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Intrahypophyseal Immune-Endocrine Interactions: Endocrine Integration of the Inflammatory Inputs

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Abstract

Endotoxin (lipopolysaccharide, LPS) of gram-negative bacteria has been recognized for more than 40 years as a modulator of anterior pituitary hormone production. The action of LPS was thought to be predominantly mediated through LPS-stimulated immune cell-derived cytokines, and is part of the concept of immune-endocrine crosstalk, which regulates bidirectional adaptive processes between the endocrine and immune systems during inflammatory or infectious processes. With the detection of innate immune system components in the normal and tumoral pituitary, including the Toll-like receptor 4, the target of LPS, it has become evident that LPS can directly modify the physiology and pathophysiology of the anterior pituitary. LPS-induced intrapituitary mechanisms involve the stimulation of intrapituitary cytokines, and also directly act on hormone synthesis, growth, and apoptosis of endocrine cells. This review focuses on the effects of LPS on pituitary physiology, its interaction with pro- and anti-inflammatory factors, and the molecular mechanisms involved in these processes.

Introduction

Lipopolysaccharides (LPS) are membrane components of gram-negative bacteria, and are well known in vivo modulators of the synthesis and secretion of anterior pituitary hormones. Originally, it was believed that the stimulatory and inhibitory activities of LPS on hormones may mainly be mediated through cytokines (e.g. tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6), which are induced by LPS in immune cells and which have been shown to act on anterior pituitary hormone production [1]. This is part of the concept of the immune-endocrine interaction, in which,

during inflammation or infection, elevated levels of cytokines alter the physiological hormone production to adapt the endocrine system to the needs of the organism to respond adequately to pathogens. A major adaptive endocrine process is the activation of the hypothalamus-pituitary-adrenal (HPA) axis, which leads to a strong increase in corticotropin releasing hormone (CRH), adrenocorticotroph hormone (ACTH), and finally, anti-inflammatory acting glucocorticoids. The latter prevent the self-damaging effects of the activated immune system, which would finally lead to septic shock syndrome [2]. However, as described below, not only the HPA axis, but also other hormone axes are affected and altered during the activation of the immune system.

In vitro studies on the effect of LPS on pituitary cell function in the absence of immune cells gave evidence that LPS acts through enhanced cytokines and affects the pituitary cell function directly. This was confirmed with the detection of functional Toll-like receptor 4 (TLR4), the membrane-associated receptor of LPS [3, 4], in normal and tumoral anterior pituitary cells [5–8]. As other Toll-like receptors (membrane-bound TLR1, TLR2 and TLR6, and cytoplasmatic TLR3) and cytoplasmatic NOD receptors (NOD1 and NOD2) have been found in pituitary cells [7, 9, 10], it seems that these components of the innate immune system are widely distributed in the anterior pituitary. Thus, in addition to LPS, other pathogenic bacterial, viral, fungal or protozoan compounds (glucans, glycoproteins, RNA, DNA, etc.) may directly influence the pituitary function during infectious/inflammatory processes [7, 9, 10]. At the same time, almost nothing is known about their function in the pituitary. This review will mainly address the role of LPS, its receptor TLR4 and LPS-induced cytokines in the (patho-)physiology of the anterior pituitary.

TLR4 Expression and Regulation in the Anterior Pituitary

The LPS receptor TLR4, a key component of the innate immune system [3], is not only expressed in immune cells, but also in many epithelial cell types, as these cells form the border between organisms and their environment, and are the first to be attacked by pathogens [4]. Thus, they should be able to respond to the pathogenic invasion either locally and/or by activating the immune system. Hormone producing cells of the anterior pituitary are also of epithelial origin, and TLR4 protein expression was found in endocrine pituitary cells [6]. However, co-localization studies showed that only subpopulations of each endocrine cell type expressed TLR4 under basal conditions. Nevertheless, as shown in in vitro studies in normal anterior pituitary monolayer cell culture, LPS was able to affect hormone release and growth/apoptosis of TLR4 positive endocrine cells. While only scattered endocrine cells expressed TLR4, this receptor was strongly expressed in non-endocrine folliculostellate (FS) pituitary cells [5], a pituitary-specific, non-epithelial cell type with specific characteristics [11] and

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multiple functions [12]. Recent studies found that a large proportion of FS cells represent non-lymphoid dendritic cells (DC) [13, 14]. Studies in isolated hypophyseal DC cells showed that they expressed TLR4 and its co-receptor CD14, and TNF-α, IL-1β and IL-6, and that LPS treatment strongly induced the production of these cytokines [5, 14, 15].

TLR4 was also found in some pituitary tumor cell types such as the murine FS TtT/GF and corticotroph AtT20 tumor cells and human FS PDFS tumor cells [5, 7, 10]. These cell types are often used in studies dealing with the regulation and mechanism of action of LPS and cytokines in pituitary cells.

Little is known about the regulation of TLR4 in pituitary cells. In PDFS cells, it was shown that fungal glucan enhances TLR4 synthesis through a still unknown mechanism [10]. In TtT/GF cells, NOD2, an intracellular, muramyl dipeptide-activated receptor of the innate immune system, is involved in the full activation of the TLR4-mediated response to LPS, since downregulation of NOD2 reduces the LPS-induced IL-6 secretion in TtT/GF cells [9]. Thus, during fungal or gram-positive bacterial infections, the observed glucan and NOD2-mediated stimulatory effects on TLR4 may sensitize, and thus protect, organisms against super-infections caused by gram-negative bacteria. In immune cells and several epithelial cell types, endotoxemia stimulates TLR4 expression [4]. A small but significant LPS-induced increase in TLR4 expression has also been observed in lactotroph cells [8].

Function of TLR4 in Normal Pituitary

Despite the expression of TLR4 in the subpopulations of endocrine cells, it is still believed that the TLR4-expressing dendritic FS cells are the major pituitary target of LPS [14, 16]. It is thought that the main function of these cells is to produce intrapituitary cytokines that act in addition to enhanced systemic immune cell-derived cytokines on endocrine pituitary cells during inflammation/infection with gram-negative bacteria to alter pituitary hormone secretion. As dendritic FS cells have recently been identified as the major source of IL-6, TNF-α, and IL-1β [14], these factors may influence the function of hormone-producing cells in a paracrine manner. In particular, LPS-induced intrapituitary cytokines may contribute to the activation of the HPA-axis, as all FS cell-derived cytokines are known to induce the synthesis and release of ACTH as the main stimulator of anti-inflammatory adrenal glucocorticoids. This hypothesis was confirmed in vivo [17] and in vitro in 3D-pituitary aggregate cell cultures, in which LPS-induced ACTH secretion could be prevented by a neutralizing antibody against IL-6 [18]. Therefore, acting through hypophyseal TLR4, LPS may promote HPA axis activation during bacterial infection locally through the stimulation of ACTH via intra-pituitary IL-6.

With respect to the regulation of other pituitary hormones by LPS-induced cytokines, TNF-α and, to a lesser extent, IL-6 were shown to stimulate the release of

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prolactin (PRL) from normal lactotropes [19, 20]. As estrogens were shown to induce TNF-α and TNF-α receptor expressions in lactotropes, the TNF-α-induced PRL secretion may especially be enhanced in women during proestrus [19]. PRL has an anti-inflammatory effect on activated immune cells [20] and would thus – in combination with glucocorticoids – prevent excessive activation of the immune system.

Regarding the regulation of the gonadotroph axis, it is actually not clear whether LPS can directly affect the gonadotropin production, even if the TLR4 is expressed on a subset of gonadotroph cells [21]. Several studies suggest that IL-1β and TNF-α, but not IL-6, suppress the production of hypophyseal gonadotropins [22–24]. This would contribute to the well-known downregulation of the reproductive axis and, thus, to impaired male and female reproduction during transient or chronic infections/inflammations, and to fetal loss during pregnancy [25, 26].

Growth hormone (GH) is needed for the optimal immune cell function and, therefore, circulating GH levels are enhanced during infection/inflammation. LPS can directly stimulate GH secretion from somatotroph cells through TLR4/CD14, which was detected on a subpopulation of somatotrophs. In addition, all LPS-induced cytokines (TNF-α, IL-1β, and IL-6) are also able to stimulate GH indicating the importance of this hormone for the proper immune response to gram-negative (and other) pathogens [27–29].

The aforementioned immune-endocrine interactions are well-suited to address mild or moderate local or chronic infections/inflammation. However, the situation is different in bacterial- or viral-induced severe sepsis, or systemic inflammatory response syndrome that are characterized by excessive immune system activation, which leads to strongly enhanced levels of proinflammatory cytokines. This, in turn, can lead to lethal multi-organ failure [30]. Severe sepsis is characterized by low ACTH and paradoxically elevated glucocorticoid levels [30, 31]. There is strong evidence that an impairment of glucocorticoid-degrading enzymes is responsible for the observed glucocorticoid accumulation [32]. Nevertheless, the enhanced amounts of anti-inflammatory acting glucocorticoids are not sufficient to suppress the excessive immune system activation, possibly because of glucocorticoid resistance [30].

Apart from the modulation of hormone production, LPS and LPS-induced cytokines seem to also affect the growth and apoptosis of anterior pituitary cells. IL-6 was shown to further suppress the very slow growth rate of normal pituitary cells [33], and TNF-α and LPS could induce apoptosis in pituitary cells, particularly in lactotrophs and somatotrophs [34, 35]. Estrogen was shown to sensitize lactotrophs, but not somatotrophs, to TNF-α and LPS-induced apoptosis [34], whereas the anti-apoptotic factor humanin, expressed in the normal pituitary, prevented TNF-α and LPS-mediated cell death [35]. However, as both the proliferative and apoptotic index are very low in the normal pituitary, the anti-proliferative or pro-apoptotic actions of IL-6 or TNF-α/LPS, respectively, may have little or no consequences for the cellular

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composition or size of the anterior pituitary during infections/inflammations. Ultimately, the meaning of LPS/cytokine-induced effects on growth or apoptosis of normal pituitary cells remains obscure.

Impairment of Immune-Endocrine Crosstalk in Pituitary Disorders

This article does not address the pathogenic role of TLR4 or cytokines in the development of pituitary disorders like pituitary tumors because these are often related to aberrant intratumoral overexpression and function of TLR4 or cytokines [6, 8, 12, 36]. However, some pituitary disorders have consequences for the immune-endocrine crosstalk. In particular, patients with Cushing's syndrome may have an impaired interaction between the activated immune system and the HPA axis. These patients have strong and persistently elevated glucocorticoid levels due to ACTH-producing corticotroph pituitary adenomas, or ectopic ACTH-releasing neuroendocrine tumors [37]. Similar to patients with severe sepsis, the continuously elevated glucocorticoid levels may induce glucocorticoid resistance and, thus, the impairment of anti-inflammatory glucocorticoid feedback on cytokine production during infectious/inflammatory processes. This may explain the development of severe sepsis in response to infections in some patients with Cushing's syndrome [38].

Hypophyseal immune-endocrine interactions may also be impaired during hypophysitis, a rare autoimmune pituitary disorder [39], in which immune cells, in most cases lymphocytes, infiltrate the pituitary and induce destruction of endocrine cells and, thus, alter the pituitary hormone release [40]. As corticotroph and thyrotroph pituitary cells have been reported to be the most sensitive to lymphocytic hypophysitis-induced cell destruction, affected patients often suffer from secondary adrenal insufficiency and hypothyroidism [40, 41]. Whether patients with this disease have an impaired endocrine response to infections is not known and difficult to study as they often receive glucocorticoid or other immune-suppressive therapies and hormone replacement therapy [42].

TLR4 and Cytokine Signaling in Pituitary Cells

TLR4 signaling in pituitary dendritic FS cells involves the p38 MAP kinase pathway and ultimately leads to the activation of NF-κB that, in turn, stimulates TNF-α, IL-1β, and IL-6 release [5, 43]. As TNF-α and IL-1β also signal through the activation of NF-κB [44, 45], these cytokines may further stimulate their own production in TNF-α and IL-1β receptor-expressing FS cells. In ACTH-producing corticotroph cells, in which most of the LPS/cytokine signaling studies have been performed, LPS, TNF-α, and IL-1β induce the activation of the POMC gene, coding for ACTH through specific receptors and transcription factors including Nur77, finally leading to the activation

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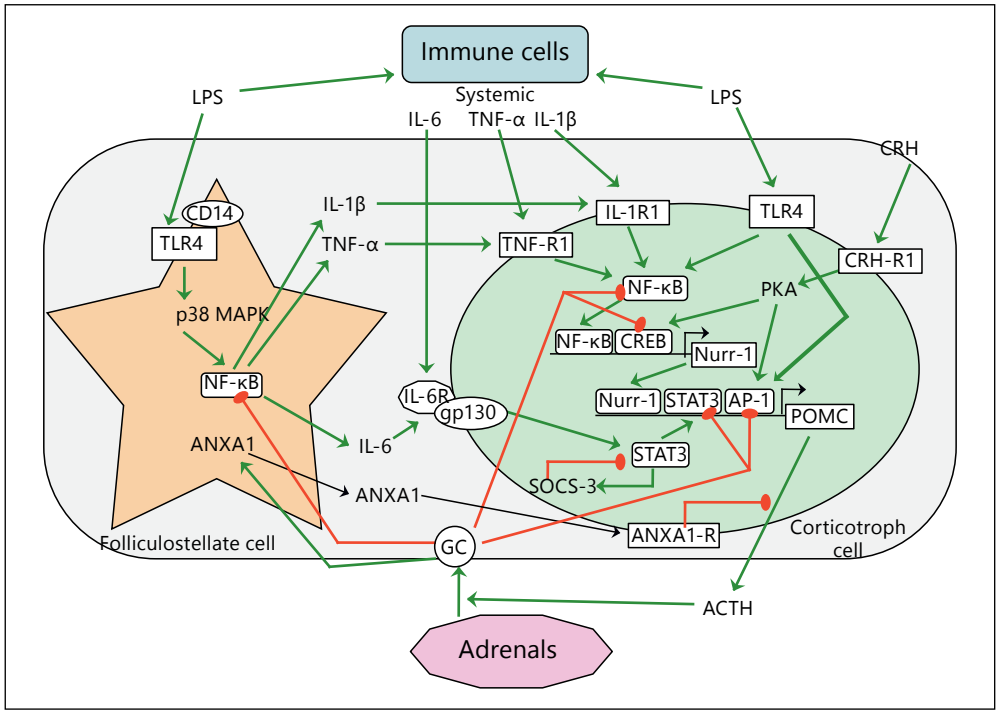

Fig. 1. Schematic overview of the intrapituitary regulation of ACTH production during LPS-induced infectious/inflammatory processes. In FS cells, LPS stimulates the production of cytokines, which together with LPS, LPS-induced systemic cytokines, and LPS/cytokine-stimulated hypothalamic CRH, upregulate the synthesis and release of ACTH through different signaling pathways (in green). Anti-inflammatory mechanisms (in red), mainly triggered by elevated levels of glucocorticoids, through the activation of the GR, downregulate ACTH production by interfering with different ACTH-inducing mechanisms.

and nuclear translocation of NF-κB [45, 46]. This factor then binds to the promoter of Nurr-1 to enhance the protein production of this transcription factor, which subsequently binds to the POMC promoter to enhance POMC mRNA synthesis leading to an increase in the ACTH production [45, 46]. CRH, the hypothalamic ACTH releasing factor, which is also enhanced during endotoxin-induced activation of the immune system, induces through the cAMP/PKA signaling, the transcription factor CREB, which like NF-κB, binds to the Nurr-1 gene promoter to stimulate ACTH production [47]. Thus, LPS/TNF-α/IL-1β and CRH share the Nurr-1-mediated ACTH stimulation machinery to induce additive or synergistic effects on ACTH production to induce the maximal release of anti-inflammatory glucocorticoids from the adrenals (fig. 1).

LPS-induced IL-6 [18, 48] stimulates ACTH production after binding to the IL-6 receptor and subsequent interaction with the gp130 signal protein, both expressed on corticotroph cells [17, 49]. Subsequently, gp130 induces the transcription factor

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STAT3, which can stimulate POMC transcription and ACTH production, probably in synergistic fashion with the transcription factor AP-1, whose component Fos is mainly induced by CRH but is also stimulated by LPS [7, 17]. In recent studies, the transcription factor nuclear factor IL-6 (NF-IL6) was detected in dendritic FS and corticotroph cells and was induced by LPS stimulation in parallel with NF-κB and STAT3 [50]. In FS cells, LPS-induced activation of NF-IL6 was involved in the stimulation of TNF-α production in a STAT3-dependent manner [50]. However, the precise mechanism of NF-IL6 action in the pituitary, and its contribution to the hypophyseal immune-endocrine interactions is still poorly understood.

The suppressive action of the activated GR to inhibit ACTH production is the most important intrapituitary anti-inflammatory signaling mechanism [51]. This involves the suppression of LPS-induced pro-inflammatory cytokine production in dendritic FS cells and the inhibition of LPS-, cytokine- and CRH-induced ACTH secretion [51]. The activated GR can regulate gene transcription through DNA-dependent transactivation, or through DNA-independent mechanisms [52, 53]. The most relevant anti-inflammatory effects of glucocorticoids occur independent of DNA through the direct inhibition of the activity of other transcription factors by transrepression mechanisms consisting of protein-protein interactions between the activated GR and NF-kB, STAT proteins or AP-1 [54, 55]. Thus, as shown in figure 1, glucocorticoids may suppress the LPS-stimulated production of IL-6 and other ACTH-stimulating cytokines (IL-1β and TNF-α) by inhibiting the transcriptional activity of NF-κB. Similarly, the direct NF-κB-mediated effects of LPS, TNF-α, and IL-1β on ACTH production may also be blocked in corticotroph cells. IL-6 stimulated ACTH production is inhibited by the interaction between the activated GR with STAT3, whereas GR/AP-1 interactions mainly suppress the CRH-induced ACTH synthesis.

In addition, the activated GR in dendritic FS cells can induce the synthesis and release of anti-inflammatory acting annexin A1 (ANXA1), which contributes to the suppression of ACTH through specific ANXA1 binding sites on corticotroph cells [14, 56]. Moreover, at least in the case of IL-6, gp130 activation will not only activate STAT3, but also SOCS-3, a natural intrinsic STAT3 inhibitor that down-regulates excessive IL-6/STAT3 induced POMC synthesis and, thus, ACTH production [17, 57] (fig. 1).

Apart from these mechanisms, post-translational modifications, for example, sumoylation, may play a role in glucocorticoid receptor action [58–60]. It has been demonstrated that sumoylation of the GR can alter its activity and interference with transcription factors, some of which are also altered by sumoylation [58–60]. However, data are still missing as to whether inflammatory processes induce sumoylation of the GR and to what extent GR sumoylation contributes to the anti-inflammatory action of glucocorticoids.

In summary, the GR-mediated mechanisms discussed above prevent the over-activation of the immune system by means of downregulating cytokine production and, through ACTH inhibition, reset the activated HPA-axis to normal levels in the post-infectious/inflammatory state.

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Summary and Conclusions

With the detection of innate immune system-related Toll-like and NOD receptors in normal and tumoral pituitary cells, it has become evident that the pituitary is the target of corresponding receptor ligands. So far, only TLR4 expressed both in normal pituitary and in a subset of pituitary adenomas, has been investigated in detail. The intrapituitary TLR4 is activated by its ligand LPS, a cell wall component of gram-negative bacteria, and induces various cellular signal components (MAP kinases, c-Fos/AP1, NF-κB, Nurr-1, STAT3, NF-IL6, etc.) by itself or by LPS-induced cytokines, such as TNF-α, IL-1β or IL-6. In normal pituitary, TLR4 and cytokines are critically implicated in the immune-neuroendocrine crosstalk during inflammation/infection, by stimulating (ACTH, PRL, GH) or inhibiting (luteinizing hormone, LH, follicle-stimulating hormone, FSH) pituitary hormones. Thus, targeting the TLR4, components of its signaling cascade (e.g. NF-κB), or LPS-induced cytokines (e.g. TNF-α, IL-6) [61], could lead to new therapeutic concepts in the treatment of impaired immune-endocrine interactions, as observed in severe sepsis, hypophysitis or Cushing's syndrome.

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