Interaction between the hypothalamo-pituitary-adrenal axis and the immunological system

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Les interactions entre l’axe hypothalamo-hypophyso-surrénalien et le système immunologique

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Les systèmes endocrinologique et immunologique sont reliés entre eux par un réseau d’interactions bi-directionnelles qui, d’une part, permettent aux hormones de moduler les fonctions immunologiques et d’autre part, permettent aux réponses immunologiques d’influencer les réponses neuroendocriniennes. Cette communication bi-directionnelle est possible, car les deux systèmes utilisent un langage chimique commun, les deux possédant des ligands similaires (hormones et cytokines) ainsi que les récepteurs spécifiques. Les cytokines jouent un rôle important dans ce dialogue. Elles modulent les réponses de l’axe hypothalamo-hypophysio-surrénalien en agissant à trois niveaux : hypothalamus, hypophyse et surrénal. Les effets aigus des cytokines s’effectuent au niveau du système central, plus particulièrement dans l’hypothalamus. Aux niveaux hypophysaire et surrénalien, les actions des cytokines sont plus lentes et ne jouent probablement un rôle qu’en cas d’exposition prolongée aux cytokines ainsi que lors d’inflammations chroniques ou d’infection. Plusieurs mécanismes ont été proposés pour expliquer le passage des cytokines de la périphérie vers le cerveau. Il pourrait s’agir d’un transport actif à travers la barrière hémato-encéphalique, d’un passage au niveau des organes circumventriculaires et de l’utilisation d’une voie neuronale par l’intermédiaire du nerf vague. Les interactions immunoneuroendocriniennes sont impliquées dans de nombreuses situations physiologiques et physiopathologiques. Ainsi les interactions avec l’axe hypothalamo-hypophysio-surrénalien représentent un mécanisme qui permet, par la production de glucocorticoïdes, de contrôler la réponse inflammatoire et évite ainsi qu’une exagération de cette réponse ne mette en danger l’intégrité de l’organisme. Le dialogue entre les systèmes immunologique et endocrinien est important pour l’homéostasie, car lorsque cette dernière est menacée, ces interactions vont produire des réponses appropriées d’adaptation permettant le maintien de l’homéostasie.

Mots-clés : Cytokines, hormones, hypothalamus, hypophyse, interactions immunoenendocriniennes.

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It is now well recognised that the immune system and the neuroendocrine system are interrelated via a bidirectional network through which hormones and neuropeptides affect immune function and, in turn, immune responses are reflected in neuroendocrine changes [1-3]. This tight communication between the endocrine and the immune system is possible because both systems speak a common « chemical language » by sharing a common set of ligands and receptors of classical hormones, neuropeptides and immunoregulatory mediators. Indeed, in addition to possessing more than 30 different types of hormonal receptors classically associated with endocrine tissues, the cells of the immune system can synthesize and secrete numerous hormones and neuropeptides [4-9].

Over the last years, it has been suggested that CRH – corticotropin-releasing-hormone –, the major stress-integrating peptide, which primarily stimulates ACTH secretion, may also directly modulate the immune system function [10-12]. Recent data have demonstrated that CRH acts centrally as an immunosuppressant agent, independent of circulating glucocorticoids. This central immunosuppressive effect of CRH seems to be mediated via the central sympathetic nervous system. CRH has also been shown to be produced by cells of the immune system. But in contrast to its immunosuppressive effect at central level, CRH peripherally secreted at sites of inflammation has pro-inflammatory effects.
Sites of inflammation contain large amounts of immunoactive CRH and neutralizing antibodies against CRH as well as Antalarmin, a novel nonpeptide CRH antagonist, diminish or prevent pro-inflammatory effects of CRH [10]. Somatostatin, another hypothalamic factor, has also been found within the cells of the immune system [8]. In contrast to CRH, somatostatin at inflammatory sites exerts anti-inflammatory effects and may participate in the anti-inflammatory action of glucocorticoids [9]. All these immune-derived hormones locally modulate a number of immune functions and play a role in the regulation of inflammation. Whether hormones produced by immune cells may function in an endocrine fashion and influence the function of other cells is still controversial [13]. However, at least one case of Cushing’s syndrome caused by ectopic secretion of ACTH by a granulomatous mass has been reported [14]. This observation suggests that some clinical endocrine syndromes might well be caused by hormones produced within the immunocytes.

The reciprocal arm of this bidirectional relationship is the modulation by the immune system of the neuroendocrine responses through messengers released by activated immunocytes, the cytokines. These substances which were initially thought to be exclusively produced by the immune system, have recently been shown to be produced by most endocrine tissues [15] and by the brain [16]. Furthermore, as for peptide hormone and neurotransmitter receptors on immune cells, cytokine receptors are also present in endocrine tissues and in the brain.

All these findings clearly demonstrate that the immune and endocrine systems speak a common biochemical language which allows them to exert profound and biologically relevant effects on one another.

Since the landmark studies by the groups of Besedowsky and Blalock, it has become apparent that cytokines have potent effects on the secretion of all endocrine axes [17, 18]. In this review, we shall however discuss only the effects on the hypothalmo-pituitary-adrenal (HPA) axis, which has remained the most extensively studied neuroendocrine system with respect to the influence of cytokines.

**CYTOKINE EFFECTS ON THE HYPOTHALAMO-PITUITARY-ADRENAL (HPA) AXIS**

In spite of some controversy in the literature, cytokines have been shown to modulate the HPA axis by acting at all three levels: the hypothalamus, the pituitary gland and the adrenal glands inducing, CRH, ACTH and glucocorticoids production (fig. 1).

**Pituitary gland level**

Since the first observation that IL-1 induced ACTH release from the corticotroph tumor cell line AtT 20...
many studies have provided evidence for a direct effect of cytokines on the pituitary [20–23]. The majority of these observations demonstrate that cytokines stimulate ACTH release from pituitary cells after a prolonged incubation time of over 8 to 10 hours, but some studies using a perifusion system disclose an effect already within minutes after stimulation [24, 25]. More intriguing, however, is the fact that several studies were unable to show any direct effect of cytokines on ACTH release [26–28]. The reason for this discrepancy is not clear but it is possible that the presence of folliculo-stellate cells may be mandatory. Indeed, it has been put forward that these cells are essential to allow pituitary effects of the cytokines [29]. This may concord with the recent demonstration of gap junction-mediated exchanges between endocrine and folliculo-stellate cells [30]. The folliculo-stellate cells therefore appear to constitute a kind of interface through which the pituitary gland perceives changes in the state of activation of the immune system.

The presence of pituitary binding sites for cytokines as well as the intrapituitary production of cytokines is consistent with their direct pituitary effect [23, 31]. Indeed, a number of cytokine receptors or the corresponding mRNAs have been localized in the pituitary (e.g. IL-1, IL-2, IL-6, TNFα, LIF). In addition, the pituitary has been shown to produce many cytokines, some of which have been localized to corticotropes (e.g. IL-2, IL-10, LIF and MIF), to thyreotropes (e.g. IL-1, MIF) and to folliculo-stellate cells (IL-6) [23, 31].

Recently, two substances — macrophage migration inhibitory factor (MIF) and leukemia inhibitory factor (LIF) — have joined the club of cytokines produced within the pituitary.

MIF, a protein produced by lymphocytes and discovered more than 30 years ago, has recently been shown to be a pituitary-derived cytokine [32] and has been proposed to serve as a pituitary hormone [32–34]. Indeed, MIF has been identified as a protein released by the corticotroph tumor cell line AtT 20 as well as by anterior pituitary cells in response to LPS stimulation. Immunocytochemical studies show that resting pituitary cells contain significant amount of pre-formed MIF. MIF secretory granules are located within corticotroph and thyreotroph cells of mice pituitary glands [35]. The pituitary intracellular pools of MIF are released by the direct action of LPS or by a specific hypothalamic releasing factor secreted during endotoxemia. We recently found that CRH up-regulated transcriptional activity of the MIF promoter in both AtT20 and isolated anterior pituitary cells, thus corroborating that MIF synthesis takes place at the pituitary level and that the hypothalamic factor CRH regulates both pituitary MIF output and synthesis [36].

Studies on the role of MIF during endotoxin shock revealed that this substance potentiates LPS-lethality, while anti-MIF antibodies conferred full protection against lethal endotoxemia [37]. These findings indicate that MIF plays an important role in endotoxic shock. Interestingly and in sharp contrast to expectations, glucocorticoids were found to induce rather than inhibit MIF production [38]. Therefore, MIF possesses a unique property in that its release is stimulated by glucocorticoids. In addition, MIF has been shown to counter-regulate or «override» the suppressive effects of glucocorticoids on the production of inflammatory cytokines, as well as to block the protective effect of the glucocorticoids against LPS-induced lethality.

Altogether, these results indicate that MIF plays a pivotal role in the immune-neuroendocrine interactions [33]. Together with ACTH and the glucocorticoids, MIF may act to modulate systemic inflammatory responses. MIF is unique in being released under glucocorticoid stimulation and in antagonizing certain effects of glucocorticoids. The observation that stress leads to the production of both anti-inflammatory (glucocorticoids) and pro-inflammatory (MIF) mediators presumes that the organism possesses potent counter-regulatory mechanisms, allowing a fine tuning of the immune and endocrine responses to inflammation, infection and tissue invasion.

LIF, a protein originally isolated as a factor inducing differentiation and suppressing proliferation of a monocytic leukemia murine cell line M1 [39] has also been found in the pituitary gland. Indeed, this cytokine is secreted by primary bovine pituitary cells in culture [40] and its gene expression has also been demonstrated in the developing human fetal pituitary (predominantly in corticotroph and somatotroph cells) and in normal as well as in adenomatous adult pituitary tissue [41, 42]. LIF mRNA was also detected in mouse and rat adenohypophysis [43] as well as in mouse hypothalamus [44].

Specific receptors of LIF are present in murine AtT20 pituitocytes, in human fetal pituitary cells (in corticotrophs and somatotrophs) and in other functional hormone-producing cells [41]. These binding sites consist of heterodimers between the specific low affinity LIF-receptor and the shared affinity converter gp130 common to IL-6, LIF, oncostatin and ciliary nerve neurotrophic factor [45]. LIF-receptor mRNA expression in normal mouse pituitary glands and hypothalami has been shown to be significantly induced by LPS in vivo [44].

LIF action occurs principally at the level of the pituitary corticotroph, where it stimulates the secretion of ACTH and the expression of POMC [41, 46–48]. It shows strong transcriptional synergy with CRH on POMC mRNA expression, mediated by a common binding element in the POMC promoter region [49] and potentia-
tes the CRH-induced ACTH secretion [48]. Most interestingly transgenic mice expressing pituitary directed LIF were found to have an increased number of ACTH positive pituitary cells, resulting in pituitary corticotroph hyperplasia [50].

Recent studies clearly demonstrate that LIF contributes to the regulation of HPA axis secretion under basal as well as under stress conditions. Indeed, the LIF knock-out mouse model not only has basal plasma concentrations of ACTH lower than those seen in the wild type littermates [51, 52] but presents a defect in the activation of the HPA axis in response to stress, to IL-1 and to inflammation or infection [53-55]. These data implicate LIF in the HPA response during inflammatory stress and suggest that the absence of this cytokine may lead to impaired physiological communication between the immune and endocrine systems. In summary, LIF is an immuno-neuroendocrine modulator which has an important function in the maintenance and regulation of the HPA axis.

Adrenal gland level

Several cytokines are expressed in the adrenal glands, but there are only very few studies demonstrating the presence of cytokine receptors within the adrenal gland [23]. IL-6 receptor mRNA has been detected mainly in the zona glomerulosa and fasciculata in human adrenals [56] and also in the adrenal medulla [57]. Direct actions of IL-1, IL-6 and TNFα on glucocorticoids secretion have been demonstrated [23, 58, 59]. If some cytokines may influence glucocorticoids secretion directly, it should be noted that the majority of the studies required incubations in excess of 12 hours to observe significant effects [60]. Thus, as with the direct effects of cytokines on the pituitary, it seems unlikely that a direct action of the cytokines on the adrenal gland can account for the rapid in vivo effects of administered cytokines on plasma glucocorticoid levels. However, in circumstances involving prolonged increases in cytokines, such as chronic inflammation, direct actions of cytokines on the pituitary and/or adrenal may well play an important role.

Hypothalamic level

In contrast to the slow onset of the pituitary and adrenal effects of cytokines in vitro, intravenous and intraperitoneal administration of cytokines in vivo cause a prompt rise (within minutes) in plasma ACTH [61-63]. The acute effects of cytokines given peripherally are mainly exerted at the hypothalamic level, by enhancing the release of CRH [62-65]. The mediation by CRH of cytokines action is further suggested by the cytokine-induced increase in CRH levels in the hypophysial portal blood vessels [65] and by the observation that the acute ACTH-stimulating effect of cytokines is abolished by prior treatment with anti-CRH antibodies [62, 65]. Furthermore, cytokines have been shown to induce rapid (within 10-20 minutes) CRH release directly from incubated hypothalamic fragments in vitro [27, 66]. The importance of the PVN source of CRH for the acute effect of the cytokines is also illustrated by the effects of PVN lesioning. Indeed, electrolytic obliteration of the rat PVN markedly reduces the rise in plasma ACTH levels produced by a number of cytokines in vivo [67, 68].

IL-1 and IL-6 not only stimulate secretion, but also biosynthesis of CRH, as demonstrated by increases in CRH mRNA levels [69-71]. Further evidence for a direct hypothalamic effect is the capability of the hypothalamus to synthesize various cytokines. IL-1, IL-6 and TNFα have all been identified within the hypothalamus [72-75].

Several possibilities have been put forward to explain the mechanism by which cytokines initiate the release of CRH. Catecholamines, prostaglandins and NO seem all to be involved [3, 76-78]. In contrast to the cytokine effects at the pituitary gland level which are prostaglandin-independent [20], those produced at the hypothalamic level are clearly prostaglandin-mediated [76, 79, 80]. The NO pathway is also involved in this mechanism of action. NO restrains the response of the HPA axis to i.v. administration of cytokines and blockade of NO formation by L-NAME augments ACTH released by circulating IL-1β [77, 78].

**Penetration of cytokines into the brain**

Collectively, the rapid effects of cytokines on hypothalamic CRH secretion in vivo as well as in vitro, together with the decrease of plasma ACTH responses to cytokines produced by inhibiting the actions of CRH provide a strong case for the brain as a primary site of cytokine action in the acute stimulation of the HPA axis. However, being water-soluble proteins of relatively large molecular weight, cytokines are not expected to cross the blood-brain barrier (BBB). Many mechanisms have been proposed by which peripheral cytokines may gain access to the brain. The BBB consists primarily of nonfenestrated endothelial cells that are connected by tight junctions and thus form a continuous cell layer that has the permeability properties of a continuous plasma membrane [81].

**Loss of BBB integrity**

Loss of BBB integrity may occur during inflammatory insults to the brain. Such disruption of the BBB can increase BBB permeability and enable not only the passage of large peptides such as cytokines, but also aug-
ments the rate of entry of cells, such as macrophages, monocytes, lymphocytes and neutrophils which are capable of cytokine synthesis and secretion, but whose passage into the normal healthy brain is very limited. However, it is clear that the initial neuroendocrine effects of peripherally administered cytokines or LPS can be observed more quickly and at lower doses than can be accounted for by damage to the BBB.

**Saturable transport system**

It has been suggested that cytokines cross the BBB by a saturable transport system [82]. Such a transport mechanism has been described for IL-1α, IL-1β, IL-1Ra, IL-6 and TNFα [83]. This mechanism affords a means of cytokine entry into the brain, even when BBB integrity is not compromised. It should however be stressed that the passage of cytokines across the BBB is still a matter of controversy, since other authors think it is unlikely that cytokines can cross the BBB [84, 85]. Many have questioned whether the small amount of cytokines entering the brain via a saturable transport mechanism is physiologically relevant and can exert rapid effects, such as those observed after peripheral injection of cytokines. Nevertheless, it seems plausible that such a mechanism may play a significant role when peripheral blood levels of cytokines are elevated for longer period of time, for example during chronic inflammation.

**Circumventricular organs**

A BBB is, however, absent or defective in small areas of the brain, the so-called circumventricular organs, which are located at various sites within the walls of the cerebral ventricles. These include the median eminence, the organum vasculosum of the laminae terminais (OVLT), the subfornical organ, the choroid plexus, the neural lobe of the pituitary and the area postrema. Being an area of the hypothalamus that is richly supplied by vasculature devoid of a functional BBB, the median eminence is a potential target for activation of the HPA by cytokines [86, 87]. Circulating cytokines can enhance CRH secretion by interacting with the CRH nerve terminals and stimulating CRF release without directly stimulating CRF cell bodies in the PVN [88, 89]. There is however some controversy [90]. Another possible site of cytokine action is the OVLT [91]. Instead of being a portal of entry of cytokines into the CNS, the OVLT could be a kind of interface where the chemical messages of blood-borne cytokines are transformed into neuronal signals, so that secondary messengers might be evoked that transmit original signals to the preoptic area [92]. The second mediators released in the OVLT and acting on surrounding neurons with efferent projections to the PVN could be a cytokine [93] or prostaglandins [94], but it could also be other neuroregulators or neurotransmitters such as serotonin or norepinephrine [95, 96].

**Endothelial cells of the vasculature**

An emerging hypothesis is that circulating IL-1 may interact with IL-1 receptors on endothelial cells of the vasculature and thereby stimulate secondary molecules such as IL-1, nitric oxyde and/or prostaglandins, which can act locally to influence neurons [97-100].

**Activation of vagal afferent fibers**

Recent studies have suggested that the neuronal pathway may convey these peripheral messages to the brain and may represent another route through which cytokines may influence the CNS without gaining access to brain parenchyma, the BBB interface or even the circulation [101]. Indeed, the vagus nerve has been shown to be implicated in mediating the LPS- and cytokine-induced corticosterone secretion following systemic administration [102-106]. The vagus nerve appears to be important in signalling the brain specifically during intra-abdominal/peritoneal infection. This is evidenced by the fact that surgical subdiaphragmatic transection of the vagus (SDVX) attenuates the rise in plasma ACTH and corticosterone concentrations produced by intraperitoneal IL-1β [102, 107]. However, when either LPS or IL-1 is administered via routes other than into the abdomen/peritoneum, SDVX has no effect on the acute activation of the HPA axis [108-110].

**Cytokine synthesis within the brain**

Recent studies have demonstrated that cytokines are also generated within the brain, thus raising the question whether such brain-derived cytokines may influence HPA axis activity [31, 111, 112]. It is therefore possible that the neuroendocrine system of rodents undergoing an infectious or inflammatory process in the periphery is influenced by cytokines generated within the CNS [23, 113].

**PHYSIOLOGIC AND PATHOPHYSIOLOGIC RELEVANCES OF THESE INTERACTIONS**

What is the physiologic and pathophysiologic importance of these interactions between the immune and endocrine systems? Cytokines are involved in the control of all anterior pituitary functions and therefore in several clinically neuroendocrine responses to inflammation. These are the activation of the HPA axis and the inhibition of the pituitary-gonadal and pituitary-thyroid
functions that occur in patients with non-endocrine disorders [114].

As suggested by Munck et al [115], the inflammation-induced activation of the HPA axis may represent a potent negative feedback mechanism through which the immune system, by stimulating the HPA axis and therefore the production of the immunosuppressive glucocorticoids, avoids an overshoot of the inflammatory and febrile effect during the acute-phase response (fig. 1).

The production of glucocorticoids allows the body to have a tight control on the local immune response, inhibiting this defense mechanism from endangering the body's integrity. Because virtually all the components of the immune response are inhibited by the glucocorticoids, the consequence of the activation of the HPA axis, will be the suppression and/or modulation of inflammatory responses to toxins or invading organisms. Therefore, any dysfunction or disruption in the communication network of the HPA axis and the immune system might be expected to result in inflammatory disease. This has indeed been illustrated by studies in the Lewis rats, a strain of rats that are unable to respond to inflammation with an increased secretion of glucocorticoids because of a genetic defect in the synthesis of CRH [13]. The susceptibility of these rats to the development of arthritis is clearly associated with the inability of their HPA axis to respond adequately to inflammatory stimuli [116, 117]. Acute arthritis develops when these rats are injected with suspension of streptococcal cell wall polysaccharides, whereas it does not develop in the Fisher rats, in which the response of the HPA axis is normal. The administration of glucocorticoids to Lewis rats suppresses the inflammation, whereas in Fisher rats suppression of adrenal function by adrenalectomy or by the glucocorticoid antagonist RU 486 produces an enhanced susceptibility similar to that of susceptible Lewis rats [117]. Recent studies have shown that these abnormalities in the Lewis rats have parallels in humans. Patients with rheumatoid arthritis present a defective hypothalamic response to immune inflammatory stimuli and have indeed an inadequate cortisol production [118].

**CONCLUSION**

The presence of cytokines and their receptors within the endocrine system coupled to the presence of various hormones and their receptors on immune cells suggest that the immune and endocrine systems represent a totally integrated circuit of information that results from a sharing of common ligands and receptors. This common chemical language allows the 2 systems to exert profound and biologically relevant effects on one another. Such crosstalk is undoubtedly important to homeostasis, since these interactions can produce various appropriate adaptive responses when homeostasis is threatened. The clinical relevance of these immune-endocrine interactions are numerous as they affect all endocrine axes.

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