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PEPTIDE HORMONES SHARED BY THE NEUROENDOCRINE AND IMMUNOLOGIC SYSTEMS[1]

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While numerous studies have demonstrated that the neuroendocrine system can control immune functions, it is only now becoming apparent that the control is reciprocal in that the immune system can control neuroendocrine functions. In this paper, recent studies which seem to provide a molecular basis for this bidirectional communication are reviewed. These studies suggest that the immune and neuroendocrine systems represent a totally integrated circuit by virtue of sharing a common set of hormones, such as corticotropin, thyrotropin, and endorphins, and their receptors. Possible hypothalamic and immunologic controls of this circuitry are discussed.

Much anecdotal evidence has accumulated over the years which suggest that the neuroendocrine system can control immune function. To date, a number of in vivo experimental observations have been made to support such a notion. These include but are not limited to classical Pavlovian conditioning of immune responses (for review, see Reference 1), positive and negative effects of brain lesioning on immune responsiveness (2, 3), and the well-known adverse effects of "stress" on the immune system (for a review, see Reference 4). Until recently, a biochemical rationale for such observations has been lacking. It is our contention that the findings of neuroendocrine peptide hormone production by cells of the immune system and hormone receptors on such cells provide the molecular basis for these interactions. In this article, we will summarize the evidence for hormones and their receptors in the immune system and suggest how they are controlled by and coupled to both immunologic and neuroendocrine functions. Lastly, the inherent bidirectionality of immune and neuroendocrine communication which is an obvious outcropping of these observations will be discussed with regard to how this may alter current concepts on the functions of the immune system.

Production of neuroendocrine peptide hormones by the immune system. Initially, virus infection of human peripheral blood cells was observed to elicit the coordinate expression of interferon-α (IFN-α), corticotropin (ACTH),[2] and endorphins (5, 6). Other IFN-α inducers such as tumor cells (6) and bacterial lipopolysaccharide (LPS) (D. H. McMenamin, E. M. Smith, and J. E. Blalock, unpublished observation) have also been shown to cause the production of these same peptides by both human leukocytes and mouse spleen cells. Subsequently, a subpopulation of mouse spleen cells (probably macrophages) was shown to constitutively produce ACTH, β-endorphin, and possibly their precursor pro-opiomelanocortin (POMC) (7). The leukocyte-derived ACTH and endorphins were shown to be identical to their pituitary gland counterparts in terms of bioactivity, antigenicity, m.w., and retention time on reverse phase high pressure liquid chromatography (5–9). Hormone production by the immune system is not limited to the POMC-derived peptides but now includes immunoreactive thyrotropin (TSH) (10), vasoactive intestinal peptide (VIP) (11–13), and somatostatin (13). This laboratory is currently evaluating the spectrum of peptide hormones which are made by the immune system and the stimuli which elicit their production. Preliminary studies using immunofluorescence, antibody affinity chromatography, and gel filtration techniques suggest that, depending on the stimulus, human leukocytes and mouse spleen cells may have the potential to produce chorionic gonadotropin (CG), growth hormone (GH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) (E. M. Smith, D. H. McMenamin, K. L. Bost, and J. E. Blalock, unpublished observations). Therefore, although further study is obviously required, at present, it appears that the immune system may produce many if not all of the known neuroendocrine peptide hormones.

Control of leukocyte production of neuroendocrine peptide hormones. At least two factors seem to determine the type of hormone which is produced by leukocytes. One is the stimulus and the second is the cell type. For instance, immunofluorescence studies with specific antisera have shown that while Newcastle disease virus (NDV) is a stimulus which 100% of human blood mononuclear cells recognize and which leads to ACTH and endorphin production by all of the cells (6), LPS elicits this response in only about 25% of the cells (possibly B cells and macrophages). Thus, one can infer that since T cells constitute a portion of the 100%, they have the potential to produce POMC-derived peptides in response to NDV but may not respond to LPS. Perhaps more interestingly, while T cells have the potential to produce ACTH and endorphins, they produce TSH in response to the T cell mitogen, staphylococcal enterotoxin A (SEA) (10). Contrariwise, we have not observed TSH production in response to a B cell stimulus such as LPS. Therefore, considering ACTH vs TSH production by T cells, the stimuli (NDV vs SEA) seem to determine the response. The role played by cell type seems evident in the observation that regardless of the stimulus only a subpopulation of T cells seems to have the potential to produce TSH. While the above arguments are largely of an infer-

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[2] Abbreviations used in this paper: POMC, pro-opiomelanocortin; VIP, vasoactive intestinal peptide; NDV, Newcastle disease virus; SEA, staphylococcal enterotoxin A.

ential nature and require confirmation with pure cell types, they nonetheless seem to suggest the importance of at least these two factors in the control of peptide hormone production.

A final control element which was quite unexpected was our observation of a possible mechanism for central nervous system regulation of leukocyte production of peptide hormones. While our original bias was that immune system production of neuroendocrine peptide hormones would be limited to induction by immunostimulants, we observed that a centrally mediated "stressor" (insulin-induced hypoglycemia) caused an increase in the percentage of ACTH-positive leukocytes in normal short children (W. J. Meyer, E. M. Smith, A. C. Morrill, A. Cavallo, and J. E. Blalock, submitted for publication). Since insulin-induced increases in the POMC-derived peptides (ACTH and endorphin) are mediated through hypothalamic release of CRF, we tested the effect of CRF on leukocytes. CRF was observed to cause the de novo synthesis of immunoreactive ACTH and β-endorphin by human peripheral blood cells (14). Interestingly, like the effect in the pituitary gland, this CRF-mediated leukocyte response could be suppressed by the synthetic glucocorticoid hormone, dexamethasone. Thus, not only are leukocyte-derived ACTH and endorphins directly induced by immunostimulation, but they also may be positively regulated by the central nervous system via CRF release.

Immunoregulatory effects of peptide hormones that are common to the immune and neuroendocrine systems. The observations of neuroendocrine peptide hormones in the immune system raised the distinct possibility that, in addition to their classical neuroendocrine actions, these peptides may also function as immunoregulatory agents (i.e. lymphokines). With this idea in mind, whenever a peptide hormone is found to be produced by leukocytes, the bona fide peptide is then tested for lymphokine activity. As was mentioned previously, two different stimuli, virus infection and a T cell mitogen, elicited the production of different hormones, ACTH-endorphins and TSH (5, 6, 10). Interestingly, the pituitary hormones in turn caused different lymphocyte responses. ACTH and α-endorphin suppressed the number of antibody-producing cells following in vitro immunization of mouse spleen cells, while TSH enhanced this response (15, 16). ACTH also suppressed IFN-γ production (17). Both TSH and ACTH acted on early events during the antibody response. At present, we can only assume that the TSH effects occurred through a TSH receptor on spleen cells. In the case of ACTH and α-endorphin, however, spleen cells were observed to have high affinity receptors for both of these hormones (15). Thus, it is tempting to speculate that, in addition to possible signaling between the immune and neuroendocrine systems, the same set of hormones and their receptors may be used for intraimmune system regulation. In this regard, it is interesting to note that TSH essentially behaves as a B cell growth (BCGF) or differentiation factor (BCDF) (10). Whether or not the immunoreactive TSH induced by T cell mitogens in lymphocytes (10) is a BCGF or BCDF remains to be determined. However, it is provocative that, while the exact number of species and composition of BCGF is still clouded, some species have m.w. similar to those of the α or β chain of TSH.

A hypothalamic immunopituitary adrenal axis. To test the possible in vivo significance of leukocyte-derived neuroendocrine peptide hormones, the following types of experiments were performed. Classically, stress responses (as determined by increased circulating glucocorticoid hormone levels) were thought to be mediated and regulated entirely by the hypothalamic pituitary adrenal axis through the following cascade (18). Central or peripheral nervous system recognition of "stressors" (cognitive stimuli) leads to release of CRF from the hypothalamus. The CRF acts on the pituitary gland to elicit increased production and release of ACTH. Circulating ACTH then causes an adrenal gland steroidogenic response and the resultant glucocorticoid hormone feedback to shut off further ACTH production (Figure 1). Our findings of virus induction of immunocyte- or leukocyte-derived ACTH suggested that, under certain leukocyte stimuli, the pituitary gland should not be required for an ACTH-mediated stress response. This concept was tested by determining whether virus-infected hypophysectomized (pituitary-less) mice would have an increase in ACTH activity and thus show an elevated corticosterone concentration. In fact, Newcastle disease virus infection of hypophysectomized mice caused a time-dependent increase in corticosterone, and immunoreactive ACTH was detectable in the spleens of these animals (9). Interestingly, like the pituitary gland, spleen production of ACTH was controlled by negative feedback via corticosteroids. A similar observation has been reported recently in a human patient (19). This individual presented with the clinical and laboratory features of ectopic ACTH syndrome. No ACTH-producing tumor was found which could account for the excess levels of this hormone. However, an inflammatory lesion was observed in which leukocytes were positive for ACTH. Removal of the inflammatory tissue returned the circulating ACTH levels to normal. Taken together, these findings strongly suggest the existence of an immunoadrenal axis in which leukocytes serve a sensory function for stimuli such as viruses or other inflammatory agents. This information is then conveyed to the adrenal glands by leukocyte-

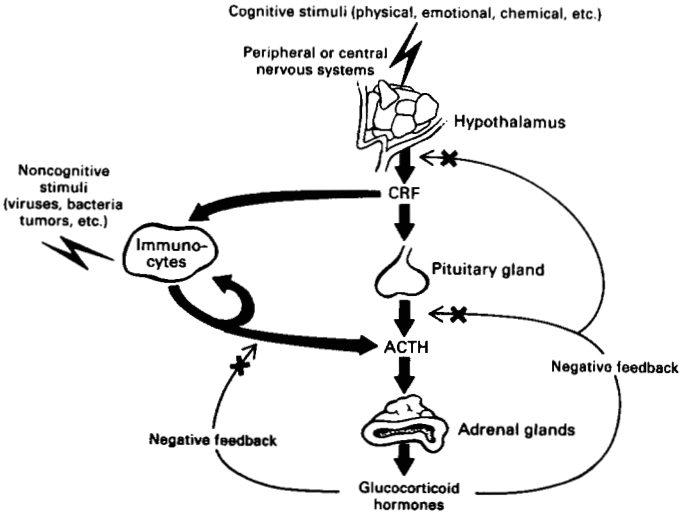

Figure 1. A hypothalamic immunopituitary adrenal axis. With the exception of feedback of immunocyte ACTH onto immunocytes, the bold arrows represent positive control while the thin arrows represent feedback inhibition. The exception was done to indicate that while ACTH suppresses interferon and antibody production, its actions on other functions such as its own production are unknown and are therefore possibly positive.

derived ACTH. Adrenal glucocorticoid hormones can in turn shut off further ACTH production (Figure 1).

Possible central or peripheral nervous system control of the immunoadrenal axis via the hypothalamus was recently suggested by two observations. One was the observation that insulin-induced hypoglycemia, which in normal short children causes a hypothalamic CRF-mediated increase in pituitary ACTH, also caused an increase in leukocyte ACTH in these individuals (W. J. Meyer, E. M. Smith, A. C. Morrill, A. Cavallo, and J. E. Blalock, submitted for publication). Secondly, CRF was directly observed to induce leukocyte ACTH in vitro, and this response was suppressed by dexamethasone (14). Thus, not only do leukocytes directly respond to immunostimulants and produce ACTH, but they may also similarly respond to cognitive stimuli via hypothalamic CRF (Figure 1). We assume that this later response may occur as leukocytes pass through the portal circulation between the hypothalamus and the pituitary gland. Immunocytes would then be regulated by either pituitary or leukocyte ACTH as well as adrenal glucocorticoid hormones. In total, these results suggest that, as well as pituitary adrenal interaction, the hypothalamus may also regulate the immunoadrenal interaction and therefore actually constitute a hypothalamic immunopituitary adrenal axis. As more is known of the production of neuroendocrine peptide hormones by the immune system and the possible regulation of these molecules by immunostimulants and hypothalamic factors, we believe that Figure 1 may serve as a model for other immune and neuroendocrine interactions. For instance, when considering immune system, pituitary, and thyroid interactions, one might hypothetically replace CRF with thyrotropin-releasing hormone (TRH), virus, or LPS with staphylococcal enterotoxin A which induces TSH, the adrenal gland with the thyroid, and glucocorticoid hormones with T3 or T4 in a putative hypothalamic immunopituitary thyroid axis.

Conclusions and predictions. Based on the above findings, it seems that the immune and neuroendocrine systems actually represent a totally integrated circuit that results from a shared set of signal molecules (hormones) and receptors. This, we believe, accounts in a biochemical way for the observation of numerous in vivo interactions between these systems. Such a view leads one to think that a primary function of the immune system is to serve a sensory function (20). It has receptors and senses noncognitive stimuli (bacteria, viruses, antigens, etc.) that are not recognized by the central nervous system. This information is then relayed to the neuroendocrine system by leukocyte-derived hormones, and a physiologic and immunologic change results. Contrariwise, central nervous system recognition of cognitive stimuli results in similar hormonal information being conveyed to and recognized by hormone receptors on leukocytes, and an immunologic and physiologic change results. It seems probable that the sensory function of the immune system may mimic the neuroendocrine system in terms of a given stimulus eliciting a particular set of hormones, and thus physiologic responses. If this proves to be the case, then the pathophysiology that is associated with a particular infectious agent, antigen, or tumor could be related to the particular hormone or set of hormones that are produced by the immune system. For instance, leukocyte ACTH may be responsible for the well-known increase in circulating corticosteroid levels observed during viral and bacterial infections. A thorough understanding of this circuitry will require knowing the number of different hormones that are produced by the immune system and the stimuli by which they are elicited. Ultimately, it is hoped that additional knowledge of the immune and neuroendocrine circuitry will provide new insights into neuroendocrine and psychologic disorders, as well as the pathophysiology of infectious diseases and tumors. Such knowledge could suggest many novel diagnostic, prophylactic, and therapeutic approaches to human disease. As one example, pituitary ACTH deficiencies could theoretically be corrected by exogenous administration of CRF which in turn would elicit leukocyte ACTH.

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