Neuroendocrine regulation of gonadotropins in the male and the female

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Abstract

For the past decade, neuroendocrinology, in general, and neuroendocrine regulation of reproduction, in particular, were strongly dominated by molecular genetics and molecular endocrinology. In very recent years, however, neuroendocrinology is taking back its place. Beyond doubt GnRH is the neuroendocrine signal for ovulation. But there are still many unexplored pathways within the ‘black box’ triggering and regulating this signal. Neuroendocrine control of reproduction starts very early in life, well before birth. Hypophyseal gonadotropin secretion is under hypothalamic control at around mid-gestation in the fetal sheep and the fetal pig. These two species could be considered as best-studied farm animals considering neuroendocrinology. This minireview thus will give in the first part a short survey of developmental processes of some of the neuroendocrine systems in the pig and sheep. In the second part, the opioidergic and catecholaminergic control of gonadotropins in adults will be briefly discussed. The last part will focus on the new less known pathways mediating effects on hormones which regulate the reproductive functions. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Neuroendocrine regulation; gonadotropins

1. Neuroendocrine regulation of gonadotropins in the fetus

The fetal hypothalo-pituitary–gonadal axis possesses the components of the regulatory mechanisms to perform most of its endocrine functions. In the pig, LH gene expression starts around day 45 p.c. (post-coitus, Granz et al., 1997; Ma et al., 1996). Pituitary LH release is measurable in the fetal pig around day 60 of gestation (Elsaesser...
et al., 1988a; Ponzilius et al., 1986). It increases with age until about day 105 (Thomas et al., 1993). In the sheep, likewise pig, LH cells are immunocytochemically visible at day 50 p.c., but FSH- and LH–FSH-containing cells can be seen from day 90 onwards (Messadou-Toumi et al., 1993). The further development seems to be somehow earlier than in the pig. In the pig, LH reaches its maximum plasma values in females around day 90 and in males, around day 110 p.c. In both pig and sheep, female fetuses have higher circulating LH levels than males and in both species, LH values decline towards the very end of gestation. The sex difference in LH secretion is also reflected at the level of mRNA with females having higher LH-β-mRNA and FSH-β-mRNA expression in the hypophysis (Granz et al., 1997). The sex difference is thought to be due to the testicular hormones present in the circulation of male fetuses (Mesiano et al., 1991). Orchidectomy, however, has no effects on plasma LH levels in male pig or sheep fetuses, although it results in a decrease in testosterone concentrations (Bremer et al., 1981; Ponzilius et al., 1986). These and the data by Brooks et al. (1995) and Brooks and Howe (1996), which show no age-dependent difference in fetal LH response to the neuroactive aminoacid, N-methyl-D-aspartate and GnRH itself (Thomas and Brooks, 1997), indicate that the decline in gonadotropin secretion shortly before birth and the sex difference in fetal gonadotropin release are not a sole matter of gonadal steroid feedback. It is noteworthy, however, that at 2 weeks postnatal age in male lambs and 5 weeks postnatal age in female lambs, LH secretion is significantly higher in fetally castrated animals in comparison to the intact controls (Bremer et al., 1981). Further, it seems that in the sheep, males are, because of in utero exposure to androgens, less sensitive to steroid feedback (in particular, progesterone) than females (Robinson et al., 1999).

GnRH perikarya are visible at around day 40 in the pig (Danchin and Dubois, 1982) and day 50 in the sheep (Mueller et al., 1981) fetal hypothalamus. An accumulation of GnRH in nerve terminals contacting the eminentia mediana has been shown on day 70 p.c. in the pig (Polkowska, 1995). Pituitary LH secretion goes under the control of hypothalamus between days 60 and 80 p.c. in the pig. Electrical stimulation of hypothalamus induces LH release in 80-day-old fetuses but not in 60-day-old ones (Bruhn et al., 1983). In vitro hypophyseal cell culture studies suggest that the gonadotropin secretion of the pituitary develops earlier in the female than in the male fetus.

Mechanisms leading to the brain sexual differentiation, which in turn result in appropriate male and female type of reproductive performance throughout the lifespan, are probably the best-studied developmental neuroendocrine event. This has been the subject of many reviews (for a recent review, see Wood and Foster, 1998) and thus will not be addressed in further details here.

GnRH, itself, seems to be actively involved in the development of gonads. Prolonged fetal treatment with buserelin after day 110 p.c. (this stage seems to be a critical period, since earlier treatments are ineffective) causes an impaired testosterone secretion in lambs after postnatal age of 28 weeks (Brooks et al., 1995; Thomas et al., 1993). Similar treatments have no or very little effects in female fetuses. Comparable observation has been reported in the pig where the pulsatile administration of GnRH at 2 h intervals over 10 days reduced the number of pituitary LH cells (Meijer et al., 1985) in male fetuses (70 and 95 days old).
It is interesting to note that GnRH antibodies applied to the mother’s circulation cross the ovine fetal–placental barrier and suppress fetal plasma LH and FSH values in male and LH values in female fetuses (Miller et al., 1998).

Our current knowledge about the systems modulating GnRH and subsequently gonadotropin release in the fetus is rather spare. Most of the existing data are concentrating on the opioid system.

Components of the opioidergic system are present in the brain and pituitary already at an early stage of development. Pro-enkephalin and pro-dynorphin genes switch on producing opioid precursors as early as day 35 p.c. in the pig (Pittius et al., 1987). At the same time, pro-opiomelanocortin (POMC) gene expression begins in the pituitary with increasing intensity towards the end of pregnancy (Ma et al., 1994). In the sheep fetus, POMC gene expression is first shown around day 70 p.c. (earlier ages are not studied). Originally, a decrease in the pituitary expression of POMC gene was reported by McMillen et al. (1988), which is not confirmed by later works. In fact, recent data by Yang et al. (1991) and Bell et al. (1998) indicate an increase in POMC mRNA levels in fetal sheep pituitary during late gestation.

Opioid receptors are not detectable until day 50 p.c. in the fetal pig brain. The predominant receptors at this age appear to be of the κ- and μ-types. The delta receptor is virtually absent before birth (Kahle and Parvizi, 1993). This is different from sheep in which the delta receptor is apparently the major opioid receptor in the fetus (Yang and Challis, 1991).

This species difference is possibly responsible for the differences in the opioidergic control of LH release in the fetal pig and the fetal sheep. Naloxone given into the chronic catheterized fetal lamb induces a prompt increase in plasma LH levels. The increment is higher in fetuses younger than 115 days than those older than 126 days (Cuttler et al., 1985). In contrast, the opioidergic control of pituitary gonadotropin is questionable in the pig fetus. In this species, opioid receptors are functioning well before the birth. This is evident by inhibitory action of morphine on LH release in male and female fetuses (Behrens-Herrler and Parvizi, 1992), whereas naloxone has no short-term or acute effects. An inhibitory naloxone effect, however, can be induced by treating (priming) male fetuses with daily naloxone injections. It is interesting that this sex-differentiated effect, paradoxically, resembles that of morphine. This paradoxical sex-dependent effect of naloxone can be also seen in newborn piglets (Prunier et al., 1990). Thus, the naloxone effector mechanisms in fetal and neonatal pig differ from those in adults.

A close relationship between cytokines and opioids has been reported repeatedly. Interleukin-1β can stimulate opioid synthesis in the brain and a binding of interleukins to brain opioid receptors has been reported to be feasible (Jiang et al., 1998). Any kind of so-called tissue ‘stress’ evokes activation of the opioid and the interleukin system. Phases of rapid growth, e.g. fetal growth, are considered as such physiological ‘stressful’ situations for cells.

Our recent work (Parvizi and Rohwedder, unpublished data) shows that intravenous as well as intracerebral applications of an interleukin-1β antagonist are associated with increases in plasma LH values in the female but not in the male pig fetus (Fig. 1). Opioids, as mentioned above, have also inhibitory effects on LH release in female
Fig. 1. Effects of intracerebral (A) and i.v. (B) injections of interleukin-1β in fetal male and female pigs. (C) illustrates plasma LH values before and after microinjections of 60 ng (□) or 120 ng (■) interleukin-1β or 2 μl saline (●) into the MBH in ovariectomized pigs.

Fetuses. This coincidence may suggest that the effect of the interleukin antagonist is mediated by brain opioid receptors. Immunoendocrinology is a rapidly expanding field which is presumably standing at the very beginning of a long way. The significance of cytokines for development and maturation of the hypothalamic–pituitary–gonadal system is not known yet.
Fetal hypothalamic–pituitary axis obviously plays a central role in initiation of parturition in some species such as sheep. The neuroendocrine trigger chiefly stems in the nucleus paraventricularis (PVN) and CRH is the primary neuropeptide. Destruction of fetal PVN around gestational day 120 prolongs pregnancy in the sheep. Parturition does not occur in ewes with treated fetuses until 157 days gestation at which the fetuses must be removed by caesarian section (McDonald and Nathanielsz, 1991). Oxytoxin and vasopressin, together with the dopaminergic system, are assumed to regulate hypothalamic CRH secretion (Matthews, 1999; Matthews et al., 1996). There seems to be a fine regulated interplay among prostaglandin E₂, placental CRH, and the fetal hypothalamic–hypophysal–adrenocorticotropic axis to control and initiate parturition (Chan et al., 1998; Keller-Wood, 1998; Thorburn et al., 1991).

2. Neuroendocrine regulation of gonadotropins in adults

The brain sexual differentiation, which gives the females the ability to induce a gonadotropin surge in response to estradiol, is a quantitative rather than qualitative phenomena in domestic animals. The incompetence of males for LH surge secretion is due to the failure of estrogens to activate the hypothalamic pulse generator for surge release of GnRH. Male characteristics including sexual behaviour are imposed on the developing brain by organizational action of gonadal testosterone during a critical period which is around mid-gestation in domestic animals. The active steroid molecule is possibly the brain estradiol which can be synthesized by aromatization of testosterone in situ. Distinct structural properties, such as the sexually dimorphic nucleus of the preoptic area, are results of the organizational effects of steroids (Jacobson et al., 1985, 1989). The lack of estradiol-induced synaptic plasticity of arcuate neurones in males is also attributed to the inability of males to display an estrogen positive feedback. Long-term estrogen deprivation induced by long-term ovariectomy causes a brain desensitization for estrogen positive feedback (Stickan et al., 1999). Estradiol results in a LH surge in short-term ovariectomized (30 days) but not in long-term ovariectomized (100 days) sows (Fig. 2). Interestingly, estradiol appears to increase the sensitivity of castrated male pigs to GnRH at the pituitary level (Fig. 2). Our previous studies confirm the selective alteration of brain sensitivity to oncoming stimulations by steroids (Parvizi and Eldendorff, 1980). Priming of the amygdala with microinjections of testosterone changes the responsiveness of the amygdala to electrical stimulation from inhibition to stimulation of LH. For this, two mechanisms are conceivable, one of which alters the sensitivity of amygdaloid neurones to regulatory inputs arriving from extra amygdaloid structures such as the olfactory system or hypothalamus. The other may alter the outgoing signal from the amygdala to such structures. Reciprocal functional connections between such systems are known (Dyer et al., 1976; Renaud, 1976). The action of steroids can be alternatively explained on the basis of ‘two neuron pool’ theory suggested by Sawyer (see Sawyer, 1991), now more than 25 years ago. The selective inhibition or facilitation of the respective pool of neurones could lead to the differential response. Involvement of steroid-sensitive neurones in mediating the function of neurotransmitters and neuropeptides is also conceivable. Steroids not only selectively accumulate in the brain but they can be also produced in different brain regions. Steroid action in the brain was a
fashionable issue in the late 1970s. The subject received a new name ‘brain steroids’ in the 1990s, and is an often discussed topic at present.

Catecholestrogens can be considered as such brain steroids. These hydroxylated estrogens modify LH secretion in fetal as well as in adult pigs. However, their effect does not always resemble that of estradiol. This is particularly obvious in the fetus (Parvizi, 1986; Parvizi and Ellendorff, 1975, 1983). Although catecholestrogens bind to brain sites (Parvizi et al., 1985), their modulatory effect on LH secretion is most probably due to the modification of central neurotransmitter (mainly catecholaminergic) systems. This capability of catecholestrogens is receiving increasing attention particularly in relation with the endocrine active environmental substances. In this context, it is necessary to emphasize that some of the so-called ‘xenoestrogens’, which are found in the environment, do not act directly as estrogens or antiestrogens by binding to estrogen receptors. They rather influence the estrogen metabolism (Hanf, 1997). Most of these compounds, although biologically quite active, have a very low affinity for estrogen receptors. Catecholestrogen production can be enhanced in the present of xenoestrogens. Catecholestrogen, which can be produced in the brain, accumulates in specific brain nuclei (Parvizi et al., 1985). Furthermore, they modulate catecholamine turnover rate (Parvizi and Wuttke, 1983) by modifying catechol-o-methyltransferase, tyrosin hydroxylase activity and catecholamine reuptake.

Catecholaminergic-mediated control of gonadotropin secretion was long assumed to be exclusively of stimulatory nature. It is now, however, generally accepted that catecholamines have dual effects on LH secretion. Their stimulatory or inhibitory action is obviously dependent to the brain site actively involved, e.g. microinjections of norepinephrine into the third ventricle enhances LH release in both male and female spayed pigs (Parvizi and Ellendorff, 1980, 1982), whereas its microinjection into the
basolateral amygdala attenuates LH secretion (Parvizi and Ellendorff, 1982). The stimulatory effect is apparently dominant when the signal for the preovulatory LH surge is in process. In contrast, the inhibitory route is only active during stages of tonic LH secretion. Catecholamine synthesis inhibitors, DDC (diethyldithiocarbamate) and methallibure, completely abolish the estradiol-induced LH surge (Elsaesser et al., 1998; Kraeling and Barb, 1990; Kesner, 1988). It is noteworthy that both DDC and methallibure are carbamate compounds. Carbamates, closely related to DDC, are worldwide used as pesticides. Thus, it is conceivable that environmental pollution with these compounds can prominently and directly modify the neuroendocrine events and consequently the reproductive function in animals and in the human.

Another important neuroendocrine pathway is composed by opioids. Currently, it is agreed that in mammals, the endogenous opioid peptides are derived from four precursors (Table 1). Pro-dynorphin, pro-enkephalin and POMC are the classic ones. The new generation of endogenous opioids, nociceptin/orphanin FQ, is processed from pro-nociceptin/OFQ and is the endogenous ligand for ORL₁ (opioid-receptor-like) receptor (Meunier et al., 1995). Another mammalian opioid family is presumed to be driven from yet discovered pro-endomorphin, which gives rise to endomorphin-1 and endomorphin-2. These latter two opioid families are not studied in farm animals yet. Endomorphins, which are shown in discrete rat brain areas, are the only very selective endogenous mammalian opioids. They are endogenous ligands for the μ-receptor (Table 2).

Genes encoding the three well-known classical opioid receptors are already cloned. The Mor-1, Dor-1 and Kor-1 genes give rise to μ-, δ- and κ-opioid receptors, respectively, and possibly also to their subtypes. An orphan receptor called ORL₁, which has a very high homology with the other three opioid receptors, was identified in recent years (Mollereau et al., 1994). All cloned opioid receptor types, in common with the somatostatin receptor, belong to G₁/G₂-coupled super family of receptors. They all possess the same general structure consisting of an intracellular C-terminal tail, seven-transmembrane regions and an extracellular domain.

Opioidergic neurones are in close relation or co-existence with the other peptidergic or neurotransmitter systems. In the rat, co-operations between the inhibitory neurotransmitter GABA, catecholamines, oxytocin, vasopressin and opioids have been shown (Chieng and Williams, 1998; Dyer et al., 1991; Summy-Long, 1989). Very little is known about the mode of action of opioids in farm animals. But, it is well known that they strongly modulate the gonadotropin and neurohypophyseal hormone secretion in different reproductive phases. Our previous results and those of other investigators (Barb

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<th>Precursor</th>
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<td>POMC</td>
<td>β-endorphin</td>
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<td>Pro-enkephalin</td>
<td>Met-and leu-enkephalin</td>
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<td>Pro-dynorphin</td>
<td>Dynorphin A, B and A (1–8) α and β neoendorphin</td>
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<td>Pro-nociceptin/OFQ</td>
<td>Nociceptin</td>
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<tr>
<td>Pro-endomorphin (awaiting discovery)</td>
<td>Endomorphin-1 and-2</td>
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Table 2

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<td>Endomorphin -1 and 2</td>
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<td>DAMGO</td>
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<td>α-receptor</td>
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<tr>
<td>U-69593</td>
<td>α-receptor</td>
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<tr>
<td>Nociceptin/OFQ</td>
<td>ORL₁</td>
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et al., 1992; Cosgrove et al., 1991; Kraeling and Barb, 1990) suggest that the effects of opioids on gonadotropin secretion are age-, sex-and steroid-dependent.

Met-enkephalin inhibits LH secretion in males but has no effects in females, whereas β-endorphin and Leu-enkephalin may modify LH secretion independent of gonadal steroids in male and female pigs. Naloxone enhances plasma LH values when given into the mediobasal hypothalamus of cyclic (diestrous) sows with high circulating progesterone but not in ovariectomized sows (Parvizi et al., 1993). Furthermore, opioids amplify feedback (MBH-mediated) control of gonadal steroids on LH secretion (Parvizi, 1988; Sribhen and Parvizi, 1986). Recently, it has been shown that treatment with an opioid antagonist (WIN 44, 441–443) causes a nearly sixfold increase in the percentage of GnRH neurons in the mediobasal hypothalamus (MBH) expressing Fos in ewes in luteal phase (Boukhliq et al., 1999).

Albeit the general notion that opioids act via central neuroendocrine pathways, there are some indications for a role of peripheral opioidergic mechanisms in the control of hormone secretion. Plasma β-endorphin levels are two to three times higher during pregnancy than during estrous cycle (Fig. 3) and the level can be enhanced by cloprostenol (a prostaglandin analog). Noteworthy, there are no significant changes in peripheral blood levels of opioids during the estrous cycle (Aurich et al., 1993). Interestingly, there are also no cycle-dependent fluctuations in opioid receptor concentrations in the hypothalamus, amygdala, hippocampus and striatum (Kahle and Parvizi,

![Fig. 3. Immunoreactive β-endorphin levels in different stages of cycle and pregnancy in the pig.](image-url)
A direct opioidergic action on adenohypophyseal hormone secretion is evident in vitro. Interestingly, \( \beta \)-endorphin increases the basal LH release from male and female pituitary cells in culture, but it blocks GnRH-induced LH surge (Fig. 4) (Baratta and Parvizi, unpublished). In contrast to these findings, Barb et al. (1990) reported that \( \beta \)-endorphin decreases pituitary LH release in vitro.

The neuroendocrine bases of lactational anestrus are still not elucidated in whole, but accumulating pieces of evidence urge the involvement of both neuro(end)ocrine and circulating nutrients (Quesnel and Prunier, 1995). Suckling per se seems to play a major part. Immediately post-partum, sows have relatively high plasma LH concentrations until a suckling-induced inhibition of LH release occurs 24–55 h post-partum (Sesti and Britt, 1993; De Rensis et al., 1999). Furthermore, a transient weaning of piglets for 6–24 h results in concomitant rise in plasma LH values (Parvizi et al., 1976; Mattioli et al., 1986; Armstrong et al., 1988a).

It is postulated that the low gonadotropin secretion during the first half of lactation is an outcome of low GnRH secretion and depressed sensitivity of the pituitary. Opioids are supposed to be one of the key neuropeptides lowering the GnRH input during lactation.

![Fig. 4. In vitro LH release from perfused pituitaries (female pigs) in response to \( \beta \)-endorphin (●, panel A). Pituitaries were challenged with GnRH 240 min after \( \beta \)-endorphin (panel B). (▼) Saline + GnRH, (●) saline and \( \beta \)-endorphin.](image)

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1993)
lactation. Naloxone induces LH release during lactation (De Rensis et al., 1998; De Rensis and Foxcroft, 1999) and morphine applications after weaning attenuate the weaning-induced LH rise and prolong the time from weaning to first estrus (Armstrong et al., 1988b), whereas naloxone has opposite effects (Yang and Parvizi, unpublished data).

3. Neuroendocrine control of seasonal gonadotropin release

Seasonal breeding in sheep and horse is governed by photoperiod. The signal requires a neuroendocrine transduction. The underlying neural mechanisms, however, are still poorly understood. Concerning photoperiod, dopamine, opioids and melatonin are possibly the best-known mediators between brain and gonadal function (for review, see Herbison, 1995; Alonso-Solis et al., 1996; Gallegos-Sánchez et al., 1998). A large body of evidence supports the unequivocal action of dopamine. Surgical (Havern et al., 1991) or chemical (Thiery et al., 1989) disruption of dopaminergic neurones of A15 nucleus as well as dopaminergic receptor antagonists results in a significant increase in pulsatile release of LH in sexually inactive animals during off season. Dopaminergic A14 and A15 neurones can be activated by estradiol during anestrus, but not in breeding season. Estradiol receptors have been localized on dopaminergic and opioidergic neurones in the infundibular A12 cells (Lehman et al., 1993) and on GABA neurones in the preoptic area (Skinner and Herbison, 1997). All these receptors seem to be photoperiod-dependent. Previous work did not show localisation of estradiol receptors on A14/A15 dopaminergic neurones (Lehman and Karsch, 1993). This has led to cascade theory, postulating that a cascade of events reaches A14 then A15 and from there, the GnRH system (Havern et al., 1994). Recent works demonstrating direct effects of estradiol on A15 neurones (Gallegos-Sánchez et al., 1997) weakens, however, this postulation. In the ewe, dopamine antagonists enhance, while dopamine receptor agonists inhibit, the amplitude of LH pulses during non-breeding season (Gallegos-Sánchez et al., 1998). Likewise, in the ram, dopamine antagonist, sulpiride, slightly stimulates LH release and markedly enhances the stimulatory effect of naloxone only under long days (Torotonese, 1999), showing that dopamine pathways inhibit both GnRH and opioid neurones as part of photoperiodic control of gonadotropin release.

The situation in the horse seems to be different. There is apparently no interplay between dopamine and opioids in the control of LH release in stallions (Aurich, Gerlach, Aurich and Parvizi, unpublished data). In the mare, sulpiride treatment during late seasonal anestrus advances the first ovulation in the year and increases plasma FSH concentration; however, the treatment has no effect on LH secretion (Besognet et al., 1996). Conversely, opioids inhibit LH secretion during the breeding season in luteal phase in mares (Behrens et al., 1993) and outside the breeding season in stallions (Aurich et al., 1996).

GABA neurones are probably playing an ample role in mediating the gonadal steroid feedback control on gonadotropin release. During the breeding season, preoptic GABA neurones are influenced by progesterone to inhibit LH secretion (Robinson and Kendrick,
1992; Blache et al., 1996) in the sheep. These neurones mediate the inhibitory action of estrogens in non-breeding season (Scott and Clarke, 1993).

Disruption of photoperiod causes changes in melatonin secretion and seasonal estrous cycle. Immunization against melatonin in ewes (O’Callaghan et al., 1999) and hypothalamo-pituitary disconnection in rams exposed to long days and short days (Lincoln and Clarke, 1998; Lincoln et al., 1996) confirm that melatonin acts on hypothalamus to mediate effects of photoperiod on GnRH-induced gonadotropin release. But, melatonin action on prolactin is brought about by Mel-1α receptors within the pars tuberalis. This section of pituitary has been shown to secrete a factor called ‘tuberalin’ (Hazelrigg et al., 1996; Morgan et al., 1996), which is a candidate for a paracrine mediator of melatonin actions such as modulation of prolactin secretion within the hypophysis.

The sensitivity of the hypothalamic–hypophyseal system seems to be fundamentally different in the mare and the ewe. Comparative studies evaluating gonadotropin response to GnRH administration revealed a unique hypothalamic–hypophyseal axis in mares resistant to GnRH receptor downregulation (Porter et al., 1997).

4. Future explorations and less known pathways

The discovery of opiate receptors and endogenous opioids in mid 1970s was the start of a new era not only in neuroendocrinology. Future works will not only focus on new opioid generations, but there are at least three other less explored neuroendocrine pathways to be traced. These are: (1) gaseous transmitters such as nitric oxide (NO) and carbon monoxide (CO); (2) cytokines; and (3) neuroendocrine-active environmental substances ‘xenohormones’, which are in close relation to gaseous transmitters.

One of the most striking discoveries in the recent years is the finding that the environmental pollutants such as toxic gaseous, NO and CO are produced in mammals and eventually mediate functions such as neurotransmission, endocrine signalling, immunological defense and a few more. They are in many ways unusual; unlike all other (classical) neurotransmitters, CO and NO have no receptor protein molecules and they are not stored in synaptic vesicles. NO neurones have been located in the vicinity of GnRH neurones and it has been suggested that NO stimulates GnRH release directly (Bhat et al., 1996) as well as indirectly (Bonavera and Kalra, 1996). Systemic applications of nitric oxide synthase (NOS) inhibitor prevent the steroid-induced and preovulatory LH surge (Bonavera et al., 1994). Injection of n-NOS antisense oligonucleotides into the third ventricle also inhibits the steroid-induced LH surge in ovariectomized rats (Aguan et al., 1996). A hypothetical model elucidating the role of NO in the control of the preovulatory LH peak has been proposed by Brann et al. (1997) (Fig. 5).

Cytokines have been long shown to play a major role in reciprocal connections between immune and neuroendocrine system. Little is known about cytokine regulation of gonadotropins in farm animals. Our findings indicate that interleukin-1β modulates LH release in an age-dependent manner in female pigs. Microinjections of interleukin-1β into the MBH lowered LH levels in eight out of 10 castrated female pigs, while identical microinjections were without any effects in castrated males (see Fig. 1). The attenuation
Fig. 5. A proposed model for central role of NO in the preovulatory LH surge (Brann et al., 1997, modified). GC = guanylate cyclase, Cox = cyclooxygenase, NE = norepinephrine, E₂ = estradiol-17β, P₄ = progesterone.

of LH release is also the assumed effect of interleukin in adult rats (for review, see McCann et al., 1998; Kalra et al., 1998).

5. Conclusion

On the verge of the new century, we know that GnRH is the neuroendocrine signal for ovulation but it seems that we still have not explored all feasible routes triggering this signal.

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