

## The role of immunological system in the regulation of gonadoliberin and gonadotropin secretion

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Received: 29 September 2008; accepted: 13 February 2009

### **SUMMARY**

This article reviews data concerning the interactions between immune and neuroendocrine systems in the regulation of reproduction processes at the hypothalamic and pituitary level during immunological stress. Hypothalamus seems to play the most important role in the inhibitory action of immune challenge on the gonadoliberin (GnRH) and gonadotropin secretion as well in the inhibition of the reproductive functions. The administration of endotoxin as a model of immunological stress could alter circulating concentrations of luteinizing hormone (LH) *via* actions at the hypothalamus through altered GnRH secretion, or at the level of the pituitary *via* inhibition of LH production and release in response to GnRH. At the central level, interleukin (IL)-1 $\beta$  seems to play the most important role in the suppression of GnRH secretion during immune challenge. The inhibitory action of this cytokine on GnRH may involve different neural mechanisms: direct action on the GnRH neurons through the IL-1 receptors or indirect action involving other mediators such as

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opioids, catecholamines,  $\gamma$ -aminobutyric acid, prostaglandins or nitric oxide. *Reproductive Biology* 2009, **9**, 1: 11-23.

**Key words:** reproductive axis, cytokines, immune-neuroendocrine interactions

## INTRODUCTION

Homeostasis is an essential requisite for the survival of a living organism, maintenance of which is coordinated by neural, endocrine and immune systems. Interactions between these systems have long been recognized with the most known immunosuppressive effects of glucocorticoids. However, there is a growing realization that other hormones, peptides and neuropeptides have immune effects as well and that immune cell products may profoundly affect endocrine function [6]. In recent years, the bi-directional communication between the neuroendocrine and immune systems has received considerable attention. Interconnections between the immune and the neuroendocrine systems are complex and widespread: neuroendocrine cells express various cytokines along with their receptors, whereas immune cells synthesize neurohormones and also express the corresponding receptors [5]. A large body of evidence suggests that cytokines are the main mediators between the immune and neuroendocrine systems. More than 100 cytokines have been described that make up a large and diverse family of polypeptide regulators produced widely throughout the body. Historically the term “cytokine” has been used to refer to the immunomodulating agents such as: interleukins (IL), lymphokines, monokines, chemokines, tumor-necrosis factors (TNF), interferons and growth factors [1]. Apart from playing a crucial role in local immune response, cytokines can reach general circulation and thus affect distinct endocrine organs, where they act either by themselves or through the release of intermediators such as prostaglandins (PG), nitric oxide (NO), neuropeptides or neurotransmitters [31].

Although interactions between the immune system and the hypothalamic-pituitary-adrenal axis (HPA) have been extensively investigated,

there is evidence suggesting that the immune system may also modulate the hypothalamic-pituitary-gonadal (HPG) axis. The perfectly operating reproductive system settles successful completion of reproduction and species perpetuation, while immune system prevents invasion of foreign antigens and ensures the surviving of the host. There is clinical evidence that impaired reproductive functions may accompany infectious states. Immune stress has profound effects on female reproductive health ranging from disruption of cyclicity [26] to loss of pregnancy [33]. The network of interactions between reproductive and immune systems is complicated and specific for each level of the HPG axis. The objective of this article is to review data concerning interactions between the immune system and HPG axis at the level of the hypothalamus and pituitary gland. The main focus of this article will be on the influence of immune/inflammatory challenges, such as bacterial endotoxin, on gonadoliberein (GnRH) and gonadotropin secretion and the role of cytokines in these processes.

## **HYPOTHALAMUS**

The hypothalamus appears to be a critical site in the suppression of reproductive axis during immune challenge. To study how immune stressors cause reproductive dysfunction, bacterial endotoxins (i.e. lipopolysaccharide – LPS) have been used as a model of immune challenge. Endotoxins are the pathogenic moieties of gram-negative bacteria and through a complex cascade of cytokines, neural afferents and other mediators induce pathophysiological responses throughout the body, very similar to a true bacterial infection [36]. A large part of the brain's response to LPS has been attributed to the action of cytokines and other acute phase reactants. On the other hand, Chakravaty and Herkenham [10] showed that endotoxin may target the brain by activation of TLR4, the signaling LPS receptor, independently of systemic cytokine action. The authors demonstrated the expression of TLR4 transcripts in a mouse's brain in the meninges, ventricular ependyma, circumventricular organs, as well as in the vasculature and in the parenchymal microglia. Their findings highlight the presence of a LPS signalling receptor in resident cells

of the mouse brain and suggest its critical participation in shaping the CNS response to circulating endotoxin.

There are various mechanisms mediating anti-reproductive action of immune stress such as severe illnesses, infections or endotoxin treatment. Increased activity of the HPA axis is associated with immune challenge such as LPS treatment [12]. Generally, an increased stress response is coupled with a depressed reproductive function [37]. Indeed, there is an increase in hypophyseal portal concentration of the corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) in sheep following endotoxin administration [11]. The increase in CRH and AVP in ovariectomized ewes occurred in the same time frame as endotoxin inhibition of GnRH and luteinizing hormone (LH) pulsatility [3]. However, it is unlikely that CRH alone is responsible for the suppression of LH pulsatility since central CRH administration resulted in an increased pulse frequency and an increased mean LH concentration in sheep [25].

Activation of an immune response by LPS administration causes activation of the HPA axis with a consequent release of corticosteroids. Debus et al. [13] showed that although cortisol itself inhibited pulsatile GnRH and LH secretion in sheep, the marked release of cortisol by LPS administration was not required for the inhibitory effects of bacterial endotoxin on LH secretion. The authors concluded that more than one pathway must be responsible for the immune-mediated inhibition of reproductive activity, and one of these involves enhanced cortisol secretion. The interpretation of the role of corticosteroids in the response to immunological challenge is difficult. The co-involvement of cortisol in the inhibition of the reproductive function induced by bacterial endotoxin appears to be at odds with the recognized immunosuppressive role of glucocorticoids. Also, the corticosteroids must participate in the negative feedback regulation of the HPA axis inhibiting their own secretion [2]. Thus, although activation of the HPA axis can inhibit reproductive function and the HPA axis is activated in response to immune challenge, it is unlikely that activation of the HPA axis alone is responsible for the suppression of reproductive functions during immune stress.

The release of some potent proinflammatory cytokines during illness, infections or after LPS administration, such as  $\text{TNF}\alpha$ ,  $\text{IL-1}\beta$  or  $\text{IL-6}$ , is

likely to play a central pathophysiological role in the inhibition of the neuroendocrine reproductive axis. In rats, systemic LPS treatment inhibited secretion of both LH and GnRH and concomitantly stimulated the release of the three cytokines in the hypothalamic medial preoptic area (MPOA; [38]). Intracerebroventricular (icv) injections of IL-1 $\beta$ , IL-6 and TNF $\alpha$  lowered the plasma LH level in castrated rats; on a molar basis IL-1 $\beta$  was the most potent inhibitor of LH secretion. In contrast, the peripheral administration of either of the cytokines was without effect [32]. Centrally injected IL-1 $\beta$  also blocked ovulation in most treated rats. A previously published study revealed that IL-1 $\beta$  potently suppressed LH release through the blockade of GnRH secretion [38]. Infusion of IL-1 $\beta$  directly into MPOA, a region rich in GnRH perikarya, markedly decreased GnRH secretion in rats bearing a push-pull cannulae in the median eminence (ME; [30]).

The results of our studies on anestrus ewes [Tomaszewska-Zaremba, unpublished] indicated that LPS significantly decreased the GnRH mRNA level in MPOA, simultaneously with an increased IL-1 $\beta$  gene expression in hypothalamic structures (MPOA, mediobasal hypothalamus, anterior hypothalamic area and ME). IL-1 $\beta$  injected into the III-rd ventricle of anestrus ewes, resulted in the decrease of LH $\beta$  mRNA in the anterior pituitary. Earlier reports have presented contradictory effects of IL-6 and TNF $\alpha$  on the GnRH-LH system. Although one *in vivo* study reported that central administration of IL-6 inhibited LH secretion [32], other reports demonstrated no effect of IL-6 *in vivo* [19, 38]. With respect to TNF $\alpha$ , several *in vivo* studies agreed that this cytokine is inhibitory to the GnRH-LH system [19, 32]. In our experiments on anestrus ewes [Tomaszewska-Zaremba, unpublished] we did not observe any significant effect of endotoxin on IL-6 and TNF $\alpha$  gene expression in studied hypothalamic structures.

A comparison of suppressing effects of several proinflammatory cytokines on reproductive system revealed that IL-1 $\beta$  is the most potent inhibitor. This suggests that the antigonadotropic effects of immune challenge are most likely attributable to the action of centrally released IL-1 $\beta$ . IL-1 $\beta$ -immunopositive neurons and fibres have been visualized in the human and rat hypothalamus [8, 21] and IL-1 receptors are present in the rat brain [19] providing an anatomical basis for the putative interaction of IL-1 with the

secretion of hypothalamic hormones. Early studies showed that small doses of IL-1 $\beta$  injected into the brain of the rats lowered GnRH release during the proestrus afternoon and completely inhibited the spontaneous expression of the immediate early gene *c-fos* which is expressed in GnRH cell nuclei during the same period of the cycle [29]. Rivest et al. [30] showed that prolonged infusion with IL-1 $\beta$  inhibited GnRH gene expression in rats which reflected ability of the cytokine to inhibit the activity of GnRH perikarya. In another study, no significant change in GnRH mRNA level in the MPOA was observed in castrated male rats. IL-1 $\beta$  decreased the translational efficiency of the transcribed GnRH mRNA [20]. In this study the authors provided evidence that central administration of IL-1 $\beta$  suppresses the translational activity of GnRH mRNA.

In our experiments on sheep we observed that IL-1 $\beta$  injection into the III-rd ventricle significantly decreased GnRH mRNA levels in MPOA and in median eminence [Tomaszewska-Zaremba, unpublished]. To gain a better insight into the precise cellular and molecular mechanism of cytokine action on the hypothalamic GnRH neurons, Igaz et al. [18] used a novel neuronal cell line expressing GnRH (Gnv-4 cells). The Gnv-4 cells expressed the IL-1 receptor and the IL-1 receptor accessory protein, a mandatory component of the IL-1 signal transduction pathway. The finding that Gnv-4 cells express IL-1 receptor suggests that GnRH neurons may possess the cellular machinery to respond directly to this cytokine. On the other hand, it was revealed that cytokines may influence the hypothalamic GnRH synthesis and release by active brain mediators such as endogenous opioids, prostaglandins, hypothalamic catecholamines,  $\gamma$ -aminobutyric acid (GABA) or NO.

Opioids in the hypothalamus are well known to influence the concentration of GnRH/LH. The possible involvement of opioid-dependent pathways in mediating the inhibitory action of IL-1 $\beta$  on reproductive processes in rats was tested by Rivier and Vale [32]. They observed that a prior blockade of opioid receptors by naloxone, a treatment which by itself did not alter the ovulatory process, reversed the inhibitory effects of IL-1 $\beta$  on reproductive processes. These results suggest that increased brain levels of endogenous opioids influence the ability of immune mediators to interfere with reproductive functions. In non-humans primates central administration of naloxone

blocked endotoxin suppression of LH [40]. It was demonstrated in pharmacological studies with specific antagonists of opioid receptor subtypes that activation of the  $\mu$ -1 receptor subtype was required to transmit the IL-1 $\beta$  signal. Furthermore, IL-1 $\beta$  upregulated hypothalamic proopiomelanocortin (POMC) mRNA and increased the concentration and release of  $\beta$ -endorphin, the primary ligand of  $\mu$ -1 receptors [19].

Prostaglandins seem to be other important cellular regulators in the mechanism of suppression of GnRH/LH concentration during immune challenge. The experiments with either non-selective or selective cyclooxygenase-2 inhibitors, consistently impaired ovulation, indicating the essential role of COX-2/prostaglandins in the ovulatory process. Indomethacin, a potent inhibitor of both COX-1 and COX-2, induced several ovulatory alterations consisting of a decrease in the number of effectively ovulated oocytes, trapping of oocytes inside the luteinized follicle, as well as an abnormal follicle rupture at the basolateral sides, with a release of the oocyte and follicular fluid to the interstitium. The characteristic alterations of a follicle rupture induced by indomethacin are also induced by selective COX-2 inhibitors [16]. Rettori et al. [28] in *in vivo* experiments on ovariectomized rats and *in vitro* experiments on mediobasal hypothalamic fragments showed that IL-1 $\alpha$  suppressed LH release but not follicle stimulating hormone (FSH) release. The LH suppression resulted from an almost complete cessation of pulsatile release of LH which might be caused by inhibition of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>)-mediated release of GnRH. Growing evidence suggests that a number of cytokines mediate this inhibition *via* PG-dependent pathways. For example, the blockade of PG synthesis by indomethacin, a cyclooxygenase inhibitor, can prevent the IL-1 and TNF $\alpha$ -induced inhibition of LH secretion in the gonadectomized rats [41]. This indicates that prostaglandins are essential for the suppressive actions of endotoxin on the pulsatile mode of GnRH/LH release [17]. On the other hand, prostaglandins do not seem to be essential mediators of the estradiol-induced LH-surge [9].

The role of catecholamines as mediators of the suppressive action of IL-1 $\beta$  on GnRH secretion has not been widely investigated. Hypothalamic catecholamines are known to participate in the regulation of GnRH/LH

secretion. On the other hand, many experiments proved that cytokines released during bacterial infections influence CRH and adrenocorticotrophic hormone release through the catecholaminergic system [31]. Thus, it is possible that catecholamines are involved in the suppressive action of IL-1 $\beta$  on GnRH/LH secretion. Recent experiments on rats showed that IL-1 $\beta$  suppresses LH surge by decreasing noradrenaline levels in the MPOA, and L-dopa can be used to counter this effect [34].

The role of GABA and NO is less known in the regulation of GnRH release during infection, endotoxin or IL-1 $\beta$  treatment. Mc Cann et al. [23] demonstrated that NO plays a key role in inducing the changes in the release of hypothalamic peptides induced during infection by cytokines. Interleukin-1 blocks the NO-induced release of GnRH from GnRH neurons, thereby blocking pulsatile LH but not FSH release. The studies of Felder et al. [15] indicated that IL-1 inhibited NMDA-stimulated GnRH release by affecting the activity and release of hypothalamic GABA.

## **PITUITARY GLAND**

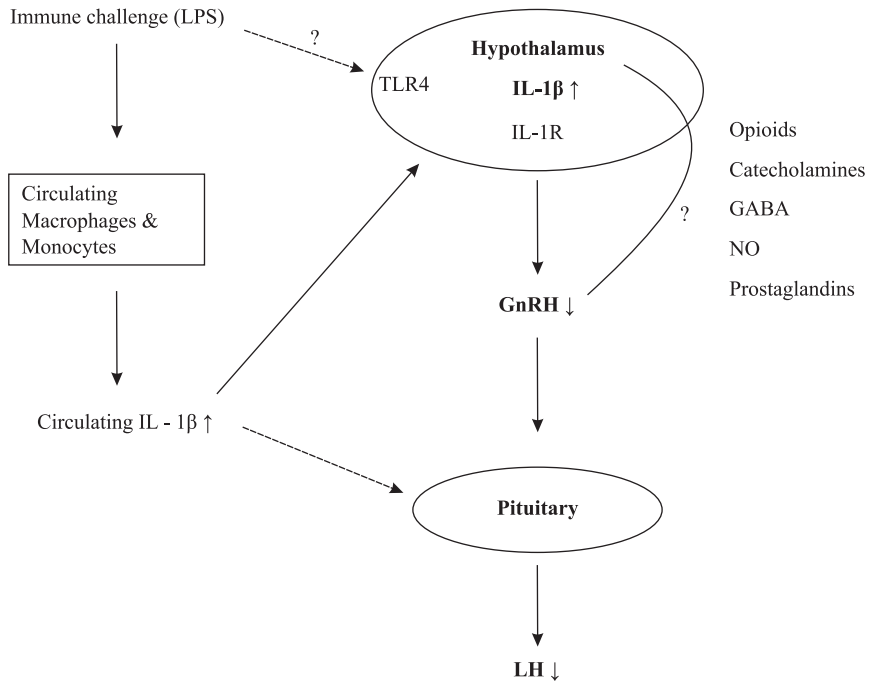
Whereas most studies support the role of the hypothalamus in completing the endocrine-immune loop, early work showed that the deafferented pituitary could produce hormones in response to endotoxin challenge [22] and, more specifically, that local action of cytokines in the pituitary can directly affect hormone release [3]. Administration of endotoxin inhibited tonic LH secretion and blocked the preovulatory LH surge in a number of species including rats [27], sheep [3], cattle [35] and non-human primates [40]. In our experiments on anestrous ewes, endotoxin significantly decreased expression of LH and LH-receptor (LH-R) genes in the anterior pituitary. These results correspond with a significant decrease in serum LH concentration in LPS treated animals [Tomaszewska-Zaremba, unpublished]. The inflammatory response to endotoxin could alter circulating LH concentration at the level of the pituitary *via* inhibition of LH production and release or inhibition of the LH response to GnRH stimulation. LPS administration in ovariectomized ewes resulted in an uncoupling of GnRH

and LH pulses suggesting the possibility of inhibition of LH secretion at a pituitary level [39].

On the other hand, there is evidence that IL-1 profoundly alters the secretion of several pituitary hormones. With respect to the effects on gonadotropin secretion, IL-1 $\beta$  stimulated LH release *in vitro* from dispersed mice anterior pituitary fragments [4]. Murata and Ying [24] in an experiment on cultured rat anterior pituitary cells showed that IL-1 $\beta$  can inhibit FSH secretion and stimulate LH secretion. Pretreatment with IL-1 $\beta$  inhibited GnRH stimulated pituitary secretion of both LH and FSH. This suppressive effect may involve the suppression of a protein kinase C-dependent mechanism. In other *in vitro* studies on cells from the ovine pituitary gland, IL-1 $\beta$  and IL-1 $\alpha$  stimulated release of LH [7]. It was demonstrated in a series of studies that the injection of IL-1 $\beta$  into a lateral ventricle of castrated, female rats, resulted in a decrease in serum levels of LH and FSH accompanied by a decrease in the number of GnRH receptors [14]. These results indicate that the inhibition of gonadotropin release may be due to a decrease in the number of GnRH pituitary receptors. The latter phenomenon may be caused by a direct effect on the pituitary or by modulating the release of hypothalamic GnRH.

## CONCLUSIONS

It seems apparent that immune and reproductive systems are linked by an array of internal mechanisms of communication that use similar signals (neurotransmitters, peptides, growth factors, hormones, cytokines) and receptors. The release of some potent proinflammatory cytokines such as TNF $\alpha$ , IL-6 and IL-1 is likely to play a central role in the inhibition of the reproductive axis during immune challenge. A comparison of GnRH suppressing effects of several proinflammatory cytokines revealed that IL-1 $\beta$  is the most potent inhibitor of the HPG axis. In the brain, similarly to other organs (i.e. testis, heart), IL-1 system may act independently of the cytokines peripherally induced during immune challenge [32]. Thus, central IL-1 $\beta$  plays an important role in the control of GnRH/LH secretion. The dif-



*Figure 1.* Scheme illustrating possible mechanisms and mediators involved in the endotoxin (LPS) suppression of GnRH/LH secretion. LPS: bacterial endotoxin, lipopolysaccharide; TLR4: receptor for LPS; IL-1 $\beta$ : interleukin-1 $\beta$ ; IL-1R: interleukin-1 receptor; GnRH: gonadoliberin; LH: luteinizing hormone; GABA:  $\gamma$ -aminobutyric acid; NO: nitric oxide.

ferent neural mechanisms (fig. 1) could be involved in the suppression of GnRH/LH release by this cytokine: direct, through the IL-1 receptors on the GnRH neurons or indirect, through the other mediators such as opioids, catecholamines, GABA, prostaglandins or NO.

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