[1] H. Künzi, M. Manneberg, and R. O. Studer, in preparation.
[2] H. Sievertsson, J.-K. Chang, A. von Klaudy, C. Bogentoft, B. Currie, K. Folkers, and C. Bowers, J. Med. Chem. **15**, 222 [1972].
[3] R. Geiger, W. König, H. Wissmann, K. Geisen, and F. Enzmann, Biochem. biophysic. Res. Commun. **45**, 767 [1971].
[4] N. Yanaihara, C. Yanaihara, M. Sakagami, K. Tsuji, T. Hashimoto, T. Kaneko, H. Oka, A. V. Schally, A. Arimura, and T. W. Redding, J. Med. Chem. **16**, 373 [1973].
[5] G. R. Flouret, W. H. Arnold, J. W. Cole, R. L. Morgan, W. F. White, M. T. Hedlund, and R. H. Rippel, J. Med. Chem. **16**, 369 [1973].
[6] M. Fujino, T. Fukuda, S. Kobayashi, and M. Obayashi, Chem. pharmac. Bull. [Tokyo] **21**, 87 [1973].
[7] D. Gillessen, A. M. Felix, W. Lergier, and R. O. Studer, Helv. chim. Acta **53**, 63 [1970].
[8] Y. Okada, K. Kitamura, Y. Baba, A. Arimura, and A. V. Schally, Biochem. biophysic. Res. Commun. **53**, 1180 [1973].
[9] H. N. Rydon and P. W. G. Smith, J. chem. Soc. [London] **1956**, 3642.

Control of Secretion of Hypothalamic Hormones

L. Martini

Universita di Milano, Istituto di Endocrinologia, 20129 Milano, Italy

Data will be presented which indicate that the median eminence region of the hypothalamus is not directly responsible for the synthesis of the gonadotrophin releasing factors. It will be shown that the paraventricular region is specifically involved in the synthesis of FSH-RF, while the suprachiasmatic and the arcuate-ventromedial zones are specifically devoted to the synthesis of LH-RF.

Three experimental conditions will be discussed in which the intrahypothalamic stores of one gonadotrophin releasing factor have been modified without changing those of the other. These observations are not compatible with the hypothesis that one single hypothalamic factor controls the release of both LH and FSH as recently suggested.

In a series of *in vitro* experiments it has been shown that acetylcholine is able to liberate FSH from the anterior pituitary only if fragments of the basal part of the hypothalamus are present in the incubation media. These data have been taken as indicating that acetylcholine stimulates the release of FSH-RF from the incubated hypothalami, and that FSH-RF released under the influence of acetylcholine in turn enhances the secretion of FSH from the incubated pituitaries. It will be suggested that acetylcholine may play a major role in transferring extrahypothalamic influences to the neurons which synthesize the gonadotrophin releasing factors.

The synthetic decapeptide synthesized by Schally and his co-workers is able to release LH and FSH when injected into the carotid artery of the rat. The kinetics of the release of the two hormones under the influence of the decapeptide are quite different, LH being released more promptly than FSH. The activity of the decapeptide may be modulated by changing the levels of sex steroids in the general circulation. Apparently estrogens facilitate the release of LH, while androgens enhance the release of FSH.

Modulating Effects of Prostaglandins on the Release of Hypothalamic Hormones

J. Sandow and M. Babej

Farbwerke Hoechst-AG, Abteilung für Pharmakologie, 6230 Frankfurt-80, Germany

The prostaglandins are discussed as mediators of biological events in the hypothalamo-hypophyseal system. This phenomenon was first shown with respect to ACTH-release. A direct effect of PGE_1 was demonstrated by implantation into the medial basal hypothalamus. The effect of TRH on release of TSH *in vitro* from rat hemipituitaries is influenced by PGE_1. PGE_1 stimulates GH-release from bovine anterior pituitary tissue, PGE_1 and PGE_2 increase incorporation of labelled leucine into GH and prolactin. Zor *et al.* have studied cyclic AMP levels in anterior pituitary tissue following incubation with several prostaglandins, in order of potency being $PGE_1 > A_1 > B_1 > F_{1\alpha}$. None of them released LH in the system. Caldwell *et al.* have observed LH release by PGE_2 in a pituitary superfusion system. Both PGE_2 and $F_{2\alpha}$ stimulate LH release. Harms *et al.* have shown a neurotransmitter-like effect of PGE_2 after injection into the third ventricle PGE_2 increases plasma LH, while PGE_1 elevates prolactin. The stimulatory effects of prostagladins are antagonized or blocked by inhibitors of prostaglandin synthesis, *e. g.* 7-oxa-13-prostynoic acid. The *in vitro* effect of LH-RH on gonadotrophin release is modulated by prostaglandins. The evaluation of prostaglandin effects on hormone release

is complicated by the fact that prostaglandins also act directly at the end organ level, *e. g.* adrenal or corpus luteum *in vitro*. In conclusion, prostaglandins act at the hypothalamic, pituitary and end organ level. A primary or predominant site of action cannot be defined at present.

Cellular Regulation of the Adenohypophyseal Gonadotropic Function

Marian Jutisz

Laboratoire des Hormones Polypeptidiques, C.N.R.S., 91190 Gif-sur-Yvette, France

The data now available on the cellular mechanisms by which the secretion of FSH and LH is regulated have been obtained in part using partially purified preparations of hypothalamic origin and in part by means of the synthetic decapeptide, LH-RH, described by Schally *et al.* (1971). LH-RH acts on the release of both hormones, LH and FSH. Many experimental results, but not all, are in favour of the hypothesis that cyclic AMP is an intermediate in the action of hypothalamic hormone(s) regulating the secretion of LH and FSH. This would imply first the binding of the hormone to a specific membrane cell receptor with the subsequent activation of adenyl cyclase. Some data have been obtained on the physico-chemical aspects of the binding of LH-RH to the anterior pituitary cells or cell membranes, but although it has been stated that LH-RH increases the content of cAMP in the tissue, no one has been able to demonstrate the activation of adenyl cyclase in this system. How cAMP then promotes release of gonadotropins is still unclear. cAMP activates a protein kinase which participates in the phosphorylation processes. Phosphorylation of microtubules is possibly an important event in the release mechanism. It is also postulated that cAMP acts either by altering the permeability of the cellular membranes to Ca^{2+} or by affecting the binding of Ca^{2+} to membrane proteins. Ca^{2+} intervenes in many intracellular mechanisms and is essential for the release process.

Hypothalamo-Pituitary-Testicular Feedback Mechanism During Mammalian Sexual Maturation

D. Gupta, K. Rager

Department of Diagnostic Endocrinology, University Children's Hospital, Tübingen

and

K. Zech and W. Voelter

Institute of Chemistry, University of Tübingen, 74 Tübingen, Germany

The pubertal changes in the mammalian life are brought about by hormones, either secreted for the first time or secreted in much greater quantities than previously. The attainment of sexual maturation is however a complex process which requires maturation and interaction not only of gonads and the reproductive tract, but also of the pituitary and importantly of the neuro-endocrine mechanisms which ultimately control gonadotropin secretion. Presumably there is a marked change in the sensitivity of the hypothalamic-pituitary negative feedback centres to gonadal steroids during sexual maturation. With the shifting of the sensitivity set-points, pubertal developments may be viewed as a continuum lasting several days in the rats or several years in man, secondary sexual characteristics beginning only when a critical level of steadily increasing gonadotropin-releasing hormone is attained. Apparently the mechanism for hypothalamic regulation of pituitary gonadotropic activity and release of the releasing hormones are relatively inactive or inhibited during immature stages. A certain degree of physiological maturation of the central nervous system is evidently required before the pre-pubertal inhibition is released and the hypothalamo-pituitary mechanism becomes active.

In the current study the sensitivity of the pituitary-gonadal responses to exogenous synthetic LH-RH was evaluated in sexually immature and mature male rats. The conditioning influence of prior treatment of gonadotropins and sex steroid hormones on the feedback relationship in the pituitary-gonadal axis was also examined.

The decapeptide was administered i.v. to the animals by infusion for a 4 h period and immediately after blood was collected. LH, FSH, testosterone and 5α-dihydrotestosterone were estimated by radioimmunoassay techniques. Infusion of the decapeptide induced a considerable rise in serum LH and FSH in both mature and immature animals.