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Neuroendocrine Control of Gonadotropin Secretion during the Menstrual Cycle

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INTRODUCTION

Two modalities of gonadotropin secretion have been identified in the mammals. The basal mode is characterized by episodic gonadotropin discharge whose frequency and amplitude may vary considerably during the day in male and according to different phases of reproductive cycle in female. Additionally, in adult female, preovulatory mode is characterized by fast and high amplitude pulses constituting midcycle gonadotropin surge followed by ovulation.

GnRH (gonadotropin releasing hormone) is the primary neural signal involved in regulating gonadotropin release from the pituitary gonadotropes. It is evident that GnRH is released from the hypothalamus in a pulsatile fashion. The arcuate area (AC) of the medial basal hypothalamus (MBH) generates a signal at approximately hourly intervals to induce the release of GnRH into the hypophysial portal circulation. The hourly GnRH pulses, then stimulate the gonadotropes to release pulses of LH and FSH, which, in turn, induce morphological and secretory changes in the ovaries. The periodic pattern of GnRH discharge and complex gonadal steroid feedback actions at the pituitary and/or hypothalamus are important variables which determine the two modalities of gonadotropin, pulsatile gonadotropin and preovulatory gonadotropin surge. In addition, neurotransmitters and neuropeptides are known to play the potential role in the control of gonadotropin secretion.

The purpose of this review is to provide and to discuss recent advances in understanding fundamental underlying neural mechanism in the control of two modalities of gonadotropin secretion during the menstrual cycle.

REGULATION OF PULSATILE GONADOTROPIN RELEASE

Characteristics of pulsatile gonadotropin release during the menstrual cycle

It has been demonstrated that gonadotropins are released in rapid, rhythmic pulses, superimposed on a low level of continuous secretion (Santen & Bardin, 1973; Crowley *et al.*, 1985). Pulsatile patterns of gonadotropin secretion may be found in all vertebrates. Frequency and amplitude of LH pulse were shown to vary according to the phase of the menstrual cycle in women (Yen *et al.*, 1972; Crowley *et al.*, 1985 Filicori *et al.*, 1986; Lam & Ferin, 1987). Pulsatile increments in gonadotropin release occur every 60 to 90 minutes throughout most of the cycle but decrease sharply following ovulation and corpus luteum formation, resulting in frequency of every 4 to 5 hours during the mid and late luteal phase (Rebar & Yen, 1979; Crowley *et al.*, 1985). A comparison of LH pulse patterns between the luteal and early follicular phases shows not only stricking difference in the frequency but also in the amplitude of the LH pulse. Pulse amplitude during the luteal phase was nearly double that in the early follicular phase (Norman *et al.*, 1984; Ferin *et al.*, 1985). However, the preovulatory LH surge was characterized by high frequency, and high amplitude LH pulses (Marut *et al.*, 1981; Norman *et al.*, 1984).

Current evidence suggests that the pulsatile secretion of gonadotropins is not intrinsic to the pituitary, but a reflection of intermittent hypothalamic stimulation (Knobil, 1981; Wildt *et al.*, 1981a). Pulsatile patterns are readily detectable especially in gonadectomized subjects. The ovariectomized monkey exhibits a characteristic hourly (circhoral) pattern of LH pulsatile secretion.

The pulsatile administration of GnRH at hourly intervals to castrated animals bearing hypothalamic lesions that eliminate endogenous GnRH secretion restores circhoral LH secretion and returns gonadotropins to preexisting castrated levels. In contrast a constant GnRH infusion induces a transient rise in LH which again fall to undetectable levels. Indeed, the direct measurement of GnRH in the hypophysial portal plasma of rhesus monkeys has clearly demonstrated episodic fluctuations of GnRH levels (Carmel *et al.*, 1976). In addition, circhoral pulses of GnRH have recently been detected in the peripheral plasma of women (Elkind-Hirsch *et al.*, 1982). Thus, the normal pattern of pulsatile gonadotropin secretion appears to occur in response to the pulsatile release of GnRH into the portal circulation.

Hypothalamic GnRH pulse generator

Now, it is clearly known that GnRH release into the hypophysial portal vein is characterized by intermittent pulses superimposed on a lower level of continued secretion. The neural mechanism that governs the intermittent release of GnRH in the hypothalamus has been called as "GnRH pulse generator" (Lincoln *et al.*, 1985).

The demonstration of GnRH pulse generator activity has been provided by Clarke and Cummins (1982), who monitored fluctuations of GnRH concentrations in hypophysial portal plasma of the ovariectomized ewe. It was shown that distinct increments in GnRH concentrations in hypophysial portal plasma were observed at approximately hourly intervals and, moreover, GnRH discharges were temporally correlated with episodes of LH secretion. Similar patterns of fluctuating GnRH concentrations in hypophysial portal blood were observed in other species, including the monkey although simultaneous monitoring of intermittent LH secretion was not conducted (Carmel *et al.*, 1976; Sarkar & Fink, 1980). Furthermore, electrical recordings of neuronal activity in MBH of ovariectomized rhesus monkeys show intermittent electrical activity at hourly intervals which correlates well with the pulsatility of LH in the peripheral circulation (Knobil, 1980).

Then, question might be asked about where the GnRH pulse generator is located and how it does work: Immunocytochemical methods have demonstrated clusters of perikarya of GnRH-containing cells in the preoptic area-septal region (POA-S) and in the MBH in human, rhesus monkey, guinea pig, and rabbit (Zimmerman & Lobo, 1976; Schwanzel-Fukuda *et al.*, 1981; Silverman *et al.*, 1982). GnRH perikarya has also been found in the POA-S of rats (Merchenthaler *et al.*, 1980), but the presence of these peptidergic neuronal cell bodies in the MBH has been the subject of debate (Witkin *et al.*, 1982). Recent evidence, however, suggests that GnRH cell bodies are present in the MBH of rat (Kawano & Daikoku, 1981) and that the arcuate nucleus may contain some GnRH cell bodies (Kelly *et al.*, 1982). Thus, GnRH cell bodies are distributed in two anatomically distinct regions; one in the POA-S and the other in the MBH. There are, of course, additional GnRH cell bodies in other regions as well.

Then, question might be raised whether or not both regions are responsible for GnRH release and whether or not both regions are responsible for driving the pulsatile pattern of LH release. Despite lack of direct evidence, there are some indirect indications to support that the MBH cluster of GnRH cell bodies is crucial in driving pulsatile LH release. Complete anterior deafferentation of MBH failed to eliminate pulsatile release patterns in ovariectomized rhesus monkey (Knobil, 1974; Krey *et al.*, 1975), rat (Blake & Sawyer, 1974; Soper & Weick, 1980), and sheep (Pau *et al.*, 1982). Thus, there exists the GnRH pulse generator within the MBH (and perhaps in POA-S as well).

Then, how is the activity of GnRH neurons controlled and how does this relate to the regulation of gonadotropin secretion? Two general types of central act modulate the activity of GnRH neurons relevant to gonadotropin secretion; control by feedback action of ovarian steroids delivered by the blood, and control by other neurons through synaptic neurotransmissions. Each of these is now considered separately.

Modulation of pulsatile gonadotropin secretion by ovarian steroids

There is little doubt that changes in pulsatile LH secretory patterns during the menstrual cycle are influenced by ovarian steroids (Yen, 1980; Yu *et al.*, 1981; Ryu & Hong, 1983). Although the physiological significance of these changes in LH pulse characteristics remains to be clearly defined, it is assumed that they do play a role in the control of cyclic events.

Then, next question is that such changes in

pulsatile patterns result from actions of ovarian steroids at a central site or a pituitary site. Determination of the sites where estradiol and progesterone exert their feedback actions remains controversial.

Reviews on the site at which estradiol exerts its feedback action on gonadotropin secretion in the monkey have emphasized a hypophysial site of action (Knobil, 1980; Goodman & Knobil, 1981). The evidence is derived from experiments in monkeys bearing MBH lesions or in which the pituitary stalk has been sectioned and to which hourly GnRH pulses have been administered to elevate LH to prelesion control concentrations. Administration of estradiol to such animals in which the potential hypothalamic feedback site has been destroyed or in which the pituitary has been isolated from direct brain influences, produced a decrease in pulsatile LH secretion (Plant *et al.*, 1978b), suggesting a direct action of estradiol on the anterior pituitary. Similar estradiol effects on the pituitary gland were seen in intact monkeys in which systemic estradiol administration dampened the increase in serum LH observed after infusion of GnRH (Spies & Norman, 1975). The fact that this phenomenon has also been observed in vitro (Chappel *et al.*, 1981) confirms a direct hypophysial estradiol effect.

On the one hand, the evidence also clearly indicates that ovarian steroids, in addition to their hypophysial effects, influence gonadotropin secretion by acting at a hypothalamic sites as well. The demonstration of estradiol receptor (Phaff *et al.*, 1976; Garris *et al.*, 1981) in the MBH (with heavy labeling in the arcuate nucleus) supports this conclusion. Furthermore, estradiol injection at specific intrahypothalamic sites in monkeys bearing multiple intracranial cannulae depressed LH levels and mimicked the effects of intravenous estrogen administration (Ferin *et al.*, 1985). Most of the responsive sites were situated in the MBH, but extended to include the mammillary complex and perifornical nucleus (Ferin *et al.*, 1974). Furthermore, push-pull cannulae placed within the ventromedial arcuate nucleus of the hypothalamus revealed that in vivo release of GnRH was altered by administration of estrogen to ovariectomized rats (Ramirez & Dluzen, 1987). Such results provide evidence that estradiol can act at a hypothalamic site to inhibit LH secretion. Additional indirect evidence includes the observation that GnRH receptor concentrations are increased during the negative feedback phase of estriadiol (Adams *et al.*, 1981). Since there appears to be an inverse correlation between GnRH secretion and GnRH receptor, this experiment would also suggest that estradiol inhibits GnRH release.

Fewer experiments have investigated the site of progesterone action in primates. However, progesterone uptake occurs in the hypothalamus (Garris *et al.*, 1982). Progesterone was found to inhibit estrogen-induced gonadotropin surges in the monkey by acting at the level of CNS (Wildt *et al.*, 1981a). In sheep, progesterone decreases the frequency of LH pulse without reducing amplitude or the response to exogenous GnRH, suggesting that progesterone suppresses LH secretion by acting at the brain to decrease the frequency of GnRH pulses (Goodman & Karsch, 1980).

These results provide evidence that both steroids, estradiol and progesterone, act on CNS site as well as pituitary site to modify the secretion of gonadotropins. More convincing evidence, however, would be provided by demonstrating that both steroids influence hypothalamic GnRH pulse generator.

Regulation of the GnRH pulse generator by progesterone: Progesterone appears to act on the hypothalamic GnRH pulse generator. During the menstrual cycle, dramatic changes are observed in the frequency of pulsatile LH secretion (Yen *et al.*, 1972; Filicori & Crowley, 1983; Norman *et al.*, 1984; Reame *et al.*, 1984) and therefore, by inference, of the hypothalamic GnRH pulse generator (Plant, 1986). LH pulse frequency during the greater part of the luteal phase is markedly slower than that during the follicular phase (Crowley *et al.*, 1985). The first convincing evidence that ovarian progesterone is responsible for the deceleration of the hypothalamic GnRH pulse generator during the luteal phase was provided by Goodman and Karsch (1980) in the ewe. In women, progesterone administration in the follicular phase can affect a slowing of LH pulse frequency and an augmentation in LH pulse amplitude (Soules *et al.*, 1984). In ovariectomized monkeys, the frequency of gonadotropin discharge was reduced by progesterone (Knobil, 1981).

A neurochemical basis for the progesterone deceleration of the hypothalamic GnRH pulse generator in primates is provided by the identification of receptor for progesterone in cytosolic extract of hypothalamus in monkeys (Krey & McEwen, 1983), and by autoradiographic demonstration of heavy radiolabeling of neurons within

the arcuate nucleus after administration of synthetic progestin (Garris *et al.*, 1981). In both human and rhesus monkey, administration of naloxone, an opiate receptor antagonist, during the luteal phase of the menstrual cycle results in a dramatic acceleration in LH pulse frequency (Ropert *et al.*, 1981; Van Vugt *et al.*, 1984; Ferin *et al.*, 1985), suggesting that endogenous opioid peptides may be involved in mediating the action of progesterone to decelerate the hypothalamic GnRH pulse generator. Thus, the modulation of GnRH and consequently LH pulsatile secretion by progesterone involves an interaction with hypothalamic opioid peptide network.

In addition to the ability of progesterone to retard the hypothalamic GnRH pulse generator, this steroid is also able to exert, under certain conditions, marked facilitatory effect on gonadotropin secretion (Leyendecker *et al.*, 1976; Yeoman & Terasawa, 1984) that appears to be mediated by both hypothalamic and pituitary sites of action (Wildt *et al.*, 1981b; Yeoman & Terasawa, 1984). Progesterone is also able to block the action of estradiol that induces the preovulatory gonadotropin surge (Dierscheh *et al.*, 1973), apparently by acting on the CNS that may involve the production of a release-inhibiting factor (Pohl *et al.*, 1982).

Physiological significance of the action of progesterone in the overall regulation of the menstrual cycle remains an area of debate.

Regulation of GnRH pulse generator by estradiol: LH pulse frequency of approximately one to two pulses/h has been observed at the beginning of the follicular phase in both human (Reame *et al.*, 1984; Yen *et al.*, 1972; Backstrom *et al.*, 1982; Soules *et al.*, 1984) and monkey (Marut *et al.*, 1981), and a relatively short LH interpulse interval appears to be maintained throughout the entire follicular phase (Backstrom *et al.*, 1982; Norman *et al.*, 1984; Soules *et al.*, 1984), despite a substantial rise in circulating estradiol levels. In women, an acceleration in LH pulse frequency has actually been reported in association with the elevation in estradiol levels during the late follicular phase (Backstrom *et al.*, 1982; Reame *et al.*, 1984; Soules *et al.*, 1984). These findings suggest that physiological concentrations of circulating estradiol in contrast to progesterone and testosterone are probably incapable of decelerating the hypothalamic GnRH pulse generator in primates.

Estradiol is a major ovarian factor of the negative feedback loop that regulates gonadotropin secretion during the follicular phase of the menstrual cycle (Knobil, 1974). In the monkey, microinjection of estradiol into various neural sites in the hypothalamus (Ferin *et al.*, 1974) and miniinfusion of estradiol into the third ventricle (Chappel *et al.*, 1981) suppressed LH secretion suggesting a hypothalamic site of estradiol action in the negative feedback control of gonadotropin secretion. On the other hand, unequivocal evidence for a hypophysial site for the negative feedback action of estradiol on gonadotropin secretion has been obtained from studies of the arcuate-lesioned, GnRH-replaced rhesus monkey (Plant *et al.*, 1978a). Moreover, folliculogenesis and ovulation may be induced in hypothalamic-lesioned, ovarian intact monkeys and in women with hypothalamic amenorrhea after chronic treatment with intermittent GnRH infusions of invarient frequency, demonstrating in compelling fashion a physiologically relevant negative feedback loop between the ovary and pituitary(Plant, 1986).

Estradiol is also able to facilitate LH and FSH release, and this so-called positive feedback action plays a major role in eliciting the preovulatory gonadotropin surge in primates (Knobil, 1974; Young & Jaffe, 1976). That estradiol exerts positive feedback action on preovulatory gonadotropin surge will be discussed separately in this review.

In the monkey, distribution of ovarian steroid-concentrating neurons (Phaff *et al.*, 1976; Garries *et al.*, 1982) and of GnRH neurons generally overlap, especially in the preoptic-anterior hypothalamic and MBH regions. In view of the role that these steroids exert action on GnRH secretion, it would be logical to assume a direct cellular correlation. However, in recent studies in the rodent during which the immunocytochemical method for localizing GnRH was coupled with an autoradiographic method for detecting estrogen concentrating neurons, doubly labeled cells were not seen (Shivers *et al.*, 1983). The results suggest that genomic regulating effects of estrogens which depend on nuclear retention, are not exerted directly on most GnRH neurons, but must be mediated by other classes of neurons. Alternatively, ovarian steroids may exert their effects through nongenomic mechanism perhaps at the membrane levels. Furthermore, Melrose and Gross (1987) reported that under physiological conditions, GnRH neurons are not directly influenced by estradiol and progesterone in male rats. Although

this type of correlative study remains to be done in the primates, the results suggest that the effects of ovarian steroids on GnRH and gonadotropin secretion may be relayed by neurons other than GnRH containing neurons.

Involvement of catecholamines in the modulation of pulsatile gonadotropin release

Steroid hormones are known to affect catecholamine transmission in brain (Barraclough & Wise, 1982) and also to influence pulsatile release of LH (Gallo, 1980; Knobil, 1974; Weick, 1981). The question, therefore, arises: does change in brain catecholamines induced by ovarian steroids cause change in pulsatile GnRH-LH release ?

Dopamine (DA) transmission in the MBH was increased by the treatment of estradiol benzoate in ovariectomized rats (Advis *et al.*, 1980) while estradiol benzoate suppressed pulsatile LH release (Weick, 1977). These results suggest that increased dopamine transmission in the MBH is inhibitory to the GnRH-LH pulse generating system.

Morphological studies of the median eminence (ME) have demonstrated close apposition of DA and GnRH terminals that may permit DA to influence GnRH release (Ajika, 1980). However, it might be premature to state that DA effects on LH secretion are exerted exclusively at the ME, particularly because DA receptors on pituitary lactotrophs may influence prolactin secretions, which in turn, may modulate LH release (Beck *et al.*, 1977). Some investigators reported that DA or DA receptor stimulators suppressed serum LH levels (Beck *et al.*, 1978; Ramirez *et al.*, 1984) whereas others suggested an increase of LH soon after such treatment (Kamberi *et al.*, 1970; Vijayan *et al.*, 1978). Moreover, Jarjour *et al.*, (1986) reported that DA induced GnRH release in male rats, suggesting that this is most probably attributable to DA-induced release of hypothalamic norepinephrine (NE) which, in turn, acts through adrenergic receptors on GnRH neurons to stimulate GnRH release. More confusedly, tyrosine hydroxylase inhibitor, α-methyl-para-tyrosin (α-MPT), which lowers hypothalamic DA content had no effect on LH levels in ovariectomized rats (Donoso *et al.*, 1971). Nevertheless, it was found that when DA affected LH levels, they did so by an action on brain rather than an anterior pituitary (Ryu *et al.*, 1980) and it was inferred that action of DA transmission probably was mediated by axo-axonic contacts between GnRH and DA fibers in the ME (Schneider *et al.*, 1969). DA receptor stimulator such as apomorphine blocked pulsatile LH in rats (Drouva & Gallo, 1977), and DA infused into the third ventricle had suppressive effects on pulsatile LH (Gallo & Drouva, 1979). Pimozide, DA receptor blocker, reversed the effects of apomorphine (Gallo, 1981). Thus, increase in DA transmission suppresses frequency and/or amplitude of pulsatile LH release.

However, pimozide alone fails to alter pulsatile LH release in ovariectomized rats as does α-butaclamol, another DA receptor blocker (Drouva & Gallo, 1976; Gallo, 1981). α-AMPT decreases hypothalamic DA content and yet fails to affect pulsatile LH release in ovariectomized rats (Drouva & Gallo, 1976; Gallo, 1981). These data suggest that in rats DA transmission does not normally regulate pulsatile LH release, but that under certain conditions of drug treatments, increased DA transmission inhibits LH pulse (Drouva & Gallo, 1976).

However, conflicting data have been reported. The DA receptor blockers, haloperidol and chlorpromazine, suppressed pulsatile LH discharge in ovariectomized rhesus monkey (Bhattacharya *et al.*, 1972). This suggests that DA transmission facilitates pulsatile LH release. Interpretation of these conflicting data are difficult. However, failure to inhibit pulsatile LH release by DA receptor blocker such as pimozide is not conclusive evidence that DA transmission is not involved in LH release. Conversely, when DA receptor antagonist such as haloperidol blocks pulsatile LH discharge, this can not be taken as evidence that DA transmission normally facilitates LH pulses (Kaufman *et al.*, 1985). This may be partly due to the uncertainty about the nature of DA receptors in the hypothalamus and to the possibility that two types of DA receptors may be involved (Ojeda & McCann, 1978). For example, pimozide may act on one type of DA receptor and haloperidol on another, thereby exerting effects in opposite directions with respect to pulsatile LH release (Fink *et al.*, 1982).

The role of estradiol in NE turnover was also extensively investigated in rat brain. NE content in ME increases after ovariectomy and decreases after the treatment of estradiol benzoate in long-term ovariectomized rats (Advis *et al.*, 1980), suggesting that increases in NE stimulation of GnRH release in the ME are importantly involved in facilitating LH release.

However, this notion seems to be contradicted by the finding that EB treatment did not alter NE turnover in ME (Crowley, 1982), even though such treatment suppressed pulsatile LH secretion in long-term ovariectomized rats (Weick, 1977). These results suggest that increased NE transmission in the ME is not obligatory in facilitating pulsatile GnRH-LH secretion. However, during a normal rat estrus cycle, pulsatile GnRH (Levine & Ramirez, 1982) and LH releases (Gallo, 1981a, 1981b) occur with high frequency at a time when NE turnover is significantly elevated in MBH as well as ME at proestrus afternoon (Rance *et al.*, 1981).

It is clear that MBH-POA is richly innervated by NE systems (Palkovits, 1981) and that close apposition of NE terminals and GnRH cell bodies occurs in the MBH as well as in the POA (Hoffman *et al.*, 1982; Jennes *et al.*, 1982). Therefore, it is assumed that alterations in NE transmission might influence pulsatile release of GnRH. Then, how does NE transmission affect pulsatile LH release ? This question was first explored in ovariectomized rhesus monkeys (Bhattacharya *et al.*, 1972; Knobil, 1974). Phentolamine and phenoxybenzamine, which have α-receptor blocking property, suppressed pulsatile LH release within seconds or minutes, whereas β-blocker propranolol was without effect on pulsatile LH discharge. More recent work with this species clearly shows that effective drugs exert their actions at the MBH level rather than at the level of the pituitary (Knobil, 1980). Futhermore, Kaufman et al (1985) reported that GnRH pulse generator activity was inhibited by phentolamine. Thus, NE normally facilitates pulsatile LH output by acting through an α-receptor mechanism (Jarjour *et al.*, 1986). However, precise nature of facilitative role of NE transmission in maintaining pulsatile LH has not been clearly understood. The facilitative action of NE transmission on pulsatile LH output appears to be exerted on frequency and amplitude parameters, but the relation between episodic fluctuations in NE transmission and LH pulses does not appear to be of one-to-one variety (Estes, 1982).

Whether NE transmission is obligatory for pulsatile LH and whether NE directly influences such pulsing, is not yet clear. Experiments that assess drug effects on GnRH pulses, rather than drug effects on LH pulses might be helpful in answering the question of how NE transmission influences the hypothalamic GnRH pulse generator. Despite the accumulating data that indicate a facilitative role for NE transmission in pulsatile LH release, there are also evidence to indicate that an acute increase in NE transmission suppresses pulsatile LH release. Third ventricle infusions of NE, α-receptor agonist such as phenylephrine or clonidine, or β-receptor blocker agonist such as isoproterenol significantly and acutely suppressed the frequency of pulsatile LH release in rats (Leung *et al.*, 1982).

It is, therefore, summarized that increased DA transmission plays no crucial role in facilitating the pulse generator, especially under physiological conditions. Increased NE turnover generally appears to speed up the frequency of the pulse generator. However, under particular experimental conditions, which may lead to estradiol-induced supernormal NE transmission, an inhibitory effect of NE on the GnRH-LH pulse generator can occur. Whether or not NE transmission is absolutely essential for operation of the pulse generator has not been established.

Involvement of Opiate Peptide in the Modulation of Pulsatile Gonadotropin Release

Evidence has accumulated that endogenous opioid peptides play an important role in the control of gonadotropin secretion in the primates including the human.

β-endorphin neuronal cell bodies are preferentially concentrated in areas known to be involved in the control of gonadotropin secretion. The localization of β-endorphin within the hypothalamus which in the monkey are rich in GnRH provides anatomical evidence for interactions between β-endorphin and GnRH. These interactions may include neuron to neuron communications within the arcuate region, and area in which cell bodies for both peptides are located, or axo-axonal influences within the median eminence which contains terminals for both GnRH and β-endorphin axons (Ferin *et al.*, 1985).

A single intravenous injection of morphine or an intraventricular injection of β-endorphin resulted in a decrease in circulating LH and FSH concentrations (Ferin *et al.*, 1982). The reduction in serum LH seen after administration of opiates is the result of a reduced frequency of pulsatility rather than a reduced amplitude of each individual secretory pulse (Sylvester *et al.*, 1982). An inhibitory effect of opiates on FSH was observed as well although it was less pronounced. Similar results have been observed in the human (Reid *et*

al., 1981).

Then, does endogenous opioids themselves control gonadotropin secretion? When naloxone was injected daily throughout the entire menstrual cycle in the monkey, LH responses to naloxone were significant only during the luteal phase (Van Vugt *et al.*, 1983). During the luteal phase, administration of naloxone increased LH secretion. In contrast, naloxone was unable to stimulate LH secretion during the follicular phase. These data agree with that gonadotropin secretion was stimulated by naloxone during the luteal phase, but not the early follicular phase of the menstrual cycle in the human (Quigley & Yen, 1980). Thus, endogenous opioid peptides modify gonadotropin secretion, but they do so only under specific endocrine conditions. However, an interaction between endogenous opioid peptides and gonadotropin release is a complex one which involves ovarian hormone as well. In the human (Ropert *et al.*, 1981) and the monkey (Ferin *et al.*, 1985), LH secretion appears to be most suppressed by endogenous opioids during the luteal phase, at a time of elevated progesterone secretion.

Modulation of β-endorphin by ovarian steroids: Differential LH response to naloxone at various time of the menstrual cycle suggests that endogenous opioid secretion may fluctuate with the endocrine gonadal steroid milieu (Ferin *et al.*, 1985).

β-endorphin level in hypophysial portal vein is believed to reflect hypothalamic β-endorphin activity because axon derived from β-endorphin cell bodies in the arcuate region terminates near portal vessels. Following ovariectomy, portal β-endorphin concentration became undetectable (Wehrenberg *et al.*, 1982). Ovarian steroid replacement in ovariectomized monkeys restored portal β-endorphin levels (Wardlaw *et al.*, 1982). Thus, it appears that ovarian steroids are necessary for the release of hypothalamic β-endorphin. During the menstrual cycle, β-endorphin release was undetectable at menstruation when ovarian steroid concentrations are lowest (Ferin *et al.*, 1985). In contrast, as ovarian steroid secretion increased during the late follicular phase and luteal phase, increased amounts of β-endorphin were released into the portal circulation (Wehrenberg *et al.*, 1982). Largest amounts of β-endorphin appear to be secreted in the presence of progesterone. However, when progesterone alone was given to ovariectomized monkeys there was no increase in β-endorphin secretion (Ferin *et al.*, 1985) indicating that progesterone action usually is the consequence of a synergistic effect with estrogen (Maclusky *et al.*, 1980). Thus, hypothalamic β-endorphin activity seems to be modulated by ovarian steroids.

A role of β-endorphin during the menstrual cycle: As mentioned above, hypothalamic β-endorphin secretion into the hypophysial portal circulation fluctuates during the menstrual cycle in the monkey reaching the maximum during the luteal phase at a time when LH pulse frequency is slowest. Then, question is asked if endogenous opioid peptides participate in decreasing LH pulse frequency observed during the luteal phase. Ferin *et al.* (1985) examined the effects of naloxone infusions on LH pulse frequency. LH pulse frequency was clearly increased during the naloxone infusion period as compared to the preceding control period during the luteal phase. LH pulse amplitude, however, was unchanged by naloxone administration. Similar results were reported in women during the luteal phase (Ropert *et al.*, 1981) as well as in normal men (Ellingboe *et al.*, 1982). Thus, it is assumed that during the luteal phase a decrease in LH pulse frequency was due to an increase in endogenous opioid, resulting in inhibition of GnRH neurons.

Site and mechanism of β-endorphin action: Then, where does β-endorphin act to inhibit gonadotropin secretion? The presence of high concentration of biologically active β-endorphin in the hypophysial portal circulation suggests that it may exert direct effects at the anterior pituitary level. However, in pituitary stalk-sectioned monkeys in which the pituitary has been isolated from direct hypothalamic influences, morphine pretreatment did not affect the LH response to GnRH stimulus (Ferin *et al.*, 1982). This result is consistent with in vitro studies in the rodent, which failed to show a direct opiate effect either on gonadotropes (Cicero *et al.*, 1979) or lactotropes (River *et al.*, 1977). Furthermore, hypophysial site of action was not supported by the absence of opioid receptors in anterior pituitary (Simantov & Snyder 1977). Unfortunately, there is presently no direct in vivo evidence that the secretion of GnRH responsible for gonadotropin release is modified by β-endorphin in the primates. However, there is a sufficient indirect evidence for such a conclusion. The in vitro GnRH efflux from superfused human (Rasmussen *et al.*, 1983) or rat (Wilkes & Yen, 1981) medial basal hypothalami was increased following naloxone

perfusion. The naloxone-induced release of LH in the rat was blocked by the administration of GnRH antagonist (Blank & Roberts,1982). Thus, endogenous opioid acts to suppress the secretion of GnRH into the hypophysial portal circulation, thereby inhibiting gonadotropin secretion. The arcuate nucleus contains not only cell bodies for GnRH and β-endorphin but also a dense arborization of fibers (Ferin *et al.*, 1985), suggesting that GnRH release is changed by the interactions between GnRH and β-endorphin cell bodies within the arcuate nucleus. Some of the opioid peptide-containing fibers have been shown to form axosomatic contact with other cells of the arcuate nucleus, presumably containing other peptides or neurotransmitters (Kiss & Williams, 1983). Opioid regulation of GnRH is exerted at the level of the median eminence. Evidence indicates that intense innervation by β-endorphin and GnRH fibers, most of which orignate from cell bodies in the arcuate area, can be seen in the median eminence. This mechanism would allow for β-endorphin control at the nerve terminal at the point of GnRH release into the hypophysial portal circulation. (Ferin *et al.*, 1985)

However, whether inhibition of GnRH release by β-endorphin is the result of a direct synapse or whether neurotransmitters are intermediary has not been demonstrated in the monkey. The most obvious neurotransmitter candidates are norepinephrine, serotonin, and dopamine which have been implicated in gonadotropin secretion. In the rat, noradrenergic activity is required in order for naloxone to stimulate LH release, since this action can be prevented by prior administration of norepinephrine synthesis inhibitors or antagonists (Kalra, 1981). β-endorphin has been shown to decrease dopamine turnover in the median eminence (Deyo *et al.*, 1979), and to increase reuptake of dopamine into dopamine nerve endings (George & Van Loon, 1982). However, little is known about the effects of neurotransmitters on LH secretion in the primates.

REGULATION OF PREOVULATORY GONADOTROPIN SURGE

Preovulatory LH surge

In mammals that normally are spontaneous ovulators, the obligatory hormonal trigger for LH surge which results in ovulation appears to be estradiol, and this steroid exerts positive feedback action on the hypothalamo-hypophysial axis after reaching critical concentration in circulation for a sufficiently long period of time (Schwartz, 1969; Knobil, 1974; Kalra, 1975; Goodman & Knobil, 1981; Drouva *et al.*, 1982). The strength and duration of estrogen action required for LH surge may vary among species (Knobil, 1974; Goodman & Knobil, 1981; Krey & Parsons, 1982). In addition to estradiol, preovulatory progesterone secretion may play a facilitative role in cyclic surge of LH release in rats (Ramirez *et al.*, 1984), monkeys (Helmond *et al.*, 1980; Terasawa *et al.*, 1982), and humans (Jaffe & Monroe, 1980). These two steroids appear to be secreted in a pulsatile fashion, but the precise function of such pulsatile fluctuations on the LH surge mechanism is unknown. Two other pituitary hormones, FSH and prolactin, exhibit cyclic releases that coinside with LH surges (Ryu *et al.*, 1979, 1983; Ramirez *et al.*, 1984). LH, FSH, and prolactin can, under certain experimental conditions, exert feedback effects on neural activity (Moss, 1976) and in some cases influence DA (Moore *et al.*, 1980) or NE (Anton *et al.*, 1969) neurotransmission. Extensive studies on pulsatile LH release during the menstrual cycle have been reported in primates (Yen *et al.*, 1972; Norman *et al.*, 1984; Filicori *et al.*, 1986). However, very little information is available on alteration of the frequency and amplitude of pulsatile LH release during the preovulatory LH surge in primates including human. Terasawa *et al.* (1987), however, reported that both the frequency and amplitude of LH increase during the progesterone-induced LH surge in rhesus monkeys.

However, the most crucial and the final hormonal stimulus for the LH surge is GnRH (Schally, 1978). That an increase in hypothalamic GnRH secretion occurs in association with the LH surge can no longer be disputed in view of findings of increased concentrations of GnRH in peripheral plasma of women (Elkind-Hirsch *et al.*, 1982; Miyake *et al.*, 1983), and in hypophysial portal vein (Neil *et al.*, 1977), CSF (Van Vugt *et al.*, 1985) and hypothalamic perfusates (Levine & Spies, 1983; Norman *et al.*, 1983) of the rhesus monkey during either spontaneous or estrogen-induced gonadotropin surges. Elevations in GnRH concentrations in peripheral (Ryu *et al.*, 1976; Kalra & Kalra, 1977) and hypophysial portal plasma (Saker *et al.*, 1976; Ching, 1982; Fink *et al.*, 1982) shortly before LH surge was

also observed in rats. Thus, GnRH is required for cyclic surge of LH that results in ovulation. It is unlikey, however, that the increased secretion of GnRH during the preovulatory gonadotropin surge represents an obligatory neural signal for generation of the LH discharge because hypothalamic-lesioned monkeys and women with hypothalamic amenorrhea exhibit ovulatory menstrual cycles when intermittent stimulation with exogenous GnRH is provided (Crowley & McArther, 1980, Knobil *et al.*, 1980, Leyendecker et al., 1976). On the other hand, Norman et al. (1982) failed to restore ovultory menstrual cycles with intermittent GnRH replacement in stalk-sectioned monkeys bearing Teflon barriers. This is the only direct evidence to support that a neural signal is an essential component of the neuroendocrine mechanism that elicits the preovulatory gonadotropin surge in primates.

In rats, deafferentations that isolate the MBH from the POA (Halasz, 1969) and POA lesion (Barraclough *et al.*, 1975) result in the loss of LH surges with consequent anovulation. Thus, in rats, GnRH neurons in the POA are apparently required for LH surge to occur. It is likely, however, that some species do not require POA GnRH neurons for generation of LH surge or ovulation because rhesus monkeys continue to show LH surge and to ovulate after surgical deafferentation that separates the POA and MBH. Furthermore, arcuate nucleus lesions prevent ovulation in rhesus monkeys even when the POA is not damaged (Plant *et al.*, 1978a) and menstrual cyclicity (Knobil *et al.*, 1980) can be established by constant, pulsatile administration of GHRH to monkeys with deafferentation of the MBH and lesions of the arcuate nucleus. However, it may be premature to conclude that there is absolutely no POA influence on LH surge in such species since prenatally androgenized rhesus monkeys show a delay in menarche (Goy, 1970) and tissue anterior to the MBH has been shown to exert an influence on LH surge in rhesus monkeys (Norman *et al.*, 1976). Despite these species differences, the evidence is compelling that MBH and/or POA regions are obligatory for the cyclic surge of LH.

Modulation of LH surge by ovarian steroids

The hypothalamo-pituitary axis appears to be extremely sensitive to the circulating ovarian steroids during the cycle. Hypothalamus or pituitary has its own threshold of responsiveness to the steroids (Kalra & Kalra, 1981, 1982a, 1982b).

It is evident that estradiol is the primary ovarian signal responsible for preovulatory LH surge (Schwartz, 1969; Krey & Everett, 1973; Kalra, 1975; Simon *et al.*, 1987). Although action of estradiol in facilitating the preovulatory LH surge is essentially complete by 3:00 h of proestrus in rats (Kalra, 1975), the continued presence of elevated estradiol levels appears to augment pituitary responsivenss to GnRH and releasable LH stores (Cooper *et al.*, 1973; Kalra & Kalra, 1974) to prepare the impending GnRH hypersecretion later in the afternoon. Furthermore, there is evidence that estrogen increases the overall basal in vivo GnRH release and produces further increases in GnRH release during the preovulatory LH surge (Dulzen & Ramirez, 1986). This change appears to be attributable to increase in the frequency of GnRH release during this period.

Although progesterone may not be mandatory in eliciting LH surge on proestrus (Ramirez *et al.*, 1984), there is strong evidence that during the critical period on proestrus the circulating progesterone concentration is intimately involved in the neuroendocrine events associated with the preovulatory LH surge. Progesterone has been shown to stimulate GnRH release from the ME of estrogen-primed ovariectomized rats (Kim & Ramirez, 1982; Leadem & Yen, 1983). Injection of progesterone 2 days after estrogen priming reproduced a proestrus-type rise in the MBH GnRH levels before the LH surge (Kalra *et al.*, 1973; Fink *et al.*, 1982) while estradiol treatment alone failed to elicit similar increment in the ME GnRH levels (Kalra, 1975, Fink *et al.*, 1982). Therefore, it is suggested that circulating levels of progesterone between diestrus II and proestrus in rats, when estradiol is dominant circulating ovarian steroid, may be involved in eliciting the GnRH release.

Involvement of catecholamines in the modulation of preovulatory LH surge

Modulation of preovulatory LH surge by catecholamines has been studied almost exclusively in rats. However, even in this species, the picture is not yet complete.

Rance *et al.* (1981a, 1981b) reported changes in hypothalamic catecholamine metabolism during the estrus cycle, concluding that significant increase in NE activity and signficant decrease in DA activity occur at the time of the LH surge on the afternoon of proestrus in rats. Catecholamine

receptors have been studied as a parameter involved in catecholamine transmission related to the LH surge mechanism. It is reasonable to assume that the active catecholamine molecules released into synaptic cleft or extracellular spaces in ME (Zamora & Ramirez, 1982) bind to specific receptors in postsynaptic hypothalamic structures or in plasma membranes of axonal terminals in the ME. Such binding would then be expected to trigger intraneural events that stimulate or inhibit GnRH release and ultimately modify LH secretion from the pituitary.

Evidence supports that NE and epinephrine (E) may be involved in distinct way to accumulate GnRH in the MBH and its release into the hypophysial portal system during the critical period for LH surge on proestrus (Kalra & Kalra, 1983). Suppression of hypothalamic NE and E levels by inhibiting dopamine-β-hydroxylase (DBH) activity by a number of drugs blocked the LH surge (Kalra & McCann, 1974: Kalra, 1983) and that induced by ovarian steroids (Kalra *et al.*, 1972). However, replenishment of NE levels in these rats reversed the effects of DBH inhibitor on LH surge (Kalra *et al.*, 1972; Kalra & McCann, 1974). Blockade of α-adrenergic receptors inhibited preovulatory and steroid-induced LH surges (Kalra *et al.*, 1972; Kalra & McCann, 1974; Clifton & Sawyer, 1979, 1980) perhaps by blocking α_1-adrenergic receptors (Drouva *et al.*, 1982). However, the precise contribution of α-and β-receptors to the LH surge mechanism has not been clearly determined, because no changes in numbers of these receptors have been detected in rat brain during the estrus cycle (Wilkinson *et al.*, 1979a, 1979b) and too few studies have been done on the regulation of hypothalamic α-and β-receptor numbers by exogenous steroid treatments. Intraventricular injections of NE or E on proestrus elicited LH release (Krieg & Sawyer, 1976; Gallo & Drouva, 1979). Administration of NE elicited GnRH release from the ME in vivo (Krieg & Ching, 1982) and in vitro (Negro-Vilar & Ojeda. 1978). Furthermore, there is general agreement that several regions in the septal-preoptic tuberal pathway innervated by NE neurons display increased amine activity before and during the LH surge on proestrus and the surge induced by ovarian steroids (Crowley *et al.*, 1978; Rance *et al.*, 1981). In species other than rats, data on catecholamine modulation of LH surges are quite scarce. In women, increases in serum NE levels have been noticed during ovulation (Badano *et al.*, 1978). Pimozide and fusaric acid are reported to inhibit midcycle LH release in healthy women (Weiner & Ganong, 1978). It has become evident that E may play a prominent role in evoking GnRH release during the critical period on proestrus in rats. A centrally active E synthesis inhibitor, LY 78335 (2, 3-dichloro-α-methylbenzylamine), administered before the critical period on proestrus blocked the LH surge and ovulation (Kalra, 1983). Aslo, there is evidence of increased E turnover in the MBH in association with the LH surge in rats (Adler *et al.*, 1983).

The mechanisms whereby augmented adrenergic transmission may facilitate the formation and accumulation of GnRH in the median eminence-arcuate nerve terminals before the LH surge have not been clearly understood. Advis *et al.*, (1983) have proposed that GnRH increments may, in part, be resulted from decrease in GnRH degrading enzymes in the ME. Interestingly, when GnRH accumulation was blocked by suppression of adrenergic neurotransmission (Simpkins *et al.*, 1980), the decrease in GnRH degrading activity in the ME was abolished (Advis *et al.*, 1983). Another possibility is that there is de novo synthesis of GnRH in response to neurogenic stimuli on proestrus or to progesterone in estrogen primed ovariectomized rats (Kalra & Kalra, 1979; Simpkins *et al.*, 1980; Wise *et al.*, 1981). A few studies have attempted to delineate the intraneuronal sequence of events provoked by presumed release of NE and E in assoication with the preovulatory trigger of LH surge (Ojeda *et al.*, 1979a; DePaolo *et al.*, 1982). Prostaglandin E_2 (PGE_2) stimulates LH release in steroid primed rats suggesting that PGE_2 may participate in the preovulatory LH release (Ojeda *et al.*, 1979a). There is evidence that estradiol stimulates PGE_2 release (Ojeda & Campbell, 1982) and PGE_2 stimulates in vivo and in vitro GnRH release (Gallardo & Ramirez, 1977; Ojeda *et al.*, 1977). Furthermore, it has been shown that NE evokes PGE_2 release from ME by activating α-adrenergic receptors (Ojeda *et al.*, 1979b, 1982). PGE_2 synthesis rises to highest levels during late proestrus in MBH (Ojeda & Campbell, 1982). This finding suggests that estradiol, which is known to play an obligatory role in inducing preovulatory LH surge (Goodman & Knobil, 1981), triggers the increased synthesis of PGE_2. DePaolo *et al.*, (1982) postulated that initially the preovulatory GnRH hypersecretion from the ME nerve terminals may

be due to augmented release of PGE_2 evolved by NE and thereafter, as the LH surge progressed, continued GnRH secretion may occur as a result of enhanced responsiveness of GnRH nerve terminals to PGE_2.

SUMMARY

Two modalities of gonadotropin secretion, pulsatile gonadotropin and preovulatory gonadotropin surge, have been identified in the mammals.

Pulsatile gonadotropin secretion is modulated by the pulsatile pattern of GnRH release and complex ovarian steroid feedback actions. The neural mechansim that regulates the pulsatile release of GnRH in the hypothalamus is called "GnRH pulse generator". Ovarian steroids, estradiol and progesterone, appear to exert thier feedback effects both directly on the pituitary to modulate gonadotropin release and on a hypothalamic site to modulate GnRH release; estradiol primarily affects the amplitude while progesterone decreases the frequency of the pulsatile GnRH. Steroid hormones are known to affect catecholamine transmission in brain. MBH-POA is richly innervated by NE systems and close apposition of NE terminals and GnRH cell bodies occurs in the MBH as well as in the POA. NE normally facilitates pulsatile LH release by acting through α-receptor mechanism. However, precise nature of facilitative role of NE transmission in maintaining pulsatile LH has not been clearly understood. Close apposition of DA and GnRH terminals in ME might permit DA to influence GnRH release. Action of DA transmission probably is mediated by axo-axonic contacts between GnRH and DA fibers in the ME. Dopamine transmission does not normally regulate pulsatile LH release, but under certain conditions, increased DA transmission inhibit LH pulse. Endogenous opioid acts to suppress the secretion of GnRH into hypophysial portal circulation, thereby inhibiting gonadotropin secretion. However, an interaction between endogenenous opioid peptides and gonadotropin release is a complex one which involves ovarian hormones as well. LH secretion appears to be most suppressed by endogenenous opioids during the luteal phase, at a time of elevated progesterone secretion. The arcuate nucleus contains not only cell bodies for GnRH and β-endorphin but also a dense aborization of fibers suggesting that GnRH release is changed by the interactions between GnRH and β-endolphin cell bodies within the arcuate nucleus.

The frequency and amplitude of pulsatile LH release seem to be increased during the preovulatory gonadotropin surge. Estradiol exerts positive feedback action on the hypothalamo -pituitary axis to trigger preovulatory LH surge. GnRH is also crucial hormonal stimulus for preovulatory LH surge. It is unlikely, however, that increased secretion of GnRH during the preovulatory gonadotropin surge represents an obligatory neural signal for generation of the LH discharge in primates including human. Modulation of preovulatory LH surge by catecholamines has been studied almost exclusively in rats. NE and E may be involved in distinct way to accumulate GnRH in the MBH and its release into the hypophysial portal system during the critical period for LH surge on proestrus in rats. However, the mechanisms whereby augmented adrenergic transmission may facilitate the formation and accumulation of GnRH in the ME-ARC nerve terminals before the LH surge have not been clearly understood.

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