

MINIREVIEW
NEUROENDOCRINE REGULATION OF LUTEINIZING HORMONE
AND FOLLICLE STIMULATING HORMONE: A REVIEW

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Since the pioneering studies of Everett, Sawyer and Markee (1) it has been generally accepted that the central nervous system (CNS) regulates the secretion of the pituitary gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH). However, great gaps still exist in our understanding of the neural mechanisms that regulate the secretion of these hormones. The purpose of this review is to provide the reader with a concise overview of this topic. Gaps, inconsistencies and future directions of this area of research are also presented.

ANATOMICAL CONSIDERATIONS

The central nervous system communicates with the anterior pituitary through a vascular route. Specialized neurons within the preoptico-hypothalamus (a neural region located in the ventral portion of the diencephalon) synthesize the decapeptide, luteinizing hormone releasing hormone (LHRH) (2-4). LHRH is secreted from neuronal terminals into a specialized capillary network that surrounds the median eminence, a circumventricular organ. Following entry into the pituitary portal vasculature, this neurohormone is delivered to the anterior pituitary (5) where it interacts with pituitary gonadotropes and stimulates the synthesis and release of LH and FSH. Since LH and FSH are secreted in pulses, it is assumed that each gonadotropin pulse occurs as a result of a pulsatile discharge of hypothalamic LHRH (6). Thus, an important feature of communication between the CNS and the pituitary is the pattern with which it occurs.

LHRH PULSE MODES

Indeed, the pituitary gland responds only to pulsatile modes of LHRH delivery and exhibits the phenomenon of down-regulation when exposed to a "square-wave" of LHRH (6). Hypogonadotropic hypogonadism produced in female rhesus monkeys by placement of extensive radiofrequency lesions in the medial basal hypothalamus (MBH) may be reversed and ovulatory cyclicality restored by pulsatile but not continuous infusion of LHRH (6,7). In addition to an absolute requirement for a pulsatile mode of LHRH exposure, pituitary responses differ depending upon LHRH pulse frequency. Slower LHRH pulse frequencies elicit a greater FSH/LH release ratio whereas increased frequencies result in a greater LH/FSH ratio (6,8). Alterations in LHRH pulse frequency have been proposed as the mechanism by which a single releasing hormone governs the release of two pituitary gonadotropins (8). In addition, pulse amplitude and duration of LHRH may also be an important means of information transmission (9). Thus, in our developing neuroendocrine model, we envision LHRH neurons, located in the ventral portion of the brain, to discharge quanta of LHRH in a pulsatile fashion to stimulate gonadotropin synthesis and release. The frequency and amplitude of these pulses affects the type of pituitary response.

What dictates the frequency of hypothalamic LHRH discharges? The existing endocrine milieu appears to be an important factor. LHRH pulse frequency varies during the ovulatory cycle (10). Gonadectomy increases LHRH pulse releases, which result in elevated levels of LHRH in pituitary stalk blood and a rise in peripheral gonadotropin concentrations (11). Replacement of gonadal hormones to castrates slows LHRH pulse frequency, reduces the rate of pituitary gonadotropin secretion and results in a reduction of circulating LH and FSH levels (11). Prolonged exposure to high physiologic levels of estradiol reverses this inhibitory effect upon hypothalamic LHRH pulse frequency and results in a surge of gonadotropins (11). Alteration in LHRH pulse frequency induced by the hormonal milieu serves as a prime example of neuroendocrine transduction. Circulating levels of gonadal steroid hormones interact with steroid-sensitive neural tissue (12). As a result of steroid-neuronal interactions, firing rates of certain hypothalamic neuronal systems are affected (13,14). Transduction of endocrine (gonadal steroids) to neurophysiological (firing rates of estradiol-sensitive tissue) signals results in an alteration in LHRH pulse frequency and, therefore, pituitary gonadotropin secretion.

How and where does the transduction of steroidal to neurophysiological information occur? Distinct neuroanatomical regions play important roles in regulation of gonadotropin release. Studies that employ electrical recording, neural disconnections or lesions, and electrical and electrochemical stimulations have clearly implicated a broad expanse of neuronal tissue within the preoptico-hypothalamus as being critically involved in the transduction phenomenon (15,16). The neuroanatomical boundaries of this area are: the rostral aspect of the preoptic area (above the optic chiasm) through the hypothalamus and funnelling caudally toward the median eminence (above the pituitary stalk). The majority of LHRH-producing cell bodies are located within the preoptic area (2-4,15). Ablation of these cell bodies or placement of a surgical cut between the preoptic area and the medial basal hypothalamus blocks the occurrence of the midcycle gonadotropin surge but not steroid-induced reductions in gonadotropin secretion. This information suggests that distinct areas of the preoptico-hypothalamus regulate different gonadotropic responses to gonadal steroids. Rostral areas appear to control positive feedback actions (i.e., the midcycle gonadotropin surge) whereas steroid-modulated gonadotropin negative feedback is focused within the basal hypothalamus (15,16). Thus, the frequency of LHRH release into the pituitary portal system is influenced by the surrounding hormonal milieu. The CNS monitors the existing endocrine state and alters the firing rates of LHRH neurons within the preoptico-hypothalamus.

LHRH NEURON NEUROTRANSMITTERS

What is the neuropharmacologic basis for transduction of endocrine to neurophysiological information at the level of the hypothalamus? The hypothalamus contains significant concentrations of a variety of neurotransmitters including dopamine, norepinephrine and epinephrine (17-19). Further, dense concentrations of adrenergic receptor sites are located within the preoptico-hypothalamus (20-23). These transmitter systems are influenced by the surrounding endocrine environment. Gonadal steroids alter the concentration and turnover rates of many neurotransmitters and their receptors in the CNS and elsewhere (15-17,24-26). Hormonally modulated changes in the activity of tyrosine hydroxylase (the rate limiting enzyme in catecholamine biosynthesis; 27) and monoamine oxidase (28) have also been demonstrated. Although the hypothalamus is rich in catecholaminergic activity, most (80%) of these neurotransmitters are synthesized by extrahypothalamic neurons (29,30). Noradrenergic cell bodies located in the lateral tegmentum nucleus, tractus solitarius and dorsal motor nucleus of vagus project to the preoptico-hypothalamus via the ventral tegmental pathway and the medial forebrain bundle and innervate virtually all hypothalamic nuclei (29,31). These midbrain catecholaminergic cell bodies have been shown to regulate LHRH release in rats (32,33). Further support for a role of midbrain catecholaminergic neurons in the control of reproductive processes is provided by the observation that 40-80% concentrate estradiol

(34). Neurons that concentrate ^3H -estradiol have also been identified within the preoptic area, anterior hypothalamic area, arcuate nucleus and median eminence (12). Many hypothalamic neurons that concentrate estradiol also stain positively for tyrosine hydroxylase (35). Thus, ample neuroanatomical evidence exists to implicate extrahypothalamic catecholaminergic neurons in the regulation of pulsatile discharges of hypothalamic LHRH. Furthermore, disruption or reduction in α adrenergic neurotransmission by α methyl-p-tyrosine injection (36), reserpine treatment (37), α adrenergic receptor blockade (38), or opiate administration (39) (to reduce catecholaminergic turnover) inhibits pulsatile LH secretion in castrate animals or blocks estradiol-induced LH surge releases. An α adrenergic link in the activation of the LHRH neuron is also supported by studies in which norepinephrine or epinephrine, injected into the III ventricle of estradiol-primed rats, causes a release of pituitary LH (40-42). Estradiol-induced increases in hypothalamic LHRH release (43) and pituitary LH discharges (44) may be blocked by injections of phenoxybenzamine or prazosin, α_1 adrenergic receptor blocking agents. At the level of the median eminence, α_2 adrenoreceptors are most prevalent (21-23). Combined, this information suggests that a multi-synaptic, α adrenergic neuronal network is involved in the transduction of gonadal steroid to electrical to neurohumoral information. Extrahypothalamic and hypothalamic neurons monitor circulating levels of gonadal steroids (estradiol) and dictate (through alpha adrenergic neurotransmission) the frequency of pulsatile discharges of LHRH from hypothalamic neurons and therefore the release of gonadotropins from the pituitary.

In addition to modulation of LHRH pulse frequency, gonadal steroids appear to determine whether a neurophysiological or neuropharmacological manipulation of a particular brain region will stimulate or inhibit pituitary LH release. Electrical stimulation of the mesencephalic noradrenergic pathway in ovariectomized (ovx) rats results in the suppression of LH pulses (45). Stimulation of this same area in steroid-primed, ovx animals fails to suppress LH pulses. A similar finding has been reported with stimulation of the arcuate nucleus within the hypothalamus (46). Further, injections of NE into the third ventricle of ovx rats suppresses LH pulsatility while a similar injection in steroid-primed animals causes a release of LH (40,42,47). Effects of such treatments upon pituitary FSH secretion have not been reported. Examination of the influence of a neuropharmacologic manipulation or a neurally active drug must be carefully controlled with regard to steroid milieu. Opposite effects may be elicited in test subjects exposed to identical treatments during different reproductive states or simply by the injection of estradiol. In spite of information available about the effects of gonadal hormones upon a variety of neurophysiological and neuropharmacological parameters, our understanding of the neurotransmitter systems that regulate LH and especially FSH release through the secretion of hypothalamic LHRH is incomplete.

INTERPRETATION OF NEUROPHARMACOLOGIC STUDIES

Many studies that have attempted to determine the neuropharmacologic factors involved in the regulation of gonadotropin release have been contradictory. A variety of drugs have been injected into test animals and the effect upon gonadotropin release has been monitored. Many of the neurochemicals tested lacked receptor specificity. These substances may have served as precursors to other neurotransmitters (i.e., infused dopamine or norepinephrine being converted to norepinephrine or epinephrine). Thus, if dopamine is infused into the CNS, it cannot be determined if changes in gonadotropin secretion are due to activation of dopaminergic or noradrenergic systems. Another source of confusion has been the lack of knowledge of the effects of drugs at the receptor site. Initially, adrenergic receptors were classified according to their location. Alpha₁ adrenoreceptors were thought to be localized postsynaptically and α_2 receptors were hypothesized to be presynaptic autoreceptors (48-51). These receptors exhibit different affinities for specific neuropharmacologic agents. For instance, clonidine, an adrenergic agonist, binds with much greater affinity to α_2 receptors. Hypothetically,

activation of these presynaptic receptors with clonidine would decrease endogenous neurotransmitter release. Norepinephrine exhibits equal affinities for α_1 and α_2 receptors. Phenylephrine exhibits a preferential affinity for α_1 receptors. Shortly after it was proposed, the hypothesis was refuted that anatomical location was the basis upon which α_1 and α_2 adrenoreceptors were segregated (20). Destruction of presynaptic terminals by injection of 6-OH dopamine or lesions of noradrenergic cell bodies was not accompanied by a rapid decline in α_2 binding, in spite of the degeneration of presynaptic neurons. It is now well accepted that α_1 and α_2 receptors are present postsynaptically (52). Although the physiologic role of presynaptic receptors is in question (53), it has been demonstrated that activation of putative presynaptic autoreceptors by α agonists reduces neurotransmitter release (51,53). Saturation of presynaptic receptors with antagonists actually increases endogenous neurotransmitter release (55). The preoptico-hypothalamus contains α_1 and α_2 receptors, with the latter preferentially located in the arcuate-median eminence region (21-23). Thus, conflicting reports of hormonal responses to neuropharmacologic manipulation may be due not only to the lack of specificity of the drug, but a presynaptic effect of the drug as well. Furthermore, a variety of other neurotransmitters have been reported to affect the LHRH neuron directly, or indirectly by an influence upon the activity of catecholaminergic neurons (15,16). Receptors for many other neurotransmitter systems are heterogeneous, both in ligand binding and post-receptor events (56-61). Great care must be exerted in the execution and interpretation of neuroendocrine experiments performed with all neurotransmitter agonists and antagonists.

FSH VS LH REGULATION

In addition to the problems that surround the study of the neuropharmacologic control of the LHRH neuron, another dilemma exists. Many investigators have presented evidence that the neuroendocrine mechanisms that regulate LH and FSH are dissimilar (62-69). For instance, disruption of α adrenergic neurotransmission by the injection of drugs that affect catecholamine biosynthesis (62) or turnover (64) results in a rapid diminution in LH but not FSH pulse frequency. Further, alterations in the rate of pituitary LH secretion are accompanied by changes in catecholamine turnover within specific hypothalamic nuclei (16). Alterations in the rate of pituitary FSH secretion are not accompanied by changes in hypothalamic catecholamine content (70,71). The neurotransmitter systems that influence the release of pituitary FSH are unknown.

Although little is known about the neuroendocrine mechanisms that regulate FSH secretion, it is apparent that the release of this gonadotropin is regulated by neural mechanisms. Pulsatile FSH release is not observed from pituitary tissue *in vitro* (72). Stalk sections or total ablation of the arcuate-median eminence region does not result in continued FSH release (6,7). Electrical stimulation of CNS regions (apart from those that regulate LH release) results in a selective release of FSH (73). Ablation (74), implantation of prostaglandins (75) and deafferentation (76,77) studies support the hypothesis that a separate neural region regulates FSH secretion.

As mentioned above, the frequency of LHRH pulse releases influences the relative proportions of LH and FSH released. However, recent studies suggest that many of the elevations in FSH secretions cannot be explained on the basis of alterations in LHRH pulse frequency. Indeed, a controversy exists as to the involvement of LHRH in the release of FSH. Immunoneutralization of LHRH (62,66,78) or injection of LHRH antagonists (79,80) exerts dramatic effects upon LH pulsatility in serum while not affecting FSH. Contrary to these findings, increases in pituitary portal blood immunoreactive LHRH concentrations have been observed during times of selective FSH releases (during estrus or after ovariectomy) (11,81). Furthermore, data are available to suggest that a specific releasing hormone (distinct from LHRH) regulates the release of FSH (82,87). Cyclic fluctuations in hypothalamic FSH releasing activity have been observed without changes in LHRH bioactivity (84-87). The neuroanatomical location of neurons that synthesize a putative FSH releasing hormone remains a mystery.

Thus, the reproductive neuroendocrine system provides a unique model that may be employed to study the interaction between gonadal steroids, central nervous tissue, neurosecretory cells and anterior pituitary hormones. Research efforts in reproductive neuroendocrinology have elucidated the mechanisms that regulate the release of pituitary LH. Progress in our understanding of the neural regulation of FSH secretion is occurring at a much slower rate. Information about the interactions between gonadal steroids, nervous tissue, neurotransmitter systems and the hypothalamic LHRH neuron is accumulating steadily. With the availability of refined techniques such as neural microdissection methods, specific neuropharmacologic agonists and antagonists, single unit neural recordings and immunohistochemistry, the gaps and inconsistencies that presently exist will be overcome.

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