Effects of releasing factors on hypothalamic neurons

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EFFECTS OF RELEASING FACTORS ON HYPOTHALAMIC NEURONES

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Summary

Our previous reports on the effect of locally applied polypeptides such as ACTH, the releasing factors TRF and LRF on single unit activity of hypothalamic neurones have been confirmed and extended by several workers. These polypeptides also exhibit behavioural effects. The concept that such hormonal polypeptides may exert neurotransmitter as well as neuromodulator function has gradually become acceptable.

Zusammenfassung

Die hypothalamischen Regulations-Peptide - "Releasing"-Faktoren - TRF und LRF sowie das Polypeptid ACTH können, mikroiontophoretisch appliziert, die neuronale Aktivität von einzelnen im Hypothalamus gelegenen Neuronen verändern. Andrerseits können diese Polypeptide aber auch das Verhalten beeinflussen. Als Arbeitshypothese für weitere Untersuchungen wird vorgeschlagen, zu prüfen, ob diese hypothalamischen Regulations-Peptide im Zentralnervensystem nicht auch als Neurotransmitter und/oder Neuromodulatoren wirken könnten.

Are hypothalamic releasing factors genuine neurotransmitters which, during phylogenetic development, have assumed additional control over the anterior pituitary at a time when such a need arose? With a view to this we have investigated some electrophysiological correlates of polypeptide actions on the brain. As a suitable technique for the exploration of the central nervous system, the method of microiontophoresis (STEINER, RUF and AKERT, 1969; STEINER, 1971) was used. This technique provides a means of testing the sensitivity of brain neurones to neurotransmitters and related substances, such as polypeptides.

This report is mainly a review of our work with the pituitary polypeptide adrenocorticotropin (ACTH), the hypothalamic polypeptides thyrotropin releasing factor[1] (TRF) and luteinizing-hormone releasing factor[1] (LRF) and the thyroid hormones triiodothyronine (T_3) and L-thyroxine (T_4). All these investigations were carried out on male albino rats under urethane or chloralose-urethane anaesthesia (for technical details see STEINER, 1975).

ACTH. The effect of corticotropin (tetracosactide) on steroid-sensitive neurones was tested (STEINER, RUF and AKERT, 1969). 75 % of these cells were activated by ACTH. These neurones could play a role in the feedback control of corticotropin releasing factor (CRF) and ACTH secretion by the anterior pituitary.

Hypothalamic releasing factors, TRF and LRF. It has been found that TRF and LRF not only function as peptidergic messengers to the anterior pituitary glands but also have direct behavioural effects (PRANGE et al., 1972; PFAFF, 1973). From the extent of their distribution within the brain (PALKOVITS, 1977; HÖKFELT, 1977) it may well appear that these substances not only regulate the activity of anterior pituitary gland, but have direct neuronal effects in their own right. TRF, applied by microiontophoresis, inhibited the discharge rate in 10 % of the investigated hypothalamic neurones (STEINER, 1973; STEINER, 1975). This type of inhibition is shown in figure 1. All TRF sensitive cells are located in the basal hypothalamus. Systemically applied TRF (20 µg/kg i.v.) was also tested, and similar results were obtained. On the other hand, we have observed an activation of the same neurones by locally applied thyroid hormones, such as triiodothyronin (T_3) and L-thyroxin (T_4). That such polypeptide-sensitive neurones are also targets of peripheral hormones thus can hardly be doubted any longer. The same can be said for LRF-sensitive neurones. With LRF (STEINER, 1975) 29 neurones in the basal hypothalamus and the preoptic area were tested, in each region one neurone was inhibited (ca. 6 %) (cf. DYER and DYBALL, 1974; KAWAKAMI and SAKUMA, 1974; MOSS et al., 1975; RENAUD and MARTIN, 1975; RENAUD et al., 1975). Polypeptide neurones have also been depressed by dopamine locally delivered.

Identification of polypeptide-sensitive neurones by remote electrical stimulation. To this end a stimulating electrode was inserted into the homolateral preoptic area and attempts were made to drive cells localized in the basal hypothalamus and which were demonstrably sensitive to TRF by electrical stimulation (cf. DYER and CROSS, 1972). Two neurones could be driven from the preoptic area, one of which was inhibited by the local application of TRF, as well as by locally delivered dopamine. This TRF-sensitive neurone did not respond to LRF.

[1] Synthetized by Dres. D. GILLESSEN and R.O. STUDER, Diagnostic Research Department, F. Hoffmann-La Roche & Co. Ltd., Basle

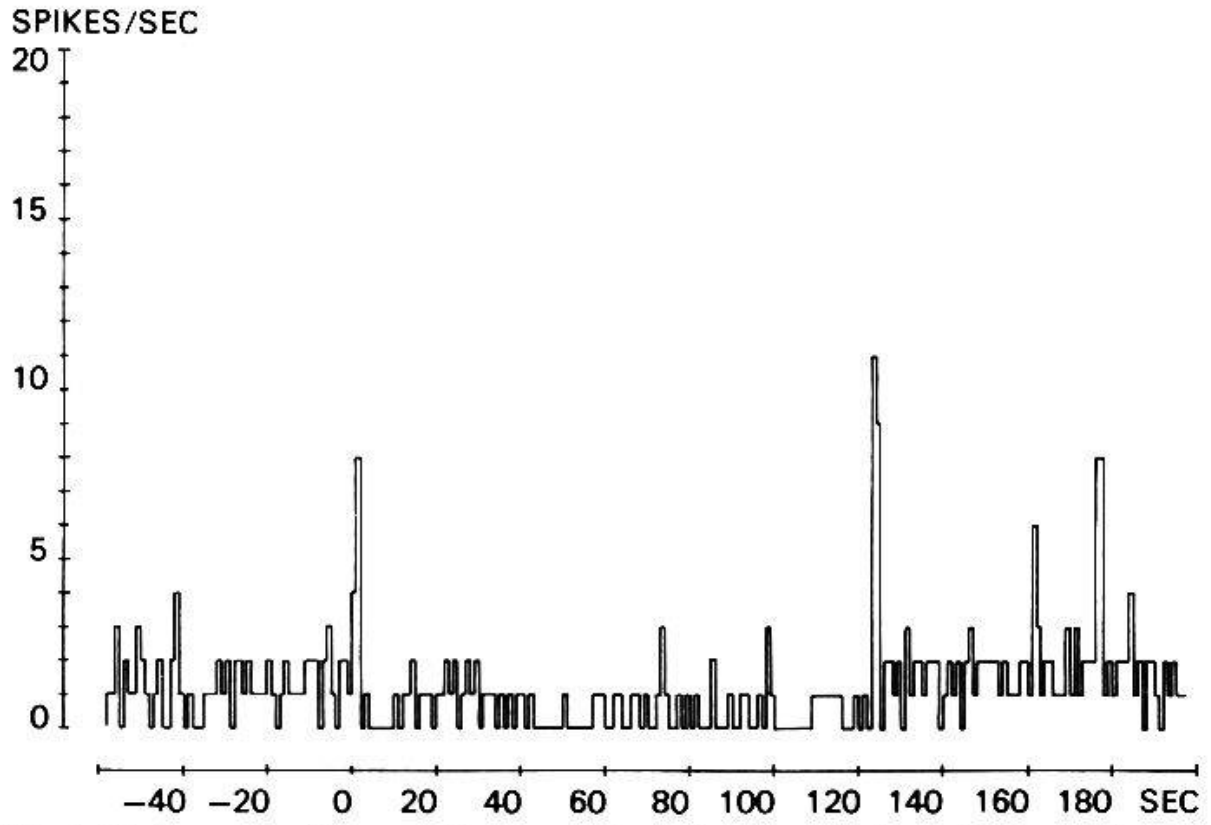

Fig. 1. Discharge rate histogram of a neurone in the basal hypothalamus. Horizontal bar denote duration of iontophoretic delivery of TRF with a current of 20 nA.

These results demonstrate that hypothalamic regulatory peptides - releasing factors - can influence neuronal activity of hypothalamic neurones. On the other hand, we know from other workers (PRANGE, 1972; PFAFF, 1973) that such polypeptides, e.g. TRF and LRF (as well as ACTH, DE WIED, 1966), can also have behavioural effects. The question raised at the beginning as to whether hypothalamic regulatory peptides are primary neurotransmitters is still open, but represents an adequate working-hypothesis. Moreover, the question could be extended to include functions as neuromodulators as proposed some years ago (STEINER, 1971; STEINER, 1974): neuromodulators are substances that are able to alter neuronal activity or neuronal responsiveness. In the future, this dual hypothesis (neurotransmitter versus neuromodulator) should be tested rigorously in various brain regions and employing all available methods (biochemical, electrophysiological, anatomical, pharmacological) at hand.

De Wied, D.: Inhibitory effect of ACTH and related peptides on extinction of conditioned behavior in rats. Proc. Soc. Exptl. Biol. Med., 122, 28-32 (1966).

Dyer, R.G. and Cross, B.A.: Antidromic identification of units in the preoptic and anterior hypothalamic areas projecting directly to ventromedial and arcuate nuclei. Brain Res., 43, 254-258 (1972).

Dyer, R.G. and Dyball, R.E.J.: Evidence for a direct effect of LRF and TRF on single unit activity in the rostral hypothalamus. Nature (London), 252, 486-488 (1974).

Hökfelt, T.: Immunocytochemistry of releasing hormones. Not published paper read at the Symposium "Releasing Factors" of the Swiss Academy of Medical Sciences, October 28, 1977.

Kawakami, M., and Sakuma, Y.: Responses of hypothalamic neurons to the microiontophoresis of LH-RH, LH and FSH under various levels of circulating ovarian hormones. Neuroendocrinology, 15, 290-307 (1974).

Moss, R.L., Kelly, M., and Dudley, C.: Responsiveness of medial-preoptic neurons to releasing hormones and neurohumoral agents. Federation Proc., 34, 219 (1975).

Palkovits, M.: Neurochemical Anatomy of the Neuroendocrine Hypothalamus. Bull. Schweiz. Akad. Med. Wiss. 34, Nr. 1 - 3 (1978).

Pfaff, D.W.: Luteinizing hormone-releasing factor (LRF) potentiates lordosis behavior in hypophysectomized ovariectomized female rats. Science, 182, 1148-1149 (1973).

Prange, H.J., Wilson, I.C., Lara, P.P., Alltrop, L.B. and Breese, G.R.: Effects of thyrotropin-releasing hormone in depression. Lancet, 1972 (II), 999-1002.

Renaud, L.P. and Martin, J.B.: Thyrotropin releasing hormone (TRH): depressant action on central neuronal activity. Brain Res. 86, 150-154 (1975).

Renaud, L.P., Martin, J.B. and Brazeau, P.: Depressant action of TRH, LH-RH and somatostatin on activity of central neurones. Nature (London) 255, 233-235 (1975).

Steiner, F.A.: Neurotransmitter und Neuromodulatoren. Georg Thieme-Verlag, Stuttgart, 1971.

Steiner, F.A.: Effects of locally applied hormones and neurotransmitters on hypothalamic neurons. Endocrinology, Proc. 4th Int. Congr. Endocrin., Washington, 1972. Int. Congr. Ser. No. 273, pp. 202-204, Excerpta Medica, Amsterdam, 1973.

Steiner, F.A.: Neurotransmitters and neuromodulators, Proc. 4th Int. Congr. Neurogenet. Neuroophthalmol. 1973. Acta Genet. Med. Gemellol. (Roma) 23, 123-128 (1974).

Steiner, F.A.: Electrophysiological mapping of brain sites sensitive to corticosteroids, ACTH, and hypothalamic releasing hormones in W.E. Stumpf and L.D. Grant eds. Anatomical Neuroendocrinology, Int. Conf. Neurobiology of CNS-Hormone Interactions, Chapel Hill, 1974, pp. 270-275, Karger, Basle, 1975.

Steiner, F.A., Ruf, K. and Akert, K.: Steroid-sensitive neurons in rat brain: anatomical localization and responses to neurohumours and ACTH. Brain Res. 12, 74-85 (1969).

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