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Neuroendocrine Control of Pituitary Gonadotropin Release

Kyungza Ryu, Ph. D.

Department of Pharmacology,
Yonsei University College of Medicine,
Seoul, Korea

"圖 文 抄 錄"

腦下垂體 性腺刺戟호르몬 分泌의 神經內分泌的 調節

延世大學校 醫科大學 藥理學敎室

柳 京 子

뇌하수체의 성선자극 홀몬 분비 세포는 혈액내 estradiol양의 변화에 따라 LH와 FSH를 분비하므로써 주기적인 변화를 보인다. 성선 자극 홀몬의 분비는 성선 자극 홀몬을 합성하고 보유하는 두가지 형태의 능력의 크기에 의하여 조절되며 이들을 조절하는 것은 시상하부에서 분비되는 황체형성 홀몬-분비 홀몬(LH-RH)과 난소에서 분비되는 estradiol이다. LH-RH는 성선 자극 홀몬 분비세포에 작용하여 성선 자극 홀몬 합성, 저장 및 분비를 촉진시키며 estradiol은 LH-RH의 기능을 확대하고 LH-RH가 self-priming효과를 나타내도록 유도하기도 하며 LH-RH의 성선 자극 홀몬 분비 기능을 저해하기도 한다. Estradiol은 기저성 성선 자극 홀몬을 분비시키기 위하여 negative feedback작용을 하고 배란성 성선 자극 홀몬을 분비시키기 위하여는 positive feedback작용을 하며 feedback작용 부위는 시상하부 및 뇌하수체 전엽이다. 또한, estradiol이 feedback작용을 하여 성선 자극 홀몬의 분비를 조절하는 데는 LH-RH뿐만 아니라 중추신경-시상하부에서 분비되는 dopamine, norepinephrine, prostaglandin등이 참여한다.

I. INTRODUCTION

It is the purpose of this review to provide recent discussions on the operating characteristics of the hypothalamic-pituitary-ovarian axis and to attempt to relate this axis to functional system for controlling the cyclic release of gonadotropin.

To account for the regulation of cyclic gonadotropin release, recent reports on the interaction of the hormones at the levels of the CNS-hypothalamus, the pituitary, and the ovary will be reviewed.

II. THE CNS HYPOTHALAMIC-PIYUITARY-OVARIAN AXIS

1. The ovary

The ovary is composed of two endocrine structures related both morphologically and functionally: the follicular complex, i.e. granulosa, theca and stromal cells, and corpus luteum. The follicle has dual functions of oogenesis and steroidogenesis. The functional interaction between follicular cells results in steroid production which serves not only as a feedback

signal to the hypothalamus and pituitary but also provides local regulatory function (Lunenfeld, et al., 1975). Evidence indicates that intraovarian estrogen, androgen, and progesterone modulate follicular growth and maturation; gonadotropin-stimulated production of estrogen causes increased ovarian uptake of FSH, and hence accelerated follicular maturation. Intraovarian androgens function to inhibit follicular maturation (Louvet et al., 1975) and thereby induce follicular atresia. It is apparent that not only the stimulation by FSH and LH, but also the stimulating and inhibiting effects of intraovarian concentrations of estrogen and androgens are essential for the control of follicular growth. A suppressive effect of progesterone on the number of cytoplasmic estrogenic receptors has been demonstrated (Hsueh et al., 1975), suggesting that intraovarian progesterone may also be critical for a local control mechanism.

Thus, ovary possesses at least three known biological characteristics to regulate hypothalamic-pituitary-ovarian axis. Ovary exerts an appropriate sequence of negative feedback for the tonic gonadotropin release and positive feedback action for the midcycle surge (Yen et al., 1974a) to hypothalamus and pituitary gland. Ovary has a differential feedback effect on the release of LH and FSH (Tsai and Yen, 1971) regardless of whether or not a separate FSH-RF exists. Ovary also has a local regulatory function, within the ovarian units, on follicular growth and maturation, separable from but interrelated with the gonadotropin action (Lunenfeld et al., 1975).

2. The pituitary

The gonadotropes in pituitary represent target cells whose functional components are gonadotropin synthesis, storage, activation, and release. The controlling inputs are estradiol and LH-RH. LH-RH may be considered to be a primary positive drive with estradiol exerting a positive effect on synthesis and storage but a negative or impeding action at the level of release.

It is now well established that ovarian estradiol exerts both negative (Tsai and Yen, 1971; Yen and Tsai, 1971) and positive (Monroe et al., 1972; Yen and Tsai, 1971, 1972) feedback effects on both the hypothalamus and the pituitary. How these two feedback control signals operate in coordination has not been fully understood. The availability of the synthetic LH-RH proved the proposal made by Bogdanov (1963) that estrogen exerts its effect directly on the pituitary (Jaffe and Keys, 1974; Keys and Jaffe, 1975; Lasley et al., 1975; Nillius and Wide, 1972; Vandenberg et al., 1974; Wang and Yen 1975; Yen et al., 1972b, 1974b, 1975) as well as on the CNS (McEwan et al., 1974; Spies and Norman, 1975; Stumpf et al., 1975).

Changing pituitary responses to varying amounts of LH-RH suggest that the variations in the amount of LH-RH delivered to the pituitary represent a significant factor in the control of the pituitary gonadotropin output (Lasley et al., 1976). The pattern of pituitary response to submaximal dose of LH-RH (Rebar et al., 1973) over a period of several hours, either by repeated pulses (10ug at 2 hour intervals) or by constant infusion (0.2ug/min.), suggests that gonadotropins exist in two distinguishable pools or activities: one immediately releasable and the other requiring continued stimulus. The first pool may be defined as a measure of pituitary sensitivity and probably reflects acutely releasable gonadotropin. The second pool, storage pool, is regarded as a measure of pituitary reserve and includes a component of a yet unmeasurable amount of newly synthesized gonadotropin. The two functional pools of LH are demonstrable in all phases of the menstrual cycle in synchrony with the cyclicity of ovarian steriod levels. (Yen, 1978) From the early to the late follicular phase, second pool is preferentially augmented. The first pool become enlarged during late

follicular phase, suggesting shift of LH from the much larger second pool to the readily releasable first pool. This shifting from second to first pool seems to be achieved by the self-priming effect of LH-RH (which appears to convert reserve pool to releasable pool) at that time. Although both sensitivity (pool 1) and reserve (pool 2) increase dramatically near the midcycle, at the time of midcycle surge, sensitivity exceeds reserve. This phenomenon may be related to the endogenous release of LH-RH and the development of a self-priming effect of LH-RH at this time. The self-priming effect of LH-RH is manifested as an augmented gonadotropin release and this effect is estrogen-dependent. Thus, a buildup in pituitary reserve, together with the self-priming effect of LH-RH which is induced by rising levels of estradiol, may dictate the pituitary quota required for the midcycle surge of gonadotropin. During the midluteal phase when maintains high progesterone as well as estradiol, the large second pool is maintained as in the late follicular phase, but the first pool is smaller (Hoff et al., 1977). This phenomenon is probably not due to an inhibitory effect of combined estradiol and progesterone on LH-RH mediated gonadotropin release but is probably caused by the extremely low endogenous release of LH-RH at the midluteal period (Wang et al., 1976 a b); this minimizes the self-priming effect of LH-RH and results in a reduction of first pool activity. The low levels of LH found during the luteal phase of the cycle (Santen and Boardin, 1973; Yen et al., 1972a) may represent yet undefined progesterone action on the neuronal mechanism involved in LH-RH release. In summary, LH-RH not only induces synthesis-storage (pool 2) and release (pool 1) but also activates the second pool, converting it to and enlarging the first pool. These effects of LH-RH are amplified by the presence of estradiol which appears to provide a "permissive" actions for LH-RH on gonadotropin synthesis-storage and activation, probably by increasing the number of receptors for LH-RH on the gonadotropes. This permissive action of estradiol appears to be selective, for estradiol also impedes the LH-RH mediated LH release.

3. The CNS-hypothalamic component

The CNS-hypothalamus regulates gonadotropin secretion by diverse neuronal inputs converging upon the medial basal hypothalamus and operating through neurotransmitters which lead to the release of LH-RH by the neurosecretory neurons and subsequent release of pituitary LH and FSH (Halasz, 1972; Wurtman, 1971).

1) The brain as an endocrine organ

The recent demonstration of specific receptors (Davies et al., 1975) or binding sites for gonadal stroids in the brain as well as in the pituitary supports the concept that the brain participates in specific neuroendocrine events (McEwan et al., 1974; Stampf et al., 1975).

The brain not only serves as a target for steroid hormones but also possesses the capacity of synthesis and secretion of numerous peptide hormones de nove such as LH-RH, T-RH and somatostatin. The presence of these peptides in many regions of the CNS and in nerve terminals made the postulation of the existence of peptidergic neurons in the brain, analogous to the catecholaminergic systems, with axon terminations on the hypothalamic-pituitary portal vein.

Further the brain, particularly the hypothalamus, possesses the capacity for steroid transformations (Naftolin et al., 1975). Four biochemical transformations seem to be considered.

(a) aromatization of androgen to estrogen
(b) 5α reduction of testosterone
(c) 5α reduction of progesterone
(d) catechol estrogen formation (Fishman and

Norton, 1975). But the physiological significance of these remains to be elucidated.

2) The hypothalamus

Current concepts invoke a dual mechanism for the neural control of the cyclic secretion of gonadotropic hormone (Barraclough and Gorski, 1961; Halasz, 1969; Flerko, 1974). The first, termed the tonic mechanism, maintains a tonic basal secretion of LH and FSH. The tonic mechanism consists of tubero-infundibular neurons in the hypophysiotropic area (ventromedial arcuate nucleus) which synthesize and release LH-RH into the hypophysial portal vein. The second mechanism involves the preoptic-anterior hypothalamic area and may be termed a cyclic mechanism (Flerko, 1974), being indispensable in the maintenance of the cyclic release of LH-RH.

The dramatic changes in pituitary function during the menstrual cycle indicate fluctuations of LH-RH secretion in the hypothalamus. During the late follicular and midluteal phases of the cycle, when pituitary capaicty and the self-priming effects of LH-RH are high, the relatively low basal gonadotropin secretion normally found is due to the low endogenous LH-RH release. The modest increase in basal LH secretion just prior to the onset of the midcycle surge (Ross et al., 1970; Yen et al., 1970) may reflect the begining of incremental LH-RH secretion; increased amounts of LH-RH have been found at the time of the midcycle surge in the portal blood of rhesus monkeys (Carmel et al., 1975, Neill et al., 1977) and peripheral blood of human (Arimura et al., 1974).

The increased pituitary capacity, the development of the estrogen-induced self-priming effect of LH-RH, and the increments in LH-RH release may be required to induce midcycle surge of gonadotropin.

3) Neurotransmitters as mediator

Some controversy still exists over the mechanism of neurotransmitter-hypothalamic pituitary hormone interaction. Collu (1977) proposed 3 hypothesis. Hypothesis 1, the most accepted theory, is that neurotransmitters elaborated in extrahypothalamic or intrahypothalamic neurons are liberated at the synaptic junction with a peptidergic neurons, thereby modulating the release of a hypothalamic hormone into the portal hypophysial circulation. Hypothalamic hormones, in turn, will modulate the release of anterior pituitary hormones. Hypothesis 2 depicts the existence in the hypothalamus of neurons elaborating both neurotransmitters and hypothalamic hormone which could interact in the neuron itself or at the level of pituitary. Hypothesis 3 represents the possibility that neurotransmitter and hypothalamic hormones are secreted into the cerebrospinal fluid of the third ventricle. Neurotransmitter could either interact with hypothalamic hormones at the pituitary level after being carried through the median eminence into the portal hypophysial circuration by special cells called tanycytes, or modulate the activity of peptidergic neurons adjacent to the third ventricle.

Evidence has been accumulated that CNS serotonin, dopamine (DA) and norepinephrine (NE) containing neuronal pathways are involved in regulating the secretion of LH (Axelrod, 1975: Fuxe et al., 1977: Karla et al., 1972: McCann and Moss, 1975: Porter et al 1977: Sawyer et al., 1974). These biogenic amines in the brain regions, particularly the hypothalamus were suggested to affect neurons which contain LH-RH. Utilizing microspectrofluorometry and LH-RH antiserum, Fuxe and associates (1977) have demonstrated that DA and LH-RH nerve terminals are aggregated in the same area of the lateral external layer of the median eminence (ME). The NE terminals are mainly found in the subependymal layer and to some extent in the medial external layer which contains a mixture

of DA and NE nerve terminals. This morphological evidence indicates the potential interaction between DA, NE, and LH-RH nerve terminals at the ME. Convincing evidence is now available for a causal relationship between estrogen and the changes in catecholamine (CA) turnover in the hypothalamus (Fuxe et al 1977). The high doses of estradiol benzoate (EB, 1.5-60ug) to castrated female rats induced a marked and selective acceleration in the DA turnover with concomitant lowering in serum LH and FSH. An opposite trend occurs in the NE nerve terminals. When a smaller dose of EB was used (0.1 μg), LH secretion increased and this was accompanied by an increase in NE turnover and a reduction of DA turnover. Lebranc et al., (1976) have demonstrated that dopamine infusion (4 μg/kg/min.) induced a highly significant decline in serum LH in human. The administration of dopamine agonists, L-dopa (0.5gm, orally) and bromocryptine, elicited a similar decline (Lachelin, et al., 1977). The demonstration of an inhibitory effect of DA on LH release in human for the first time adds critical support to the hypothesis that inhibitory feedback control of LH-RH secretion by estrogen is partly exerted at the hypothalamic level by activation of tuberoinfundibular DA neurons. The inhibitory feedback action of estrogen is also exerted at the level of the pituitary by impeding the releasing actin of LH-RH.

4) Brain prostaglandins as mediators

The brain can synthesize and release prostaglandins (PG's) (Samuelsson, 1964). Evidence suggests that PG's play an important role in the modulation of neurotransmission by influencing either the release or the postjunctional action of neurotransmitters (Brody and Kadowitz, 1974).

PGE and F series has been known to stimulate the release of LH and FSH by the pituitary (Batta et al., 1974: Ratner et al., 1974). Other studies demonstrated that PGE_2 as well as PGF_2 elicits gonadotropin release by enhancing the release of endogenous LH-RH rather than by a direct effect on the pituitary gonadotropes (Eskay et al., 1975: Ojeda et al., 1975). Harms et al., (1976) have shown that the PGE_2 acts directly on LH-RH neurons, independent of biogenic amines, for the release of LH-RH, since the PGE_2 effects can not be modified by adrenergic, depaminergic or cholinergic blocking agents. Evidence that ovulation can be blocked in rats by treatment with inhibitors of PG synthesis (Orczyk and Behrman, 1972) support that PG's play a mediating role in the neuroendocrine regulation of gonodotropin secretion.

5) The triggering mechanism in LH-RH release at mid-cycle

The exact mechanism for the initiation of hypothalamic LH-RH release and resulting LH surge at midcycle has not been clarified.

(1) Estradiol

Estradiol per se may not be the direct triggring agent for the LH surge, but it does modify the cellular activity of both pituitary and the hypothalamus via positive feedback so that endocrine event is arranged for the midcycle release of LH and FSH. At the pituitary level, estradiol augments the responsiveness of gonadotropes to LH-RH: this is represented by an elevated sensitivity and reserve. The interaction between estradial and CNS neuronal activity is not clear, but evidence suggests that estradiol augments NE and inhibits DA neuronal activity, both of which may contribute to the acute LH-RH release by LH-RH neurons in the hypothalamus.

(2) Progesterone

A positive feedback effect of progesterone in the estrogen-primed pituitary has been known. A single injection of progesterone in hypogonadal women pretreated with es-

trogen is followed by a LH-FSH surge (Yen and Tsai, 1972). Progesterone appears to exert a facilitatory action on gonadotropin release through a combined action on the amplification of pituitary sensitivity and on the release of LH-RH (Cumming et al., 1972). It has been reasoned that a preovulatory secretion of progesterone by the maturing follicle might represent the final message for the initiation of the midcycle surge. However, evidence for a measurable increase in the circulating progesterone prior to midcycle LH surge has not been found.

(3) Prostaglandins

The interaction between PG's and CA's may cause transient vasodilation (Brody and Kadowitz, 1974) and consequently an increase in blood flow in the hypothalamic-hypophysial portal vessel without an actual increase in LH-RH release. An increase in local PG production may stimulate LH-RH neurons directly to release LH-RH.

(4) NE/DA ratio

Since NE stimulates and DA inhibits the activity of LH-RH neurons (Fuxe et al., 1977), an increase in NE/DA ratio may induce LH-RH release. Estrogen at sufficient levels has the ability to do so.

(5) Catechol estrogen

In situ formation of catechol estrogen may serve as a biochemical link between estrogen and catecholamines in the modulation of neuronal activity (Ball et al., 1972: Fishman and Norton, 1975).

It is speculated that the increased availability of estradiol for binding in the hypothalamic site would accelerate the formation of catechol estrogen, which, in turn, may induce LH-RH release through two possible mechanisms:

(a) Catechol estrogens are effective competitive inhibitors of degrading enzyme catechol-O methyltransferase (Ball et al., 1972), and the consequent increase in the NE would facilitate LH-RH release.

(b) Reduction of the negative feedback action of estradiol in LH-RH neurons via effective competitions by catechol estrogens for the estrogen receptors (Davies et al, 1975).

The mechanism by which the release of LH-RH is terminated is unknown. The marked increase of the gonadotropin concentration in the hypothalamus, via retrograde portal blood flow, may constitute the short-loop feedback system in termination of the secretory activity of the LH-RH neurons (Miyake et al., 1976).

III. SUMMARY

Pituitary gonadotropes, as target cells, exhibit cyclic changes in terms of LH and FSH release in synchrony with the estradiol levels. The ultimate release is determined by the relative size of the two pools of gonadotropins, which is regulated by the two controllers: LH-RH and estradiol. LH-RH appears to serve as a primary drive on the gonadotrope, stimulating gonadotropin synthesis, storage, and release. Estradiol amplifies the action of LH-RH and induces the development of a self-priming effect of LH-RH except that it impedes LH-RH mediated gonadotropin release. Negative and positive feedback action of estradiol is revealed to operate by different mechanisms. The pituitary capacity increases severalfold from early to late follicular phase, which is considered to be prerequisite for the development of mid-cycle surge. CNS-hypothalamic dopamine, norepinephrine, and prostaglandins, as well as LH-RH, are involved in the negative and positive feedback effects of estradiol. The possible mechanisms in the triggering of LH-RH release for the initiation of midcycle LH-RH surge are considered.

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