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The Study of GnRH Control of Reproductive Function

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ABSTRACT

The activity of the hypothalamic-pituitary-gonadal (HPG) axis is controlled by gonadotropin-releasing hormone (GnRH). GnRH, gonadotropins, and gonadal sex steroids are secreted in a pulsatile fashion. As the peripheral plasma concentrations of GnRH are too low for the existing assay systems, the pattern of pulsatile release of gonadotropins is often utilized for the indirect estimation of hypothalamic GnRH activity. In addition, the long-term pulsatile administration of exogenous GnRH in selected states of GnRH deficiency provides important information on the regulation of the HPG axis.

Because of the limits of each approach, both investigational tools should be used complementary for the study of GnRH role in the control of pituitary and gonadal function. This article reviews recent information on GnRH physiology acquired with the use of these methods.

THE STUDY OF THE HYPOTHALAMIC-PITUITARY AXIS

The endocrine control of reproductive function is dependent upon a chain of hormonal interactions driven by the hypothalamic secretion of gonadotropin-releasing hormone (GnRH). GnRH stimulates the secretion of LH and FSH, which, in turn, regulate the production of gonadal steroids. The peripheral blood concentration of GnRH is extremely low and its measurement cannot be carried out reliably in a manner similar to pituitary and gonadal hormones. Better estimations of GnRH secretion can be obtained by measuring the hormone in the hypothalamic-pituitary portal circulation after appropriate surgical preparation (1,3), or from the median eminence with the use of a push-pull perfusion cannula directly inserted in the brain (11).Naturally, these procedures are only applicable in particular experimental set-ups and usually cannot be utilized

in human studies.

Indirect methods for the determination of GnRH secretion have been devised to overcome these technical difficulties. Since 1970 (6) it has been known that LH is liberated from the pituitary in a pulsatile fashion, supposedly reflecting a similar pattern of GnRH secretion. Therefore, the study of spontaneous LH pulses offers an insight into the regulation of the hypothalamic-pituitary axis. On the other hand exogenous administration of GnRH in animals (10)or humans (5) devoid of hypothalamic GnRH activity has been utilized to restore normal pituitary function, providing information on the possible "program" of physiologic GnRH secretion.

The indirect methods for the study of GnRH secretion can be divided into three main subgroups:

a. In vitro models: they employ pituitary glands or isolated pituitary cells to test the in vitro response to different regimens of GnRH infusion and/or the modulatory influence of other hormones (13).

b. In vivo observation of endogenous pituitary secretion: it consists of the study of the pulsatile patterns of gonadotropin release in normal and abnormal human subjects (15)and in peculiar animal models such as the seasonal ram (12).

c. Ablation-replacement models: they utilize pulsatile GnRH administration in hypothalamic-lesioned animals (10)or in human subjects with absent or defective endogenous GnRH secretion (5).

In this brief review we will concentrate on the two latter indirect methodologies, as well on the direct estimation of hypothalamic GnRH secretion.

DIRECT MEASUREMENT OF HYPOTHALAMIC GnRH SECRETION

GnRH has been measured by radioimmunoassay in the pituitary portal circulation of animals and humans (1,3). It was established that GnRH is released in a pulsatile mode (3), and that, in general, LH pulses correspond to simultaneous GnRH episodes of secretion from the hypothalamus (4). However,a recent report (11)indicates that not all GnRH pulsations are "conducted" at the pituitary level, suggesting that a partial block of hypothalamic stimuli may occur. This finding has important implications in the analysis of endogenous gonadotropin secretion as it proves that the rate of LH pulsatile release cannot be equated with certainty to the rate of GnRH firing. In the near future it may be pos-

sible to assay GnRH levels from the cerebrospinal fluid of laboratory animals (17). This new technique would semplify the evaluation of GnRH secretion and might extend the practice of direct GnRH measurement to a wider range of experimental applications.

ENDOGENOUS GONADOTROPIN SECRETION IN THE MENSTRUAL CYCLE

A pulsatile pattern of LH secretion was initially identified in the monkey (6) and later confirmed in the human male (14). In the first extensive study of gonadotropin pulsatility in the human female, Santen and Bardin (15) showed that remarkable changes in amplitude and frequency of LH pulses occur throughout the menstrual cycle. More recent and detailed studies have better defined these changes. In the follicular phase (FP) the frequency of LH pulsations increases from about 1 pulse/106 min in the early follicular phase to 1 pulse/82 min in the proximity of the midcycle surge (2). Furthermore, these LH pulses are reflected at the ovarian level by correspondent episodes of estradiol secretion. In the luteal phase (LP) we have shown that LH pulsations of greater magnitude are present, but that these pulses are more infrequent than in the FP and that such slowing of LH pulses is apparently related to the duration of exposure to progesterone (7). Once again, LH pulses are reverberated at the gonadal level by coincident bursts of progesterone secretion from the corpus luteum (8). This latter finding indicates that corpus luteum adequacy cannot be correctly ascertained by single plasma progesterone estimations in the mid-luteal phase.

These data suggest that the frequency of GnRH-induced LH pulsations is modified in the normal menstrual cycle and that the peak frequency is reached around the time of ovulation.

ABLATION - REPLACEMENT MODELS

The first protocol of exogenous administration of GnRH in a pulsatile fashion were tested by Knobil's group in monkeys whose endogenous GnRH secretion had been eliminated by selective hypothalamic lesions (10) These studies clearly demonstrated that:

a. Only pulsatile GnRH administration can restore the normal pituitary secretion of LH and FSH.

b. Continuous GnRH infusion eventually suppresses gonadotropin secretion.

c. A fixed regimen of GnRH administration (one pulse at hourly intervals) can re-establish an endocrinologically normal menstrual cycle in female monkeys.

d. The administration of pulsatile GnRH to pre-pubertal monkeys can stimulate gonadotropin secretion, gonadal steroidogenesis, and eventually ovulation.

These findings confirmed the central role of GnRH at all stages of sexual maturation and suggested more rational and physiologic approaches for the therapeutic use of GnRH.

Pulsatile GnRH administration via automatic infusion pumps is now extensively utilized in humans as a method of induction of ovulation in the female (16) and to obtain pubertal maturation and fertility in the male (9). Nevertheless, some key physiologic questions are still unresolved. For instance, we have previously seen that in normal women the frequency of LH pulsations is extremely variable during the menstrual cycle, while a fixed regimen of exogenous GnRH pulses (one every 60-120 min) is usually capable of inducing ovulation and normal corpus luteum function. Are the changes of the LH secretory rythm in the menstrual cycle of any physiologic importance? are these changes merely the result of modifications of pituitary sensitivity to the GnRH signal, with no concomitant modification of the GnRH firing rate?
The answer to these questions may derive from the use of the new protocols of GnRH administration based on the observation of LH secretion in the normal menstrual cycle, which are now being tested by our group.

CONCLUSIONS

The hypothalamic-pituitary-gonadal axis is a physiologic unit in dynamic balance. GnRH, gonadotropins, and sex steroids are all secreted in a coordinated pulsatile fashion. The pacemaker of this system is GnRH, so that absent or deranged secretion of this hypothalamic hormone is not compatible with normal reproductive function.

The observation of the pituitary secretion of gonadotropins may offer a useful reflection of GnRH activity. Nevertheless, in this experimental set-up we cannot discriminate between basic GnRH stimulation and modulation and block phenomena that may occur at the pituitary level. On the other hand, in the ablation-replacement model the achievement of appropriate gonadal stimulation does not necessarily guarantee that a properly physiologic mode of GnRH

administration has been reached. Therefore, both approaches should be used in a complementary fashion, to provide accurate information for the understanding of GnRH secretion. Despite its attractive therapeutic usefulness, it should always be remembered that exogenous GnRH administration is primarily an invaluable investigational probe into the regulation of the hypothalamic-pituitary-gonadal axis.

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