# HYPOTHALAMIC CATECHOLAMINES (CA) AND THE SECRETION OF GONADOTROPINS AND GONADOTROPIN RELEASING HORMONES

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IT IS now well established that the function of the pituitary is modulated by the hypothalamus (Ht) (HARRIS, 1970). In this paper we shall discuss the role of catecholaminergic mechanism on the alteration of the release of luteinizing hormone releasing hormone (LH–RH), follicle-stimulating hormone releasing hormone (FSH–RH), and prolactin release inhibiting hormone (PR–IH), which in turn regulates the release of luteinizing hormone (LH), follicle-stimulating hormone (FSH) and prolactin. *In vitro* and *in vivo* experiments have been applied to the problem. Hormones were measured by radioimmunoassays.

In the initial experiments, we measured monoamine oxidase activity (MAOA) in the entire Ht and different Ht regions, in the amygdala and cerebral cortex of male and 4 day cyclic female rats, using radioisotopic methods (KAMBERI and KOBAYASHI, 1970).

As shown in Fig. 1, measurements of MAOA in the Ht and amygdala demonstrated cyclic changes during the estrous cycle. Extracts from the whole Ht show a peak of activity at P1 of the day of proestrus. A dramatic fall in MAOA occurred in the afternoon of the day of proestrus (P3). Subsequently, there was a smaller peak of MOAO on the day of estrus. Lowest levels occurred at P3, D1 and M2. The amygdala, also showed cyclic changes with an increase at P1 and peaking at P2 on the day of proestrus. The cerebral cortex possessed much lower levels of MAOA and showed no cyclic changes (Fig. 1). Cyclic changes were found when various Ht zones were dissected and measured individually. The median eminence showed the highest activity throughout the cycle, mirroring the levels of MAOA of the whole Ht. MAOA in other Ht-zones (anterior, lateral, posterior) was considerably less. No cyclic changes in MAOA have been found in the Ht of male rats (KAMBERI and KOBAYASHI, 1970).

Number of studies recently have shown that 17$\beta$-estradiol is a major ovarian hormone responsible for preovulatory release of gonadotropins. Recently we have found that $\alpha$-methylthyrosine, an inhibitor of CA synthesis, when injected to the 4 day cycling rats, in the morning of the day of diestrus (D2) prior to the day of proestrus, affectively inhibited the proestrus rise in 17$\beta$-estradiol, abolished cyclic changes in MAOA in the Ht and amygdala during the day of proestrus (Fig. 1), and prevented proestrus surge of gonadotropins. This result suggests that CA are involved in regulation of secretion of gonadotropins, but do not specify which of the CA are in question.

In our further work, we decided that these results would have to be supplemented by further experiments, before the role of CA as synaptic transmitters could be considered established. For this purpose different CA compounds and CA-depleting or

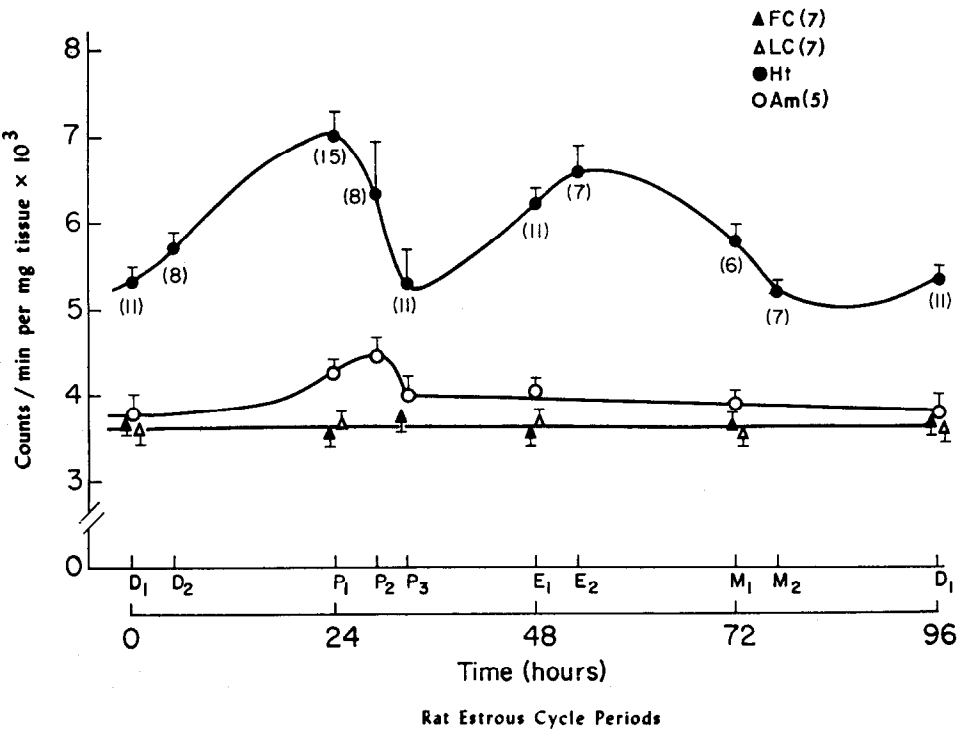


FIG. 1.—Brain monoamine oxidase activity during the estrous cycle. The number of rats analysed is in brackets; each point represents the mean ± SEM. Abbreviations: FC, frontal cortex; LC, lateral cortex; Ht, hypothalamus; Am, amygdala; D, diestrus; P, proestrus; E, estrus; M, metestrus; D1, P1, E1, M1 = 10 a.m.; D2, P2, E2, M2 = 3 p.m.; P3 = 6–7 p.m. (From KAMBERI and KOBAYASHI, 1970.)

adrenergic blocking agents were applied to the problem under *in vitro* and *in vivo* conditions (KAMBERI, 1973a, b). It was found that, of the CA, epinephrine and norepinephrine in relatively higher dose levels (5–100 μg) and dopamine in lower doses (~1 μg) had a stimulatory effect on release of LH, FSH, and an inhibitory effect on the release of prolactin (KAMBERI *et al.*, 1970a, b; 1971a, b). The effect of CA on LH, FSH, and prolactin release were observed only when anterior pituitary halves have been co-incubated in the presence of ventral hypothalamic fragments or CA were administered intraventricularly. The CA precursor, L-3,4-dihydroxyphenylalanine (L-dopa), injected systemically, also stimulated the release of gonadotropin and inhibited the release of prolactin (KAMBERI, 1973a, b). The effects of CA tested were actually on the discharge of hypothalamic hypophysiotropic hormones, since we have demonstrated that LH–RH, FSH–RH, and PR–IH activities in hypophysial portal blood (KAMBERI *et al.*, 1969; 1970c, d; 1971c) were elevated after intraventricular injection or co-incubation of pituitary halves in presence of hypothalamic fragments (KAMBERI *et al.*, 1970b). Conversely, no effect was observed when CA agents were infused directly into anterior pituitary *via* a cannulated hypophysial portal vessel or were incubated in the presence of anterior pituitary halves alone (KAMBERI *et al.*, 1970a, b; 1971a, b, c). It was found that this effect of CA on release of LH–RH, FSH–RH and PR–IH, could be potentiated, when clonidine-HCl, a noradrenergic

stimulating agent, is simultaneously administered with the CA. It is tempting to postulate that CA can enter the intracellular pool of the hypothalamus, be taken up by adrenergic nerve terminals, and subsequently re-released as norepinephrine or some other active monoamine metabolite, through which the discharge of LH–RH, FSH–RH and PR–IH is effected. Furthermore, this stimulatory effect of CA on the release of LH–RH, FSH–RH and PR–IH is linked to the α-adrenergic receptors of the hypothalamus. This is supported by our finding that administration of phenoxybenzamine, an α-adrenergic blocking agent along with CA, prevented the response seen with CA alone, whereas administration of pronethalol, a β-adrenergic blocking agent, with CA failed to do so (KAMBERI *et al.*, 1970b, e).

## SUMMARY AND COMMENTS

From these experiments, it is clear that catecholaminergic mechanism is involved in the control of gonadotropin and prolactin secretion. In both *in vivo* and *in vitro* studies, relatively small doses of dopamine and large doses of norepinephrine or epinephrine, induced the release of FSH and LH and inhibited prolactin. The release of these hormones is mediated through the hypothalamus, secondary to a discharge of FSH–RH, LH–RH and PR–IH, and this effect seems to be linked to the α-adrenergic receptors of the hypothalamus.

However, other investigators are not in uniform agreement with the above action of catecholamines on the release of FSH–RH, LH–RH and PR–IH. FUXE and HÖKFELT (1969) on the basis of their fluorescence microscopic data suggest that dopamine has an inhibitory effect on LH–RH release and a stimulatory effect on PR–IH. The recent results of Hale and SYMINGTON (1972) may help to explain these divergent findings. They found that dopamine stimulates the release of FSH from pituitaries incubated in the presence of whole hypothalami, whereas dopamine suppressed gonadotropin release from pituitary tissue incubated in the presence of stalk median eminence only. These findings suggest that two different mechanisms concerning the gonadotropin release may exist. One which involves the perikaryons of the Ht-hypophysiotropic hormone (HHH) secreting neurons upon which dopamine or catecholamines have a stimulatory action, the other may involve the nerve terminals of the HHH secreting cells upon which dopamine or catecholamines have an inhibitory effect. If so, discrepancies in results obtained by us using physiological-biochemical techniques, with those reported by Fuxe and his associates, using histofluorescence microscopy, can be easily explained. Namely, intraventricular injection of dopamine in our experiments causes an increase of dopamine in the perikaryons of HHH secreting neurons, which could be reflected in a decrease of dopamine in nerve terminals, as observed by Fuxe and his associate. It is interesting to note, however, that more recent results of LICHTENSTEIGER (1973) similarly using histofluorescence microscopy, are not in agreement with the data of FUXE and HÖKFELT (1969).

*Acknowledgements*—The author wishes to thank Miss Lynette Meyers, Miss Elisa Bacleon, and Mrs. Maria A. Kamberi for their generous assistance in the preparation of this manuscript. This work was supported by General Research Support Grant 5SO1RRO555 from N.I.H.

## REFERENCES

FUXE K. and HÖKFELT T. (1969) In: *Frontiers in Neuroendocrinology.* (GANONG W. F. and MARTINI L., eds.) pp. 47–96. Oxford University Press, New York.

HALE D. H. and SYMINGTON R. B. (1972) *S. Afr. Med. J.* **46**, 787–791.

HARRIS G. W. (1970) In: *Hypophysiotropic Hormones of the Hypothalamus: Assay and Chemistry.* (MEITES J., ed.) pp. 1–20. Williams and Wilkins, Baltimore.
KAMBERI I. A. (1973a) In: *Proceedings of the IV International Congress of Endocrinology.* (SCOW R. O., ed.) pp. 485–492. Excerpta Medica Fndn., Amsterdam.
KAMBERI I. A. (1973b) *Prog. Brain Res.* **39,** in press.
KAMBERI I. A. and KOBAYASHI Y. (1970) *J. Neurochem.* **17,** 261–268.
KAMBERI I. A., MICAL R. S. and PORTER J. C. (1970a) *Endocrinology* **87,** 1–12.
KAMBERI I. A., SCHNEIDER H. P. G. and MCCANN S. M. (1970b) *Endocrinology* **86,** 728–284.
KAMBERI I. A., MICAL R. S. and PORTER J. C. (1971a) *Endocrinology* **88,** 1003–1011.
KAMBERI I. A., MICAL R. S. and PORTER J. C. (1971b) *Endocrinology* **88,** 1012–1020.
KAMBERI I. A., MICAL R. S. and PORTER J. C. (1969) *Science* **166,** 388–390.
KAMBERI I. A., MICAL R. S. and PORTER J. C. (1970c) *Nature (Lond.)* **227,** 714–715.
KAMBERI I. A., MICAL R. S. and PORTER J. C. (1970d) *Experientia* **26,** 1150–1151.
KAMBERI I. A., MICAL R. S. and PORTER J. C. (1971c) *Endocrinology* **89,** 1042–1046.
KAMBERI I. A., MICAL R. S. and PORTER J. C. (1970e) *Physiologist* **13,** 239.
LICHTENSTEIGER W. (1973) In: *Proc. IV Int. Congr. Endocrinology.* (SCOW R. O., ed.) Excerpta Medica Fndn., Amsterdam, in press.