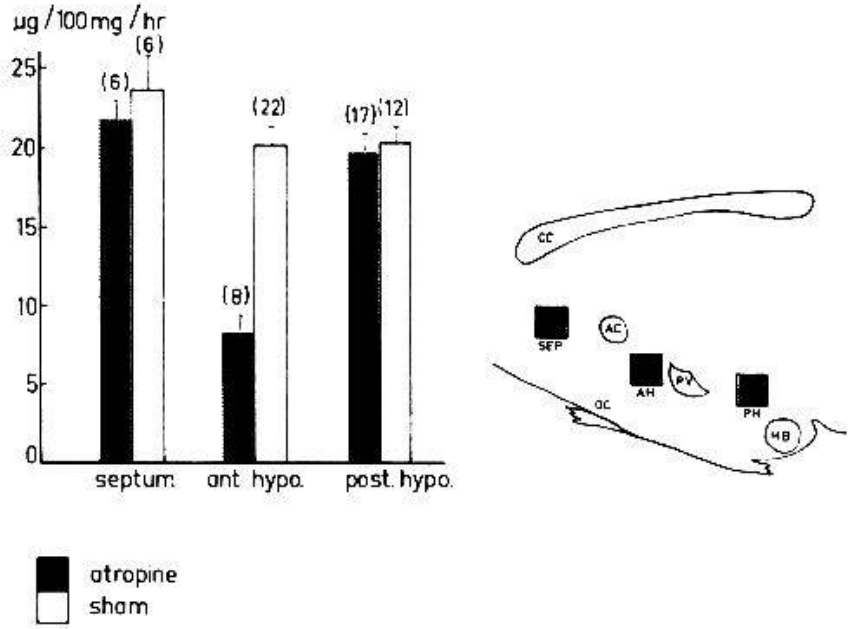

Fig. 3. *In vitro* corticosteroid production, 1 h after sham or atropine implantation into different hypothalamic sites under pentobarbital anesthesia.

stress (Hedge and Smelik 1968). This strongly suggests a cholinergic link in the afferent stimulation of the CRF neurons. Similar implants of drugs which would increase available noradrenaline on adrenergic receptor sites were completely without effect (Fig. 4).

The concept of a CRF-producing area within the anterior hypothalamus, on which a stimulatory cholinergic system and an inhibitory adrenergic

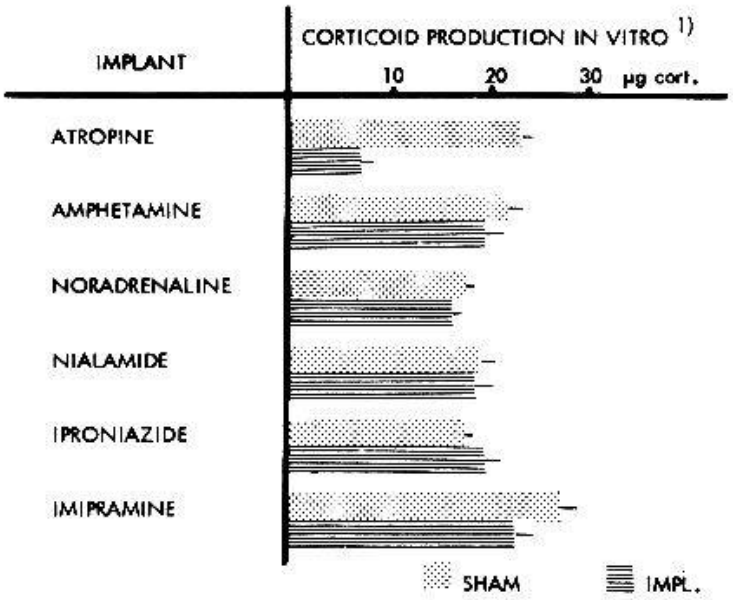

Fig. 4. *In vitro* corticosteroid production, 1 h after sham implantation or implantation of atropine or several adrenergic substances into the anterior hypothalamus under pentobarbital anesthesia.

system would impinge, is an attractive one, but the evidence is still rather circumstantial. So far, we were not able to demonstrate any role of hypothalamic monoaminergic nerve fiber systems in the control of ACTH secretion.

In considering possible monoaminergic neurons which might be involved in the control of the pituitary gland, one system deserves particular attention. This is the so-called tubero-infundibular tract, which has its cell bodies in the arcuate nucleus and sends its axons to the median eminence, where they end in the outer zone on and around the capillary loops of the portal vessel system. A portion of these fibers run through the hypophysial stalk, and their endings can be traced up to the intermediate lobe cells of the pituitary. This system has been shown to be dopaminergic, and it seems to be apt to influence pituitary function in a quite direct manner.

During the last years much attention has been paid to the possible role of this system. Its function has mainly been connected with the gonadotropic activity of the pituitary. It seems very unlikely that these dopaminergic neurons participate in the control of ACTH secretion. There is no correlation between their activity and pituitary-adrenal function (Fuxe and Hökfelt 1967; Smelik 1967).

On the other hand, we found that hypothalamic reserpine implants induced pseudopregnancy, which suggests an increased prolactin secretion (Van Maanen and Smelik 1968). Prolactin shares with MSH an inhibitory control by the hypothalamus; only for these two hormones inhibiting hypothalamic factors (PIF and MIF) are supposed to exist. There are several conditions (e.g. lactation) in which both hormones are released simultaneously by the same stimuli.

It is tempting to speculate that the tubero-infundibular dopaminergic system is involved in the regulation of these two pituitary hormones.

Studies on the regulation of MSH secretion have always been hampered by the fact that blood levels cannot be measured in experimental animals, so that the only information is derived from estimations of the pituitary MSH content. Such data are of limited value, not only because one cannot differentiate between synthesis and release, but also because there is such a variation in the MSH concentration, that the changes generally are given as a percentage.

We have tried to overcome this problem by incubation of intermediate-posterior lobes of rats *in vitro* during several hours, and determination of the amount of MSH released into the medium and the amount present in the tissue before and after incubation. In this way an estimation of the secretory activity of the gland appeared to be possible.

Incubation of intermediate lobe tissue with catecholamines initially showed a marked depression of MSH-activity in the medium, but this appeared to be due to a direct effect of the amines on the MSH-assay system, the chromatophores of the skin of the lizard *Anolis carolinensis*. However, the MSH and the amines could be separated by passing the medium through a small Sephadex G-10 column. Preliminary results with this system indicate that small amounts of dopamine, when added to intermediate lobe tissue *in vitro*, can inhibit the secretion of MSH into the medium.

It seems possible, therefore, that the tubero-infundibular dopaminergic system plays an important role in the control of some pituitary hormones.

In conclusion, the study of the role of monoaminergic pathways in the hypothalamus may be an important contribution to a better understanding of the controlling systems for the pituitary secretions. At the same time, this will render us more insight in the interrelationships between neuro-endocrine functions and vegetative or emotional processes, in which these neuronal systems also play a crucial role.

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