

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, prostaglan-

dins 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 mem-

brane cell receptor with the subsequent activation of adenylyl 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 adenylyl 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  $\text{Ca}^{2+}$  or by affecting the binding of  $\text{Ca}^{2+}$  to membrane proteins.  $\text{Ca}^{2+}$  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 5 $\alpha$ -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.



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In terms of percentage of the basal value, LH increment was more in the pre-pubertal (54 fold) than seen in the adults (32 fold), whereas the FSH increment was just opposite, being 2.5 fold for the pre-pubertal and 4.2 fold for the mature animals. Prior treatment of the animals with sex steroids and gonadotropins upset the steroid-gonadotropin feed-

back mechanism, and great divergence emerged between immature and mature animals when LH-RH was infused in them. The significance of this difference in the observed response during mammalian sexual maturation is discussed.

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### **Hypothalamic-Pituitary-Ovarian Feedback Mechanisms**

H. P. G. Schneider

Universitäts-Frauenklinik, 79 Ulm, Germany

Feedback control involves regulation predominantly by circulating levels of hormones. There are stimulatory and inhibitory as well as internal and external forms of feedback. In the classic external feedback the controlling signals are the hormones produced by the peripheral target glands. The receptors which respond to changes in circulating steroid levels by initiating a change in the secretion of gonadotropins are located in the basal medial hypothalamus, anterior hypothalamus and preoptic area as well as the anterior pituitary. The stimulatory effects of gonadal steroids which are thought to bring about ovulation in the normal animal are presumably mediated in the suprachiasmatic region and preoptic area. It is postulated that a noradrenergic synapse mediates the stimulatory effects of estrogen and progesterone on the ovulatory release of gonadotropins (cyclic release center). The arcuate nucleus-median eminence dopaminergic tract may be involved in the so-called tonic discharge of gonadotropins and in the negative feedback action of gonadal steroids.

Sex steroids also affect the response to natural and synthetic LRH. Complex interaction of sex steroids both in the hypothalamus and pituitary may evoke differential release of LH and FSH thus indicating the possible existence of separate control mechanisms for LH and FSH.

There is recent evidence for short feedback loops, also referred to as auto or internal feedback. Short systems are involved in the regulation of LH and FSH secretion. LH *via* an effect on the basal median eminence seems to inhibit its own secretion.

Inhibitory as well as stimulatory short feedback mechanisms have been described for the control of FSH secretion. This positive short feedback appears to be peculiar for immature animals and may play a role at the time of puberty.

Finally, a third type described as ultrashort feedback has been found for the control of the gonadotropin releasing hormone on its own production. There are data indicating that hypothalamic LRH content is increased following small doses of chronically applied synthetic LRH in rodents under conditions which do not alter circulating gonadotropins or pituitary sensitivity to LRH.

Control systems concepts have become widespread among reproductive neuro-endocrinologists. No sufficiently reliable data exist today which could be used to successfully apply the systems analysis approach.

### **Identification and Measurement of LH-RH in Biological Fluids by Radioimmunoassay**

S. L. Jeffcoate

Department of Chemical Pathology, St. Thomas's Hospital Medical School, London, S.E. 1

A radioimmunoassay for LH-RH has been developed using the following reagents: Synthetic LH-RH decapeptide (Hoechst) as standard; an antiserum raised in a rat to the des-glu<sup>1</sup>, his<sup>2</sup>-octapeptide of LH-RH conjugated to albumin; [<sup>125</sup>I]labelled

LH-RH decapeptide; ethanol precipitation is used to separate free and bound fractions.

The assay is highly specific for LH-RH and particularly for the C-terminus of the molecule; lack of the C-terminal amide group results in a complete loss of immunoreactivity. The sensitivity of the assay is 0.5 pg of LH-RH.

Assay of *hypothalamic extracts* after gel filtration, thin-layer chromatography and ion-exchange chromatography has shown that synthetic LH-RH and mammalian and avian LH-RH are immunochemically and chromatographically identical.