

ROLE OF CATECHOLAMINES IN REGULATION OF HYPOTHALAMO PITUITARY OVARIAN AXIS: A REVIEW

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SUMMARY

Catecholamines participate in modulation of different aspects of reproduction particularly the activity of hypothalamo pituitary ovarian axis through activation of α and β -adrenergic receptors. At ovarian level catecholamines play a significant role in the process of luteinization and secretion of ovarian steroids. They also alter the secretion of gonadotropin-releasing hormone (GnRH) through activation of different neurotransmitters and also modulate the secretion of gonadotrophins from the pituitary. However, variability in their action in modulation of the hypothalamo-pituitary-ovarian axis exists depending upon the sex, species and phase of the estrus cycle.

Key words: Catecholamines, epinephrine, nor-epinephrine, dopamine, steroids, gonadotrophins

Catecholamines are the products of sympathoadrenal system which act mainly via stimulation of α and β -adrenergic receptors to modulate the activity of different body systems including reproduction. The level of catecholamines in blood, brain, adrenal glands and in ovaries varies with the stage of the estrus cycle which indicates that there may be close interaction between the sympathoadrenal system and hypothalamo pituitary ovarian axis (Karatas *et al.*, 2001).

REGULATION OF OVARIAN STEROIDS

Under physiological conditions, the process of luteinization may be associated with ovarian acquisition of responsiveness to catecholamines (Rani *et al.*, 1983). In guinea pig, an inverse relationship exists throughout the estrus cycle between the nor-epinephrine (NE) concentration in ovary and serum oestradiol-17 β concentration, but a positive relationship persists between progesterone and nor-epinephrine. It suggests that the ovarian concentration of nor-epinephrine may be related to structural and functional changes which had occurred during transition

from the ovulatory period to the luteal phase (Garris and Dar, 1984).

Catecholamines regulate the secretion of ovarian steroids mainly through activation of β -adrenergic receptors. Beta-adrenergic receptors were found to be affecting progesterone secretion either via a cAMP dependent mechanism (Adashi and Hsueh, 1981) or by altering the activity of 3 β -hydroxysteroid dehydrogenase and 20 α -hydroxysteroid dehydrogenase (Jones and Hsueh, 1981, Hsueh *et al.*, 1983), two key enzymes needed in the biosynthesis of progesterone. Change in noradrenalin (NA) release to the synaptic cleft might exert regulation of β -adrenergic receptor content of the ovaries and in this way control ovarian steroid secretion (Ferruz *et al.*, 1991). Bovine corpus luteum can also synthesize de novo NA from dopamine (DA) and thus noradrenergic stimulation may be important in supporting the secretory functions of corpus luteum (Kotwica *et al.*, 2002).

Beta-adrenergic receptor activators like epinephrine (EP), nor-epinephrine (NE), salbutamol etc. stimulated *in-vivo* and *in-vitro* progesterone production from the luteal cells in sheep (Jordan *et al.*, 1987, Wheeler *et al.*, 1988) and cow (Condon and Black, 1976, Battista *et*

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al., 1987) but not in goat (Payne and Cooke, 1998). This refractoriness of caprine luteal cells to β -agonists may be due to lack of β -adrenergic receptors on the luteal cells in this species (Payne *et al.*, 1993), though at higher concentrations of adrenalin, progesterone concentration in plasma of caprine ovarian vein increased significantly (Payne and Cooke, 1998). Administration of non-selective β -receptor antagonists caused a reduction in plasma progesterone concentration in ewe (Wheeler *et al.*, 1988) but not in goats (Payne and Cooke, 1998) again suggesting a species difference. Incubation of rat luteal cells in monolayer culture with epinephrine inhibited the ability of human chorionic gonadotrophin (hCG) to induce cAMP and progesterone secretion, while the presence of EP in hCG-desensitized cells lead to a 40% stimulation of cAMP and progesterone production (Massicotte *et al.*, 1984).

REGULATION OF GONADOTROPINS

Several investigators have found that central nervous system catecholamine may be important in the neural regulation of pituitary gonadotrophin secretion (Kalra and Kalra, 1983, Ramirez *et al.*, 1984). Nor-epinephrine had stimulatory effect on gonadotropin release (Weiner and Ganong, 1978). According to Negro-Vilar *et al.* (1982), both NE and DA systems may be involved in the pulsatile release of LH in ovariectomized (OVX) rats. However, in OVX, pituitary stalk-transected ewes, the treatment with DA or NE did not alter plasma LH pulse frequency and basal secretion of LH and FSH (Donnelly and Dailey, 1991). Nor-epinephrine neuron transplants at the preoptic region inhibited gonadotrophin secretion in intact rats, whereas they facilitated it in OVX rats and the DA-neuron transplants appeared to exert facilitatory effects on FSH secretion in intact rats (Hashimoto, 1987). This suggests that gonadal steroids play an important role in catecholaminergic regulation of gonadotrophins. In ewes, administration of exogenous NE and DA suppressed LH secretion but a stimulatory effect of DA and NE (Prazekop *et al.*, 1975) has also been reported which may be due to difference in endocrine

status of the animals (Riggs and Malven, 1974, Deaver and Dailey, 1982).

Nor-epinephrine and EP systems have been reported to be activated before and during the LH surge in pro-estrus or after Estradiol benzoate plus progesterone treatment in rats (Honma and Wuttke, 1980, Coombs and Coen, 1983). The loss of cyclicity and decreased stimulation of gonadotropin release by ovarian steroids in old female rats is largely due to depressed catecholamine activity (Huang *et al.*, 1978). These indicate that steroid stimulation of hormone releasing centers in the central nervous system is mediated by catecholaminergic mechanisms (Krieg *et al.*, 1983).

Nor-epinephrine antagonists suppressed the pulsatile secretion of LH in OVX, hormonally untreated rats (Weick, 1978). Intracerebroventricular administration of NE was excitatory to LH secretion in OVX and OVX-steroid primed rats (Drouva and Gallo, 1979) and during pro-estrus (Kalra and McCann, 1974). This stimulatory effect appeared to be mediated via α -adrenergic receptors (Sarkar and Fink, 1981, Gallo and Kalra, 1983). This was supported by the fact that NE synthesis inhibition (Estes *et al.*, 1982) as well as α -adrenergic receptor blockers (Weick, 1978) inhibited pulsatile LH release.

Epinephrine has also been shown to be a potent catecholamine in stimulating LH release when administered intracerebroventricularly (Vijayan and McCann, 1978) while inhibitors of central EP biosynthesis completely blocked the LH surge induced by estradiol and progesterone (Crowley and Terry, 1981, Crowley *et al.*, 1982). Increase in turnover rate of adrenaline in the medial POA lead to the LH surge and administration of adrenaline synthesis blockers prevented the proestrus LH surge and ovulation (Coen *et al.*, 1985). This indicates the involvement of central EP system in the control of LH secretion.

Beta-adrenergic receptors have also stimulatory effect on gonadotrophin secretion. Involvement of a stimulatory β_2 adrenergic component in neural regulation of the pre-ovulatory LH surge along with α -stimulatory component has also been reported (Al-Hamood

et al., 1985). Activation of β_2 -receptors causes an increase in adenylate cyclase activity (Hoffman and Lefkowitz, 1980) and rise in the formation of cAMP which subsequently stimulates hormone releasing factor and pituitary hormone synthesis and secretion (Labrie *et al.*, 1979).

Alpha-adrenergic system was involved in the maintenance of basal and pulsatile LH secretion in OVX rats while the dopaminergic system in preoptic area was necessary for estradiol benzoate to suppress LH pulse frequency (Tadakoro, 1985). The preovulatory surge of LH was influenced by facilitatory α -adrenergic and inhibitory dopaminergic mechanisms (Knight *et al.*, 1982). In addition, α -adrenergic receptor antagonists and inhibitors of dopamine β -hydroxylase suppressed LH-pulse in monkeys and rats (Bhattacharya *et al.*, 1972, Gallo and Kalra, 1983). The PMSG-induced LH surge was significantly enhanced by intravenous infusion of 6-hydroxydopamine plus desipramine and reduced by 6-hydroxydopamine injected into the lateral ventricle but this inhibitory effect of 6-hydroxydopamine was reduced by desipramine (Sarkar *et al.*, 1981) suggesting the role of dopaminergic neurons in regulation of LH release but effect depends upon site of action.

An inhibitory effect of NE on LH secretion has also been reported. Endogenous release of NE elicited by activation of central NE system can inhibit LH secretion and ovulation in rats (Dotti and Taleisnik, 1982). Nor-epinephrine acting at the level of medial preoptic area, may suppress pulsatile LH release solely by decreasing LH pulse frequency (Leipheimer and Gallo, 1985) via suppression of firing rate of LHRH pulse generator (Gallo, 1984). In long term OVX rats, it was demonstrated that intracerebroventricular infusion of NE and other adrenergic agonists had a profound inhibitory effect on pulsatile LH secretion (Gallo and Drouva, 1979, Leung *et al.*, 1982). This interruption of LH release may be due to adrenergic inhibition of LHRH neurons, either directly or indirectly via inter-neurons (Condon *et al.*, 1986).

Interference with brain noradrenergic functions suppressed pulsatile LH release on diestrus day-1 of the rat estrus cycle without

altering mean FSH levels (Gallo and Kalra, 1983, Condon *et al.*, 1986). Intracerebroventricular infusion of NE and alteration in catecholaminergic neurotransmission caused rapid and potent inhibition of basal and pulsatile LH secretion with no effect on FSH (Chappel *et al.*, 1984), indicating that LH and FSH release were not always tightly coupled under hypothalamic releasing mechanism (Condon *et al.*, 1986).

A direct effect of catecholamines on pituitary in the regulation of gonadotrophin secretion has also been reported. Noradrenergic pathways usually interact directly with LH regulatory mechanisms but did not have any effect on gonadotropin-releasing hormone pulses (Clifton and Steiner, 1985). However, a direct effect of adrenalin on pituitary to alter LH secretion has not been reported in cattle (Battista *et al.*, 1987). In rat and ovine *in-vitro* pituitaries and basal LH release was unaffected by DA, NE or EP but the LH response to GnRH challenge was markedly potentiated by NE and EP as well as by β -adrenergist isoproterenol, but not by DA (Kamberi *et al.*, 1970, Swartz and Moberg, 1986). However, pituitary LH release in response to exogenous LHRH was unaltered by EP in rats (Blake, 1976). Injection of EP into anterior pituitary of rabbit stimulated LH secretion (Markee *et al.*, 1947) but infusion of NE reduced basal plasma LH and the LH response to exogenous GnRH in ewes and heifers (Deaver and Dailey, 1982, Hardin and Randel, 1983). This discrepancy between the results may be explained by the initial stimulatory effect that EP and NE exert on pituitary adrenal axis and the subsequent suppression of GnRH-induced LH secretion by ACTH and glucocorticoids. Catecholamines stimulate ACTH and glucocorticoid release (Berkenbosch *et al.*, 1981) while the ACTH or glucocorticoids reduce GnRH-induced LH release (Matteri *et al.*, 1984).

Role of catecholamines in modulation of gonadotrophin secretion at brain level has also been suggested. Positive feedback effects of the ovarian hormones on LHRH and LH secretion may be mediated through central catecholamines mainly NE and EP (Kalra and Kalra, 1983,

Ramirez *et al.*, 1984). Estrogen and progesterone primed LH surge was blocked by the centrally acting epinephrine inhibitor, but not by peripherally acting epinephrine inhibitor indicating that central EP system may mediate the positive feed back action of ovarian hormones on LH secretion (Crowley *et al.*, 1982). Steroid-stimulated adrenergic activity in the mediobasal hypothalamus was found to be associated with pre-ovulatory release of gonadotropins (MacKinnon *et al.*, 1985).

The negative feedback of estradiol on LH secretion is also mediated via catecholamines. Circulating estradiol acts on brainstem NE and EP cells (Sar and Stumpf, 1981) and suppresses central NE release via GABAergic mechanism leading to the inhibitory effect of estradiol on LH secretion (Mansky *et al.*, 1982). The dopaminergic system was found to be necessary for estradiol benzoate in preoptic area to suppress LH pulse frequency (Tadakoro, 1985). Changes in concentration of adrenalin during the estrus cycle in rat's higher brain centers has been reported to be associated with the differential output of gonadotropins over the peri-ovulatory period (Sheaves *et al.*, 1985). Seasonal inhibition of LH secretion in female sheep by negative feedback of estradiol involves the activation of monoaminergic and especially dopaminergic systems (Thiery *et al.*, 2002). Catecholaminergic structures of lateral retrochiasmatic area mediated the inhibitory effect of estrogen on secretion of LH pulses during seasonal anestrus (Thiery *et al.*, 1989) and such inhibitory catecholaminergic neural system may play a role in seasonal suppression of pulsatile gonadotropin secretion in the anestrus mare (Fitzgerald and Mellbye, 1988) and in ewes (Meyer and Goodman, 1985).

REGULATION OF GONADOTROPIN RELEASING HORMONE

There is evidence that catecholamines modulate the secretion of GnRH directly or indirectly via activation of other neurotransmitters at the brain level. Nor-epinephrine was found to be a potent stimulator of LHRH release in conscious unrestrained female rabbits (Ramirez

et al., 1986). Pulsatile LH secretion in young OVX rats appeared to be facilitated by NE stimuli of LHRH neurons (Estes and Simpkins, 1982). In rat, depletion of hypothalamic noradrenalin caused subtle changes in the endogenous release of LHRH (Inkster and Whitehead, 1984). Similarly, a stimulatory effect of noradrenaline has been reported during the onset of pre-ovulatory GnRH/LH surge (Parvizi, 2000). This effect of NE to stimulate LHRH release is through activation of neural nitric oxide synthase (McCann *et al.*, 1998).

Estrogen acts as a "trigger" for increased synthesis of LHRH and NE in the neurons of hypothalamus during pro-estrus in female rats (Barraclough *et al.*, 1982). Estrogen activates brainstem noradrenergic neurons (Rawson *et al.*, 2001) to facilitate synaptic transmission within the GnRH network which results in an increased GnRH messenger RNA expression and secretion necessary for ovulation (Herbison, 1997). This effect is mediated via α -adrenoreceptors and not via β -receptors (Nowak and Swerdloff, 1985). Similarly, in ewes, an increase in adrenaline release in preoptic area during estradiol-induced LH surge has been observed (Clarke *et al.*, 1999) and a close synaptic contact between GnRH neurons and noradrenergic neurons projecting to POA from the brainstem has been reported (Pompolo *et al.*, 2003). However, during anestrus, inhibitory effect of estradiol on GnRH/LH secretion is mediated via dopaminergic neurons (Meyer and Goodman, 1985). PMSG-induced surge of GnRH was significantly increased by intravenous 6-hydroxydopamine plus desipramine and reduced by 6-hydroxydopamine injected into the lateral ventricle (Sarkar *et al.*, 1981) indicating that effect depends upon site of action.

Thus, it can be concluded that catecholamines modulates the activity of hypothalamo pituitary ovarian axis but underlying steroid environment, season, sex, site of action and species involved play a great role in deciding whether the effect is stimulatory or inhibitory. Nor-epinephrine and epinephrine have mainly stimulatory effect on gonadotrophin secretion by acting at both hypothalamus and pituitary and their effect is mainly mediated via α -adrenergic

receptors. However, dopamine has an inhibitory effect on gonadotrophin secretion and mediate the negative feed back of estradiol by acting at hypothalamus particularly during seasonal anestrus. Catecholamines also locally regulate the secretion of ovarian steroids particularly progesterone via β -adrenergic receptors.

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