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Neurotransmitter regulation of luteinizing hormone and prolactin secretion

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Introduction

The importance of the hypothalamus for the regulation of gonadotrophin secretion has long been recognized (Harris, 1955). Extensive studies, primarily in laboratory rodents, have established that biogenic amines, particularly noradrenaline, dopamine and serotonin, influence secretion of gonadotrophins (LH and FSH) and prolactin (Weiner & Ganong, 1978). Most research on effects of biogenic amines in ruminants has been with sheep because of the relative ease of experiments, the reduced expense and the added dimension of effects of seasonality. Major techniques applied to determine areas of the hypothalamus involved include brain lesions, multiunit electrical recordings and measurements of tissue contents of neurotransmitters and of LHRH. The roles of neurotransmitters and releasing hormones have been assessed by measurement of their concentrations in the portal circulation and by exogenous treatment with these compounds or agonists and antagonists to them.

Pharmacological studies have been utilized to elucidate the neuroendocrine control of anterior pituitary function (Steger & Johns, 1985). Administration of authentic amines or congeners of these compounds provided some of the earliest evidence that the monoamines were involved with the control of LH release. Administration of the adrenergic agonist, dibenamine, blocked ovulation in rabbits and rats (Sawyer *et al.*, 1947; Everett *et al.*, 1949). In numerous studies exogenous dopamine, noradrenaline and serotonin influenced secretion of gonadotrophins and led to the development of various hypotheses regarding the roles of endogenous amines in the control of anterior pituitary function. As emphasized by Deaver & Dailey (1982), interpretation of results by this approach is influenced by the pharmacological agent used, the route of administration and the physiological state of the animal. One concern is the site of action of the biogenic amines, which do not penetrate the blood–brain barrier (Oldendorff, 1971) and therefore may act only at the median eminence or pituitary gland when given systemically. Other pharmacological agents do penetrate this physiological barrier and act centrally. Dose is important because at a low dose the agent may be an agonist and at high doses an antagonist. For example, at low doses bromocriptine is a dopamine agonist acting via D_1 receptors while at high doses it is an antagonist acting upon D_2 receptors (Kebabian & Calne, 1979). Also, a compound may antagonize the actions of more than one amine. Phentolamine, an α1- and α2-antagonist, blocks responses due to serotonin (Weiner, 1980).

The intent of this paper is to review studies that enhance our knowledge of the neuroendocrine regulation of the secretion of gonadotrophins and prolactin in domestic ruminants. We shall examine the experimental protocols used, cite pertinent results, and formulate working hypotheses that might serve for designing future studies. Of the various techniques described, only the pharmacological approach has been used to any extent with ruminants. Because of limited information concerning actions of biogenic amines on secretion of FSH, the review will concentrate on secretion of LH and prolactin.

Effects of biogenic amines on secretion of LH

Dopamine

Effects of dopamine on secretion of LH are dependent on the dose administered, season and whether the animals are ovariectomized or intact. Przekop *et al.* (1975) reported that intraventricular infusion of dopamine did not influence the release of LH in anoestrous ewes. Similarly, Deaver & Dailey (1982) reported that intravenous infusion of dopamine did not affect tonic or LHRH-induced release of LH during seasonal anoestrus. However, in ovariectomized ewes infusion of dopamine at the same time of year resulted in dose-dependent alterations of LH release (Table 1). At doses of 0·66 μg/kg/min increases in LH release were observed, while at a dose of 66·6 μg/kg/min release of LH was inhibited. The results with ovariectomized ewes could be used as evidence to support the contention that dopamine might influence the release of LH, and it is possible that the dopaminergic systems were operating at maximum capacity in intact ewes and that further stimulation of the post-synaptic pathways was simply ineffective. In fact, Meyer & Goodman (1985) provided evidence that dopaminergic systems inhibit the secretion of LH in anoestrous ewes (see below).

Different hypothalamic mechanisms might control the release of LH at different times of the year. During the luteal phase of the ovarian cycle in ewes, dopamine appears to exert primarily inhibitory effects on the secretion of LH. McNeilly (1980) suggested that dopamine might be important as an inhibitor of LH in ewes during the breeding season. Deaver & Dailey (1983), with the intravenous infusion of dopamine were able to inhibit for 30–36 h the increase in secretion of LH that normally occurs after the administration of PGF-2α. Despite this, the timing or magnitude of the preovulatory surge of LH was not affected.

Table 1. Effect of infusion of dopamine on mean concentrations of LH in plasma before and after LHRH (25 μg, i.m.) in ovariectomized ewes (adapted from Deaver & Dailey, 1982)

Dose of dopamine (μg/kg/min)	Mean conc. LH (ng/ml)	
	Before*	After†
0	12·2	220·0
0·06	17·1	307·1
0·66	14·4	124·1
6·66	−7·5	81·6

*Mean of 15-min samples for 2 h (linear, $P < 0{\cdot}05$, quadratic, $P < 0{\cdot}05$).
†Mean of 20-min samples for 4 h (linear, $P < 0{\cdot}05$, quadratic, $P < 0{\cdot}01$).

Noradrenaline

Intraventricular administration of noradrenaline induced preovulatory surges of LH in ewes late in the anoestrous season (Przekop *et al.*, 1975). However, other investigators have demonstrated that noradrenaline inhibited tonic secretion of LH in males and females. Intravenous infusion of noradrenaline (6·6 μg/kg/min) inhibited the secretion of LH in ovariectomized ewes during the anoestrous and breeding seasons. Release of LH after administration of LHRH was diminished by infusion of noradrenaline in intact anoestrous ewes (Deaver & Dailey, 1982) and in prepubertal beef heifers (Hardin & Randel, 1983). Infusion of noradrenaline reduced the frequencies but not amplitudes of pulses of LH (Table 2) after the induction of luteal regression with

Table 2. Effects of infusion of noradrenaline on pulsatile LH in pro-oestrous ewes (unpublished data)

Dose (μg/kg/min)	No. of ewes	Frequency (pulses/6 h)	Amplitude (ng/ml)
0	4	9·75[a]	1·11
0·06	5	9·60[a,b]	1·00
0·66	5	7·00[b]	0·84
6·66	6	3·00[c]	1·10

a *vs* b, $P < 0{\cdot}10$; b *vs* c, $P < 0{\cdot}01$.

PGF-2α (F. E. Barr, D. R. Deaver & R. A. Dailey, unpublished). In the male, intraventricular infusion of noradrenaline lowered the concentrations of LH in peripheral plasma (Riggs & Malven, 1974). In contrast, *in vitro*, noradrenaline stimulated LHRH-induced release of LH from pituitaries collected from wethers, and this effect appeared to be mediated by β-adrenergic receptors (Swartz & Moberg, 1986).

Serotonin

The indoleamines, serotonin and melatonin, have been demonstrated to influence pituitary release of LH. We will address only the effects of serotonin.

Domanski *et al.* (1975) reported that intraventricular administration or infusion of serotonin into the medial basal hypothalamus delayed the onset of the preovulatory release of LH in ewes. However, intravenous infusion of serotonin was shown to exert biphasic effects on the secretion of LH in ovariectomized ewes. In contrast to the biphasic effects of dopamine, low doses of serotonin lowered concentrations of LH and higher doses increased concentrations of LH in ovariectomized ewes (Deaver & Dailey, 1982). However, in intact anoestrous and breeding ewes, intravenous infusion of serotonin appeared only to increase the release of LH. Tonic secretion of LH was decreased by intraventricular administration of serotonin in wethers (Riggs & Malven, 1974) and by intracarotid infusion in ovariectomized cows (Mondragon *et al.*, 1986).

Effects of catecholamine antagonists on LH secretion

There have been few studies of the effects of catecholaminergic antagonists on gonadotrophin secretion in ruminants and all of this work has been done in sheep. Even with this limited information, it is clear that the actions of these antagonists vary markedly with the endocrine status of the animal.

Early work by Jackson (1977) demonstrated that both an α-adrenergic (phenoxybenzamine) and a dopaminergic (pimozide) antagonist suppressed secretion of LH in ovariectomized ewes. In contrast, only pimozide consistently blocked the oestradiol-induced LH surge (Jackson, 1977). The former observation has been confirmed using phenoxybenzamine (Meyer & Goodman, 1986) and fluphenazine, another dopaminergic antagonist (Goodman, 1985). However, relatively high doses of these antagonists were required. Lower doses of pimozide and phenoxybenzamine did not affect LH, even though they produced maximal effects on prolactin and blood pressure (Meyer & Goodman, 1985).

In contrast to their inhibitory effects in ovariectomized ewes, both phenoxybenzamine and pimozide increased pulsatile secretion of LH in intact anoestrous ewes (Meyer & Goodman, 1985). This stimulatory action was observed not only with the same doses that suppressed secretion of LH in ovariectomized animals, but also was evident with 10-fold lower doses. Other α-adrenergic

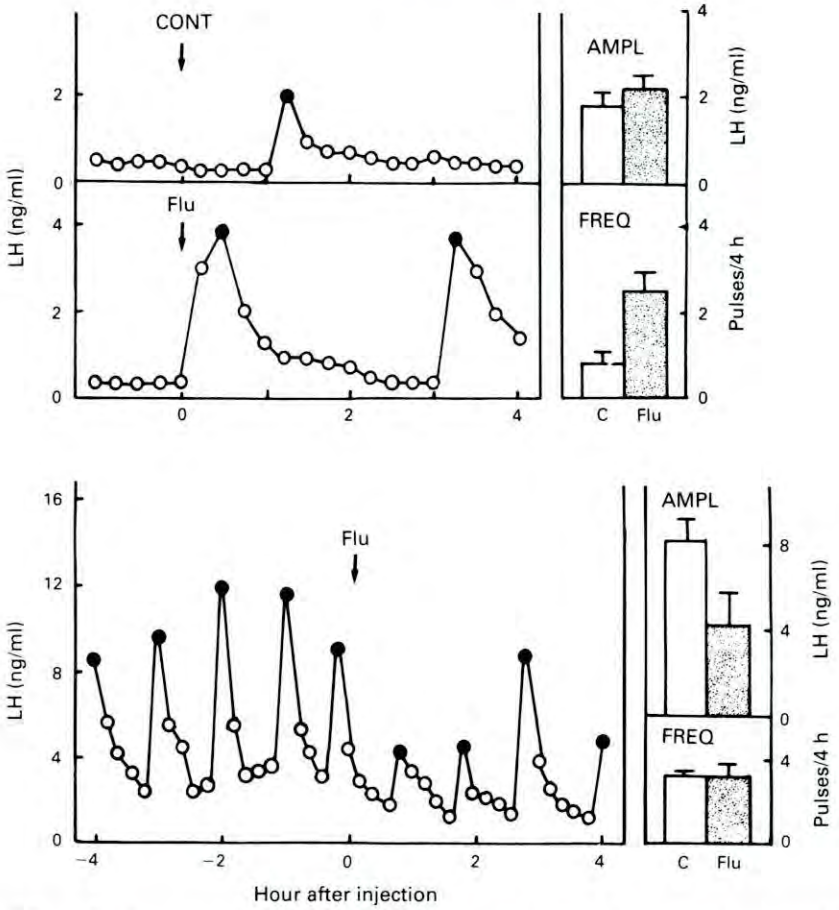

Fig. 1. Effect of a dopamine antagonist on LH secretion in ovary-intact (top two panels) and ovariectomized ewes (bottom panel). Fluphenazine (0·5 mg/kg) was injected i.v. as indicated by arrows, except in control ewes, which received vehicle. Left panels are representative LH pulse patterns. Right panels depict mean (+s.e.m.) LH pulse amplitude (AMPL) and frequency (FREQ). For intact animals data are from injected (shaded bars) and control (open bars) ewes; for ovariectomized animals data are before (open bars) and after (shaded bars) injection.

(dibenamine) and dopaminergic (fluphenazine) antagonists increased tonic secretion of LH in intact anoestrous ewes (Meyer & Goodman, 1986), whereas 6 other neurotransmitter antagonists which act on different receptor types did not (Meyer & Goodman, 1985). These results have led to the hypothesis that catecholaminergic neurones actively suppress LH release in intact anoestrous ewes.

The apparently contradictory actions of catecholamine antagonists in ewes with and without ovaries raised the possibility that at least two different catecholaminergic systems may be involved in regulating episodic secretion of LH. This possibility was strengthened by an analysis of the effects of these antagonists on LH pulse characteristics. As illustrated in Fig. 1, fluphenazine stimulates pulsatile secretion of LH in intact anoestrous ewes by increasing frequency, but inhibits LH in ovariectomized animals by decreasing amplitude. Similar differential effects of phenoxybenzamine on pulse frequency and amplitude in intact and ovariectomized ewes have also been observed (Meyer & Goodman, 1986). A second inference that can be drawn from these results was that the activity of these two systems depends upon the endocrine status of the ewe. For example, since

Table 3. Effect of dopamine antagonists on pulsatile LH secretion in luteal-phase ewes (data taken from Goodman (1985), Meyer & Goodman (1985, 1986) and unpublished results)

Treatment	Frequency (pulses/4 h)	Amplitude (ng/ml)
Control	0·8	1·7
Pimozide		
0·08 mg/kg	1·4	2·6
0·8 mg/kg	0·4	1·0
Control	1·0	0·8
Domperidone		
0·3 mg/kg	2·4*	1·5*
0·1 mg/kg	2·4*	2·9*
Control	1·2	1·8
Fluphenazine		
0·05 mg/kg	3·2*	2·1
0·5 mg/kg	2·5*	2·2
Trifluoperazine		
0·5 mg/kg	1·6	2·7

*Significantly different from control values, $P < 0·05$.

the catecholaminergic neurones suppressing LH pulse frequency appeared to predominate in anoestrous ewes, an ovarian hormone, probably oestradiol (Goodman *et al.*, 1982), may stimulate the activity of this neural system and thereby suppress LH pulse frequency.

The administration of catecholamine antagonists to intact ewes during the breeding season has yielded confusing and contradictory results. Most of this work has been done during the luteal phase of the ovarian cycle, when LH pulse frequency is slow (Baird, 1978) due to the inhibitory actions of progesterone (Goodman & Karsch, 1980). At this time of the cycle, phenoxybenzamine had no effect on pulsatile secretion of LH (Meyer & Goodman, 1985). The effects of dopamine antagonists, however, were quite variable. Two dopaminergic antagonists, fluphenazine (Goodman, 1985) and domperidone (Deaver *et al.*, 1987) markedly increased LH pulse frequency, whereas others, including pimozide (Meyer & Goodman, 1985), did not (Table 3). The ability of two different dopaminergic antagonists to increase secretion of LH during the luteal phase raises the possibility that dopaminergic neural systems actively inhibit release of LH at this time of the cycle. If this is the case, however, it is unclear why other antagonists were not effective. It is always possible that inadequate doses of the ineffective antagonists were administered. This seems unlikely since, for example, the doses of pimozide used markedly increased prolactin secretion in luteal-phase animals and also increased LH in anoestrous ewes (Meyer & Goodman, 1985). Another possibility is that the variability in responses reflects the selectivity of a subclass of dopamine receptors. For example, the D_1 receptor for dopamine has a higher affinity for fluphenazine than for pimozide (Kebabian & Calne, 1979). However, none of the established dopamine receptors has a selectivity that accounts for the variability in the responses to the four dopamine antagonists tested to date. Further work with antagonists selective for only one of the dopamine receptors may be needed to resolve this issue.

Possible sites and mechanisms of action of biogenic amines

Knowing the site of action of exogenously administered amines is crucial for interpretation of the results from experiments outlined above. Studies using laboratory rodents have demonstrated that turnover rates for various neurotransmitters within discrete hypothalamic nuclei can change in

opposite directions during the oestrous cycle (Barraclough & Wise, 1982). Implicit in these findings is the concept that assigning simply a positive or negative role to a particular transmitter may be inappropriate. When infusing catecholamines or indoleamines intravenously one would expect relatively low increases in the hypothalamic content of these substances due to the existence of the blood–brain barrier (Oldendorff, 1971). These biogenic amines could affect the stalk median eminence or any of the other circumventricular organs which have been shown to contain LHRH neurones, since these are outside the blood–brain barrier.

Reductions in LH pulse frequency after administration of biogenic amines are probably indicative of inhibition of LHRH release, which has been shown to be pulsatile in ewes (Levine *et al.*, 1982; Clarke & Cummins, 1982). *In vitro*, noradrenaline suppressed the release of LHRH from the median eminence of pro-oestrous and ovariectomized cows (Zalesky *et al.*, 1986). Weesner *et al.* (1986) concluded from in-vitro studies that a neurochemical from the medial basal hypothalamus may exert an inhibitory effect on LHRH release from the median eminence of mature bulls. These observations are further supported by the fact that antagonists to various catecholamines caused decreases in episodic discharges of LH. However, a direct effect of biogenic amines at the level of the pituitary cannot be ruled out.

Previously, investigators concluded that dopamine, noradrenaline and serotonin had no or only minor effects on the secretion of gonadotrophins at the level of the pituitary (McCann, 1983). These conclusions have been drawn mainly from observations that incubation of amines with pituitary cells *in vitro* failed to affect secretion of LH. In contrast, Dailey *et al.* (1978) demonstrated that in stalk-sectioned rabbits, dopamine inhibited LHRH-induced release of LH. In addition, concentrations of serotonin were greater in the anterior pituitary than in the median eminence of the cow (Piezzi *et al.*, 1970), and Wheaton *et al.* (1972) suggested that serotonin might be released from the median eminence at oestrus in sheep. The possibility that amines might act directly on gonadotrophs is supported by identification of receptors for these transmitters in pituitaries from various species (Nunez *et al.*, 1981; Johns *et al.*, 1982).

Prolactin

We have suggested, as a working hypothesis, that gonadotrophin secretion is regulated by stimulatory (LHRH) and inhibitory (neurotransmitters) secretions from the hypothalamus; the effects are modified by hypothalamic changes with season; and neurotransmitters may exert control at the median eminence. A prototype can be drawn from studies on secretion of prolactin in sheep (Fig. 2a).

Concentrations of prolactin were reduced by treatment with 2-bromo-α-ergocryptine (Niswender, 1974) and ergocornine hydrogen maleinate (Louw *et al.*, 1974), both dopamine receptor agonists. Treatment of sheep with phenoxybenzamine, an adrenergic receptor antagonist, or arginine, increased serum concentrations of prolactin (Davis & Borger, 1973). Treatment with both compounds resulted in a greater than additive effect, suggesting separate sites or mechanisms of action. From results in ewes with permanent electrodes placed in the median eminence, Malven (1975) concluded that a prolactin-releasing neurohormone existed in the anterior median eminence and that both this substance and an inhibitory compound were present in the posterior median eminence.

After surgical disconnection of the pituitary from the hypothalamus, there was only a transient increase of prolactin in sheep (Bryant *et al.*, 1971; Clarke *et al.*, 1983; Gust, 1985) and cattle (Anderson *et al.*, 1980). These results contrast with the observations in non-ruminants (Anderson *et al.*, 1982) and suggest that ruminants have a different mechanism for regulation of prolactin secretion. Because infusions of dopamine and noradrenaline but not serotonin (Deaver & Dailey, 1982, 1983; F. E. Barr, D. R. Deaver & R. A. Dailey, unpublished) lowered prolactin concentrations in serum, and dopamine but not noradrenaline (Swartz & Moberg, 1986) inhibited prolactin secretion *in vitro*, we suggest that dopamine acts directly on the lactotroph and that

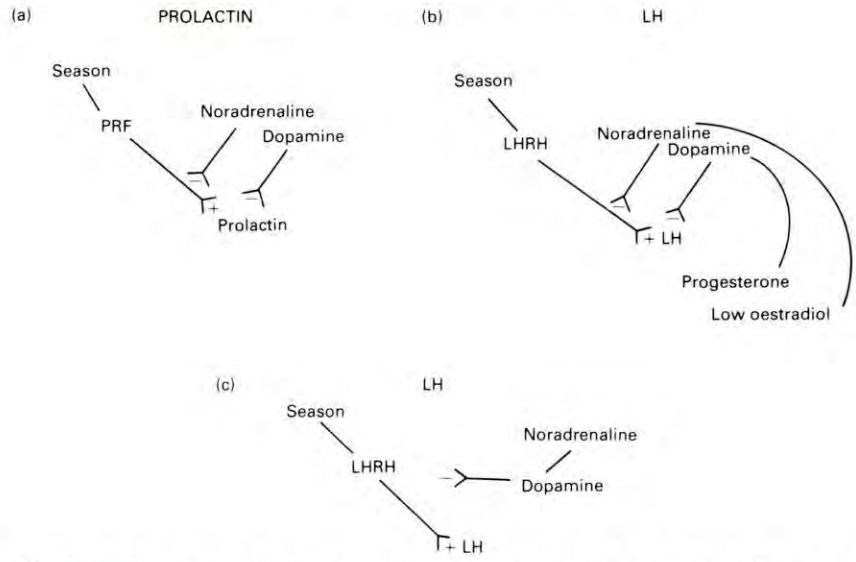

Fig. 2. Models of relationship of catecholamines and (a) prolactin and (b, c) LH secretion. See text for explanation.

noradrenaline acts either by stimulating dopamine release or by presynaptic inhibition of release of prolactin-releasing factor. The actions of dopamine and noradrenaline are the same in each season (Deaver & Dailey, 1982). Therefore, seasonal changes in concentrations of prolactin (Jackson & Davis, 1979) must be mediated by whether or not prolactin-releasing factor is being secreted.

LH

Male rats with lesions of the median eminence (Zeballos & McCann, 1977), female rhesus monkeys after pituitary stalk section (Frawley *et al.*, 1981), and ewes after stalk section (Mallory *et al.*, 1986) showed increased responsiveness to exogenous LHRH. These results suggest that inhibitory factors from the median eminence, as well as LHRH, regulate LH release. After stalk-sectioning, LH continued to be secreted in a pulsatile fashion with reduced amplitude of peaks (Gust *et al.*, 1987), which was restored by exogenous LHRH (Gust, 1985). Using stalk-sectioned ewes, Mallory *et al.* (1986) concluded that progesterone exerts inhibitory effects on LH at the hypothalamus. Based on results of treatment of luteal-phase ewes with dopamine or a dopamine receptor antagonist, progesterone might exert this inhibitory effect through a dopaminergic system (Deaver & Dailey, 1983; Deaver *et al.*, 1987) as proposed initially by McNeilly (1980). Using stalk-sectioned ewes, Gust (1985) concluded that the effects of oestrogen were at the hypothalamus, in contrast to the conclusion of Clarke & Cummins (1984) that effects of oestrogen and progesterone were at the pituitary. Thiery *et al.* (1978), using hypothalamic deafferentated ewes, concluded that the positive effect of oestrogen was in the hypothalamus.

We postulate (Fig. 2b) that, as with prolactin, dopamine directly inhibits gonadotrophin secretion and noradrenaline acts presynaptically or by modulating receptor binding to reduce effects of LHRH, as can be deduced from the results of Swartz & Moberg (1986). Progesterone would stimulate dopamine turnover while low oestradiol (anoestrus) concentrations would act through noradrenaline. As proposed by Domanski *et al.* (1980) inhibitory effects would be transmitted via serotonin to reduce the production of LHRH, which might account for seasonal effects. As an alternative (Fig. 2c), noradrenaline might stimulate the dopaminergic system and reduce secretion of LHRH.

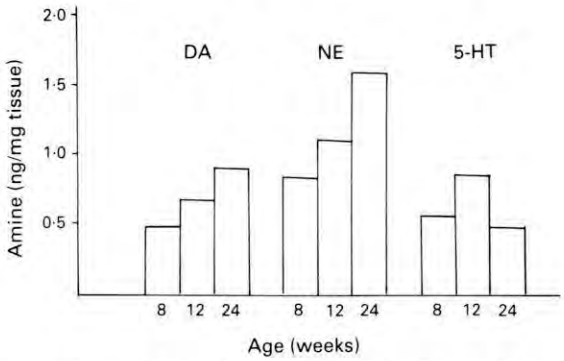

Fig. 3. Age-related changes in concentrations of dopamine (DA), noradrenaline (NE) and serotonin (5-HT) in the stalk-median eminence of Holstein bulls before puberty. The effect of age was significant for DA ($P < 0{\cdot}01$; pooled s.e.m. = 0·022), NE ($P < 0{\cdot}05$; pooled s.e.m. = 0·148) and 5-HT ($P < 0{\cdot}05$; pooled s.e.m. = 0·035). Also, concentrations of DOPAC increased significantly with age ($P < 0{\cdot}01$; data not shown).

Concluding remarks

One critical area in which few experiments have been conducted in ruminants is the determination of changes in activity of various neurotransmitter systems associated with the secretion of pituitary hormones. These types of studies are needed to support the hypotheses developed based on pharmacological data. Kizer *et al.* (1976) described the distribution of noradrenaline, dopamine, serotonin and enzymes necessary for the production of those and other neurotransmitters within the median eminence of steers. They concluded that only dopamine and acetylcholine were localized in the same regions as LHRH and might be involved with the regulation of LHRH release. Wheaton *et al.* (1975) attempted to determine effects of administration of oestradiol and L-DOPA on secretion of LH and concentrations of hypothalamic monoamines. Administration of L-DOPA blocked the occurrence of an oestradiol-induced LH surge in 3 of 4 ewes treated on Day 3 of the oestrous cycle. However, these investigators failed to detect differences in concentrations of hypothalamic dopamine, noradrenaline or serotonin after administration of oestradiol to another group of ewes on Day 3 of the cycle. This finding is not surprising considering the widely accepted view that steady-state conditions of production are often maintained even though activity of neurones is altered.

Techniques have become available, including high-performance liquid chromatography with electrochemical detectors (Mefford *et al.*, 1983) and mass spectrometry/gas chromatography (Smythe *et al.*, 1982), to determine tissue concentrations of monoamines and their metabolites. Results of these procedures agree well with the more widely accepted procedures for determining turnover rates and may provide a powerful tool for determining effects of a variety of pharmacological agents known to alter the secretion of gonadotrophins and the function of various hypothalamic neurotransmitter systems. For example, using the liquid chromatography technique. Deaver *et al.* (1985) have reported that: (1) concentration of monoamines and their metabolites in the hypothalamus changed with age, (2) plasma concentrations of testosterone were positively correlated with concentrations of dopamine, DOPAC and noradrenaline within the stalk median eminence, and (3) when testicular development was inhibited by oestradiol, age-related changes in noradrenaline did not occur (Deaver & Peters, 1986). Based on these observations, we suggest that, in male and female ruminants, catecholamines probably mediate inhibitory effects of gonadal products on secretion of gonadotrophins.

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