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## EFFECTS OF RELEASING FACTORS ON HYPOTHALAMIC NEURONES

F. A. STEINER

### 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 neuro-modulator 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. Andererseits 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<sup>1</sup> (TRF) and luteinizing-hormone releasing factor<sup>1</sup> (LRF) and the thyroid hormones triiodothyronine (T<sub>3</sub>) and L-thyroxine (T<sub>4</sub>). 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<sub>3</sub>) and L-thyroxin (T<sub>4</sub>). 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.

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

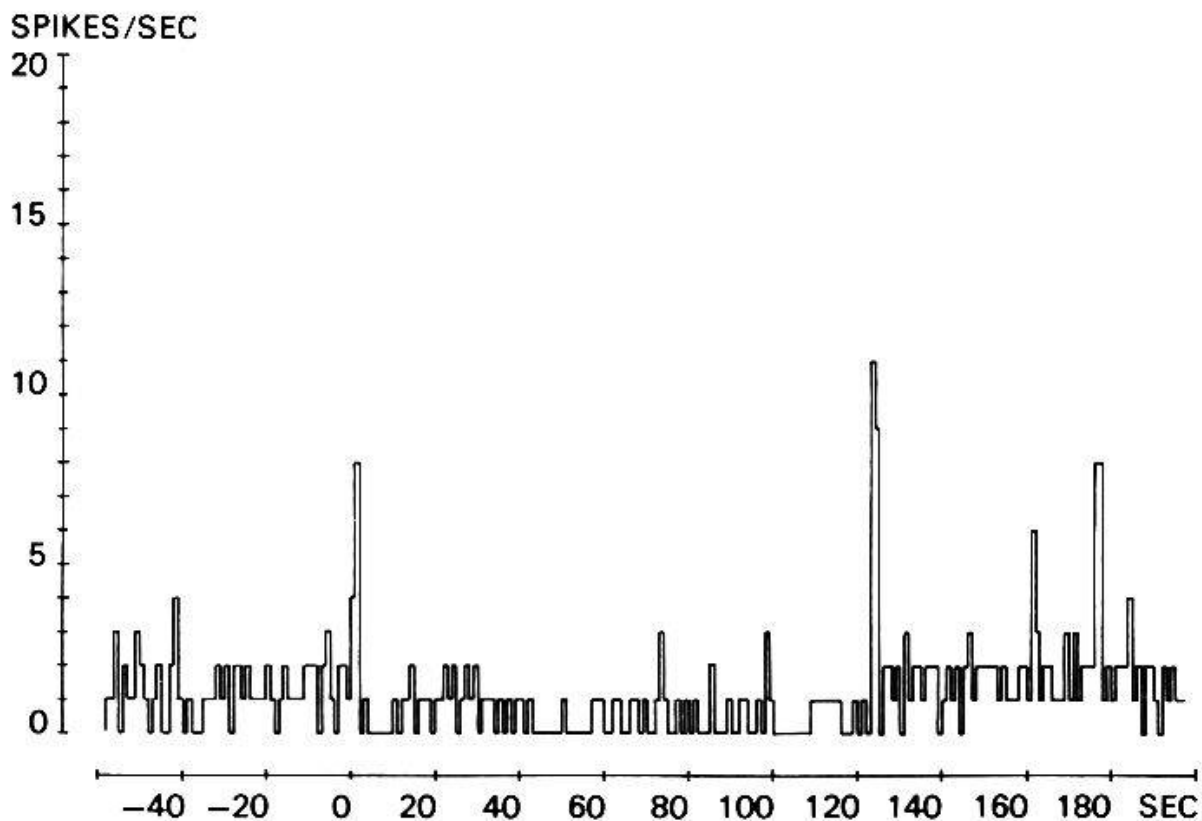


Fig. 1. Discharge rate histogram of a neurone in the basal hypothalamus. Horizontal bar denote duration of iontophoretic delivery of TRF with a current of 20 nA.

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.

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