Review

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Corticotropin-Releasing Hormone: Interactions with the Immune System

Abstract

Communication between the neuroendocrine and immune systems is crucial to host defence in both health and disease. Stress adversely interferes with the function of the immune system but the mechanism of such stress-induced immunosuppression is not well understood. Corticotropin-releasing hormone (CRH) is a 41-amino residue peptide which primarily stimulates ACTH secretion. In addition, CRH integrates a series of responses during the stress response. Over the last few years increasing evidence has suggested that CRH, the major stress-integrating peptide, may also directly modulate immune system function. Thus, recent data have demonstrated that CRH acts centrally as an immunosuppressant agent independent of circulating glucocorticoids. This central immunosuppressive effect of CRH is mediated at least partly via the central stimulation of sympathetic outflow. At a peripheral level, the presence of CRH and CRH receptors within cells of the immune system, and its complex effects directly on immune function, suggest that CRH is intimately associated with communication between the neuroendocrine and immune systems.

Introduction

Despite the self-regulating properties of the immune system, there is increasing evidence that immune function is dependent upon and determined by extra-immune system influences, and in particular is subject to regulation or modulation by neural and/or endocrine processes [1]. Communication between the neuroendocrine and immune systems is crucial to host defence in both health and disease: its centrifugal limb provides a humoral means by which the central nervous system may 'fine-tune' the immune system, and thereby bringing to bear the influence of a variety of physical, emotional and environmental factors on immune function. It is well known that stress may adversely interfere with the function of the immune system; however, the mechanism of such stress-induced immunosuppression is not well understood [2]. Stress-induced hypersecretion of glucocorticoids does not entirely explain all of the effects of the central nervous system on immune function, and additional mechanisms appear to be involved [3]. Corticotropin-releasing hormone (CRH) is a 41-amino residue peptide which primarily stimulates ACTH secretion [4]. In addition, CRH integrates a series of endocrine and behavioural responses during the stress response. Over the last few years, increasing evidence has suggested that CRH, the major stress-integrating peptide, may also directly modulate immune system function: these immunoregulatory actions of CRH are highlighted by the present review.

Effects of Stress on Immune Function

As originally described by Selye [5], stress is the state of the organism produced by diverse noxious agents (stressors) threatening to alter its dynamic equilibrium or homeostasis. It involves an acute phase, occurring over minutes or hours (general alarm reaction), and a chronic phase when repeated acute challenges or stimuli are present for a number of days (general adaptation syn-

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drome). The concept that stress may predispose to physical illness is centuries old, based on clinical observations regarding individuals who became sick following stressful situations. It was well illustrated in 1919 that among tuberculous patients, phagocytic activity decreased during episodes of emotional distress [1], and there is now accumulating scientific evidence that psychological distress and psychiatric illnesses may adversely affect the function of the immune system [7]. Stress is widely considered to suppress immune responses; based on the effects of exogenously administered steroids [2] it is generally assumed that stress-induced immunosuppression is due to an elevation of endogenous adrenal glucocorticoids. In fact, glucocorticoids reduce the number of circulating macrophages and monocytes, lyse immature T-cells, inhibit IL-1 and IL-2 production and block phospholipase A2 activity [8]. Most studies have also shown that glucocorticoids adversely affect NK cell activity [9]. However, while stressful stimuli elevate adrenocortical steroids and stressful situations can influence immune responses, there are discrepancies in the evidence suggesting a causal relationship between these events. For example, the finding that adrenalectomised animals also show immunosuppression in response to stress indicates that stress-induced alterations of immunologic reactivity are not necessarily the result of an elevation of glucocorticoid activity, and strongly suggests the involvement of other factors in mediating stress-induced immunosuppression [3]. Many, if not all, of the known neuroendocrine-derived factors involved in the stress response have been shown to possess a diversity of actions on the immune system, acting either as immunosuppressant or as immunoenhancing agents. Among these neuroendocrine factors, CRH has recently attracted attention regarding its immunomodulatory actions.

CRH as a Coordinating Message for the Stress Response

The adaptive changes occurring in response to stressors are both behavioural and physical. Among the physical responses to stress, activation of the hypothalamo-pituitary-adrenal axis with consequent secretion of glucocorticoids is of greatest importance in maintaining homeostasis [10]. Glucocorticoid secretion is the end point of a neuroendocrine cascade of events generated in the central nervous system and transduced in the medial basal hypothalamus via CRH to a neurochemical signal specific for the secretion of ACTH [11, 12]. The presence of CRH is obligatory for a normal ACTH secretory response to most stimuli, with CRH acting either in a dynamic way to drive ACTH secretion, or in a permissive fashion to determine the 'set point' for the other intrinsically weaker ACTH secretagogues [13]. Hypothalamic CRH neurons are concentrated in the paraventricular nucleus (PVN) on each side of the brain, with this hypothalamic location being highly conserved among species [14, 15]. CRH neurons in the PVN are at the very centre of a variety of neural inputs of both extra- and intrahypothalamic origin [16]. The majority of extrahypothalamic inputs arise from the limbic system, the brainstem, and the subfornical organs, carrying information related to emotional, somatosensory, and chemical stimuli, respectively. From the PVN, CRH efferent pathways are directed, in addition to those projecting in the median eminence, to autonomic-related cell groups in the brainstem and spinal cord, and also to the limbic system. These latter pathways are responsible for the well-known integrative actions of CRH in co-ordinating the metabolic, circulatory, and behavioural responses which are adaptive in stressful situations. Central administration of CRH suppresses gonadal and growth axes, [17] increases activity of the sympathetic nervous system, with the expected metabolic and cardiovascular consequences [18], and results in a behavioural pattern of increased arousal accompanied by inhibition of feeding and sexual activity [19]. These observations are compatible

with the current view that CRH neurons in the PVN act as the central executive regulator of the response to stress.

Effects of Central CRH on Immune Function

Although the essential pathophysiology of stress-induced immunosuppression has not been fully delineated, there is now considerable evidence demonstrating that central CRH is an essential agent in stress-induced impairment of immune function independent of its effect on circulating corticosteroids. Experiments based on the electrical shock stress model convincingly demonstrated that stress-induced decrement of NK activity is reversed by pretreatment with a CRH antibody or a selective CRH antagonist [20, 21]. It is of note that peripheral administration of a CRH antibody, which completely blocked electrical shock-induced ACTH and corticosterone secretion, had no effect in reversing stress-induced immunosuppression; conversely, centrally administered CRH antibody, which did not affect ACTH and corticosterone secretion, completely blocked stress-induced reduction of

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NK activity [20]. This dissociation between corticosterone secretion and stress-induced decrease of NK activity provides good evidence that it is CRH secretion at a central site, and not the secretion of glucocorticoids, which is the key factor involved in stress-induced immunosuppression. This is further supported by a series of experiments by Jain et al. [21], who observed the same degree of immunosuppression after electrical shock stress, in both intact and adrenalectomised animals, which was partially reversed by a CRH antibody and a CRH antagonist. Experiments with intracerebroventricular injections of CRH have also reproducibly shown a significant reduction in both peripheral and splenic NK cell activity in Wistar rats [22, 23]. Moreover, recent data have demonstrated that T-lymphocyte proliferation and antibody responses to a specific T-cell-dependent antigen are also diminished by intracerebroventricular administration of CRH [24]. These findings provide further substrate for the hypothesis that CRH at a central site plays a key role in immunomodulation.

CRH may also be involved in a close-loop feedback system, as it has recently been shown that IL-1 β and interferon-induced immunosuppression are mediated through CRH [25, 26]. These substances are released from activated cells of the immune system, and IL-1 in particular possesses unequivocal CRH-releasing activity in the hypothalamus [27]. Since CRH antibodies prevent cytokine-mediated immunosuppression even in adrenalectomised animals, this provides good evidence that CRH participates as a negative feedback regulator of immune cell activation. However, while there is good evidence that central CRH may mediate immunosuppressive effects, the mechanism by which this peptide interferes with the immune system is not well understood. CRH-containing neurons project to the dorsal vagal complex and the intermediolateral column, sites of preganglionic autonomic motoneurons, and multiple extrahypothalamic sites implicated in autonomic regulation contain CRH-positive perikarya. These neuroanatomical connections provide the anatomical substrate for the well-established function of CRH as the signal for a series of autonomic nervous system reactions during stress [28]. Since there is good evidence that the sympathetic nervous system is involved in the control of immunity [see ref. 29 for review], it has been hypothesized that activation of the sympathetic nervous system may represent an important mediator of the immunosuppressive effects of CRH. Irwin et al. [30, 31], in a series of elegant experiments, showed that the suppressive effect of central CRH administration of splenic NK cell activity could be blocked by the ganglion inhibitor chlorisond-

amine, chemical sympathectomy, and p-adrenergic receptor blockade. The footshock-induced suppression of splenic lymphocyte responses to non-specific T-cell mitogens was also attenuated by p-adrenergic blocking agents [32]. In fact, catecholamines are significantly increased after the central administration of CRH, and the subsequent immunosuppressive effects are highly correlated with the observed increments in peripheral catecholamines [33]. These observations provide good evidence that activation of the sympathetic nervous system may be the key factor in CRH-induced immunosuppression. However, it should be noted that although activation of the sympathetic nervous system triggered by CRH results in significant immunosuppression in lymphoid cells *confined* to the splenic compartment, it remains unclear whether activation of the CRH-sympathetic axis is responsible for a series of effects on the redistribution and function of peripheral lymphocytes attributed to autonomic activation [34].

CRH Production by Cells of the Immune System

CRH is mainly located in the hypothalamus and the central nervous system. In extra-CNS sites, CRH is principally found in the placenta, adrenal medulla and the gonads [see ref. 35 for review]. CRH localised in these sites seems to exert a predominant paracrine action, the physiological significance of which remains unclear. In addition, placental CRH is released into the peripheral circulation and is responsible for the elevated plasma levels observed during the third trimester of pregnancy [36]. The role of these elevated CRH levels is currently unclear. It is unlikely that peripheral increments of CRH contribute to the activation of the hypothalamo-pituitary-adrenal axis, since peripheral CRH is bound to a CRH-binding protein produced by both the liver and the placenta [37]: CRH is therefore unique among other hypothalamic factors in that it has a peripheral binding protein which accelerates its clearance from the body, preventing activation of pituitary corticotrophs.

In addition, there is now good evidence that CRH is produced in human peripheral blood lymphocytes. In a preliminary study, Ritchie et al. demonstrated CRH immunoreactivity in lymphocytes [38], this finding subsequently being confirmed by Stephanou et al. [39], who demonstrated CRH immunoreactivity in human B and T lymphocytes. Biologically active CRH and CRH mRNA have also been demonstrated in rat thymus cells [40-42]. Nevertheless, it is still unclear whether the CRH immunoreactivity detected in cells of the immune system repre-

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sents a molecular form similar to hypothalamic CRH. In extracted rat inflammatory tissue, high-performance liquid chromatography studies have shown a molecular form of CRH similar to that found in the hypothalamus [43]. Thymic CRH immunoreactivity in the rat also appears chromatographically identical to hypothalamic CRH. However, chromatographic studies in human lymphocyte extracts more consistently demonstrated a molecule which differs from hypothalamic CRH. Consistent with the latter findings is the demonstration in human lymphocytes of CRH-like mRNA transcripts of 1.7 kb instead of the 1.5-kb mRNA species associated with human hypothalamic CRH [39]. The exact nature of the CRH-like product in human lymphocytes thus remains unknown at present, but it may be relevant that in some species there are several CRH-like genes producing highly homologous peptides which have been identified in both the brain and spleen [44].

In addition to the detection of CRH or CRH-like molecules in cells of the immune system, there is also evidence that CRH receptors are expressed in subpopulations of immune cells. As shown by Webster and DeSouza [45], high-affinity CRH binding sites are found in mouse spleen immune cells. As in the pituitary and brain, CRH binding in splenic cells is regulated by divalent cations and guanine nucleotides: autoradiographic studies have localised CRH binding sites to the region of splenic red pulp and marginal zone regions. Since macrophages rather than B or T lymphocytes predominate at these sites, the data are consistent with an expression of CRH receptors primarily on splenic macrophages. In fact, in a series of experiments using different fractionation methods, it has been shown that specific CRH binding was almost

exclusively confined to resident splenic macrophages [46]. Similar findings have also been reported by Aydhya et al. [47]; however, in addition to macrophages and monocytes they demonstrated specific CRH binding in the T-helper, but not T-suppressor or B, lymphocytes. It is currently unknown whether CRH is also expressed in this latter lymphocyte group in the process of immune cell activation. Molecular studies using probes of the recently cloned CRH receptor will clearly clarify this issue.

Direct Effects of CRH on Immune Cell Function

It has been reported that CRH produced by cells of the immune system clearly increases during inflammation. In inflammatory tissue extracts, immunoreactive CRH reaches levels as high as those found in the hypothalamus and the placenta [43]. However, the role of CRH released at inflammatory sites by cells of the immune system remains controversial. In vivo experiments using different models of tissue injury have shown both suppressive and enhancing effects of CRH on the inflammatory process. Increased exudation of plasma proteins by antidromic nerve stimulation, thermal injury or exposure to concentrated acids into the rat paw is significantly attenuated by pretreatment with pharmacological doses of CRH [48,49]. The mechanism of the anti-inflammatory action of CRH is currently not well understood, but hormonal changes are not involved as these anti-inflammatory actions of CRH are prevented by neither adrenalectomy nor by hypophysectomy [50]. As clusters of CRH binding sites are found on blood vessels and epithelial cells [51,52], an inhibitory action of CRH on vascular permeability has been proposed as the most likely underlying mechanism of its anti-inflammatory effects. It is of interest that a fragment of the carboxy terminal amino-acid sequence of the CRH molecule is highly homologous with a sequence found within the 'coil' region of intermediate filament proteins. Since synthetic peptides with sequences based on the carboxyl terminus of the human CRH molecules and a segment of the human type II keratin retained antiinflammatory activity, it has been suggested that either endogenous CRH or peptides originating from degraded filament proteins may directly counteract the immediate inflammatory response [53]. This hypothesis, however, is opposed by the findings of Karalis et al. [54], who showed that carrageenin-induced peritoneal inflammation in rats was significantly blunted by pretreatment with a CRH antibody. These latter findings imply a stimulatory role for local CRH in the inflammatory process. Although it is difficult to explain the differences observed, it may be relevant that pharmacological doses of CRH (human or ovine) have been used in these experiments demonstrating an antiinflammatory action.

In vitro experiments examining the effect of CRH on various parameters of the immune function have also produced contradictory results. CRH has been shown to augment T lymphocyte proliferation in peripheral blood mononuclear cultures; it also stimulates the secretion of IL-1, IL-2 and IL-6, and increases the expression of the IL-2 receptor in T lymphocytes [55-57]. Kavelaars et al. [58] also showed induction of IL-1 production by monocytes. In contrast to the above findings, Hagan et al. [59] showed an inhibitory effect of human CRH on IL-1 (and the consequent IL6 secretion) from human mononuclear cells in culture. In another study, exogenous systemic administration of CRH inhibited T lymphocyte proliferation of rat mononuclear cells [21]. Uncertainty also re-

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mains regarding the action of CRH on NK cell activity. In the study of Pawlikowski et al. [60], CRH produced a significant reduction in NK cell activity. In contrast, Leu and Singh [61] reported that CRH pretreatment of peripheral mononuclear cells caused a significant stimulation of NK cell activity. The reasons for these discrepancies are currently unclear, but it may be relevant that monocytes had been depleted in the former study. In fact, CRH-induced release of H α by monocytes may, at least in part, be responsible for the observed augmentation of NK cell activity, since it was attenuated by co-incubation with an anti- β EH antibody. It is of note that several groups

have demonstrated significant induction of cAMP levels by CRH in mononuclear cell cultures, suggesting that as in the pituitary corticotrophs the cAMP pathway constitutes the second messenger for the actions of CRH on immunocytes [47, 62]. Interestingly, cAMP has been shown to suppress immune function, including human NK cell activity [63, 64].

It is also of note that in vivo experiments with peripheral administration of CRH in experimental animals have shown a decrease in various parameters of immune cell function [21]. In view of the possible therapeutic relevance of this observation, CRH was injected in cortisol-deficient human subjects: this produced no change in var-

ious immune cell function parameters, including T-lymphocyte proliferation and NK cell activity [65]. It is unclear whether these species differences are related to the blocking effects of CRH binding protein found in humans but not in the rat.

Thus, based on the experimental evidence obtained so far, it is almost impossible to allocate CRH a role as either an immuno-enhancing or immunosuppressant agent in the periphery, although it certainly possesses immunomodulatory activity. It is likely that under different circumstances CRH exerts an either stimulatory or inhibitory action on immune cell function, but further experiments are required in order to clarify its physiological and pharmacological actions.

Summary

CRH has profound immunosuppressive effects acting via stimulation of the pituitary-adrenal axis, but may also act as an immunosuppressant agent independent of circulating glucocorticoids, in part at least via the central stimulation of sympathetic outflow. The presence of CRH and CRH receptors within cells of the immune system, and the complex effects of CRH directly on immune function, suggest that peripheral CRH is intimately associated with communication between the neuroendocrine and immune systems.

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