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NEUROIMMUNOLOGY AND LYMPHOCYTE HOMING AND ADHESION

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ABSTRACT

Physical and mental health are strongly connected, with one affecting the other. Neuroimmunology investigates the physiological relevance, the pathological significance, and the cytological and biochemical mechanisms of the communication between the nervous and immune systems. The migration of lymphocytes to and from lymphoid organs is essential to the physiological regulation of the immune response, and the efficiency of cellular immune processes depends largely upon the distribution of and interaction between lymphocytes. This process is dependent upon specific homing and adhesion membrane receptors. In this paper, we report that neuroendocrine elements modulate lymphocyte homing and adhesion.

KEYWORDS: *white blood cells, neuroimmunology, lymphocyte adhesion molecules, lymphocyte homing receptors, immune response*

INTRODUCTION

Neuroimmunology, a field of psychoneuroimmunology, seeks to define and characterize the physiological relevance, pathological significance, and cytological and biochemical mechanisms of the communication between the nervous and immune systems, which interact together (1). Neuroendocrine mediators include cholinergic and catecholaminergic neurotransmitters, as well as others such as opioids and growth factors, and steroids and other hormones (2). These factors modulate immune responses, and immune mediators such as cytokines, colony stimulating factors, and other immune products, modulate neuroendocrine processes. Immune cells and neurons share receptors, gene products, and signal transduction mechanisms (3). Evidence suggests that neuroendocrine elements modulate lymphocyte homing and adhesion, which is discussed below.

Lymphocyte Homing and Adhesion

The efficiency of cellular immune processes depends largely upon the distribution of and interaction between lymphocytes since the migration of lymphocytes to and from lymphoid organs is central to the physiological regulation of the immune response (4). Lymphocyte homing is lymphoid organ-specific, lymphocyte population-specific, and lymphocyte state of maturation and state of activation-specific. Lymphocyte homing is dependent upon specific ligand/receptor interactions (5). Lymphocytes express "homing" membrane receptors, which mediate cellular and tissue

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immunity. Cells of high-endothelial venules (HEVs) express tissue-specific "vascular addressins", the endothelial ligands for homing receptors (6). Homing receptors include the leukocyte adhesion molecule-1 (LAM-1) family, represented by Leu8/TQ1 (human homologue of the murine homing receptor, Mel-14), and the homing-cellular adhesion molecule (H-CAM) family, including the CD44 cluster (7).

Cellular immune responses, including homing, are modulated by cell-to-cell interaction which is directed in part by adhesion receptors. Adhesion molecules comprise two important members of the integrin family: the leukocyte function-associated antigens (LFAs) and the very late antigens (VLAs) (8). LFA-1 consists of two membrane clusters (CD11a and CD18) and is found primarily on lymphocytes. Related membrane clusters (LFA-2: CD11b/CD18 and LFA3: CD11c/CD18) are expressed in higher density on macrophages (9). VLA-4 also consists of two membrane clusters (CDw49d and CDw29) and is expressed primarily on lymphocytes (10). The expression of homing receptors and adhesion molecules is finely regulated by cytokines and other factors, including neuroendocrine products (11-13).

The tissue-specific nature of interactions between lymphocytes and HEVs mainly depends on which homing and adhesion molecule is expressed (14). The anti-Leu8 antibody effectively prevents binding to peripheral lymph node-derived HEVs, and anti-CD44 and anti-CD49d antibodies specifically block binding to mucosal-derived HEVs (15). Differential expression of homing and adhesion molecules is also evident in virgin and memory CD4 cells and directs their specific patterns of migration (16). Virgin CD4 cells are characterized by both the cluster of differentiation CD4 and by the high molecular weight isoform of the common leukocyte antigen (p220, CD45RA) (CD4+ CD45RA+), and express relatively few homing receptors (17). In contrast, memory CD4 cells, which lose CD45RA upon exposure to an antigen during the post-thymic process of maturation to memory cells (18), express homing receptors in higher density (19).

Experimental Models in Lymphocyte Homing and Adhesion

There is a cyclic pattern of variations in cellular immunity that results from the interactions of the immune and nervous systems (20,21). Steroids show marked diurnal fluxes and have several immunoregulatory functions, including lymphocyte (preferentially CD4 cells) homing and redistribution (22). In fact, in healthy donors, diurnal changes in the number of circulating lymphocyte populations are in a consistent negative phase relationship with cortisol circadian variations (23,24).

Certain neuroendocrine changes that occur in reaction to stressful stimuli disrupt diurnal fluxes in cellular immunity (25). For example, research has shown that the anxiety from the experience of a major earthquake results in significant changes in the number and percentage of circulating lymphocytes involved in natural killer (NK) cytotoxic events (NK-acting; CD16 + or CD56 +) in healthy adults, which could perhaps be consequential to an activation of the endogenous opioid system (26). Stimulation of the neuroendocrine system associated with strenuous exercise also leads to a rise in circulating CD56 + cells and in NK activity immediately after cessation of exercise (27). These values decrease to below pre-basal levels at 120 minutes after exercise, and normalize by 20 hours, regardless of sex or level of physical training (28). Studies have shown that physical stress results in an immediate (i.e., within minutes of cessation of exercise) and significant rise in circulating CD16+ and CD56+ cells, and an elevation in NK activity (29). These outcomes are in part prevented by prior intravenous administration of the opioid receptor antagonist naloxone, thus implicating the endogenous opioid system (30). Taken together, these findings suggest that opioids are important in the specific modulation of lymphocyte homing and distribution (31).

It is still unknown whether these outcomes can be primarily attributed to vasodilation and increased tissue permeability or to modulation of lymphocyte homing and adhesion receptors. Ongoing studies are testing the role of opioids and other neuroendocrine products in the regulation of expression of homing and adhesion molecules and their ligands (32). Some studies show that established human lymphoid lines express constitutive levels of CD18, the beta-chain of LFA-1 (33). CD18 expression is unimodally "bright" in some lines, but bi-modally "dim" and "bright" in other lines. Mitogenic stimulation shifts CD18 expression from "bright" to "dim" in all tested cell lines, without altering the relative number of cells positive for this marker. Activation with atropine shifts CD18 into the "dim" region; activation with steroids fails to change CD18 expression compared to unstimulated cells; and activation with proopiomelanocortin gene products (e.g., beta-endorphin, ACTH) has mixed effects on CD18 expression (34). The Kolmogorov-Smirnov statistic indicates that these shifts in fluorescence intensity are significant. However, further research should be continued to confirm these results.

Clinical Research Models in Lymphocyte Homing and Adhesion

The relationship between hormones and cellular immunity has been effectively studied in groups of patients characterized by alterations in neuroendocrine or immune regulation. For instance, administration of dexamethasone results in a significant decrease in the number and percentage of circulating virgin, but not memory CD4 cells in normal

subjects. The number and percentage of virgin CD4 cells are not altered in patients with anorexia nervosa, who have dysregulated cortisol levels (e.g., elevated plasma cortisol), following dexamethasone administration (35).

Studies have shown that the administration of dexamethasone fails to reduce the number of glucocorticoid receptors on peripheral blood mononuclear cells and the lymphoproliferative response of these cells to phytohemagglutinin in dexamethasone-resistant (i.e., cortisol non-suppressors) patients with major depression (36). More than half of the patients suffering from depression have dysregulated steroid hormone secretion, with elevated levels of plasma cortisol and cortisol non-suppression by dexamethasone (37). This may also occur in aged patients who manifest alterations in both neuroendocrine and immune regulation (38). Clinical studies are investigating the neuroimmune regulation of lymphocyte homing and adhesion in aged subjects and patients with Alzheimer's disease (39).

Certain groups of patients with autoimmune diseases show both neuroendocrine and immune dysfunction (40). Animal models have been successfully utilized to clarify these mechanisms. For example, the non-obese diabetic mouse is a spontaneous autoimmune animal model for human type I (insulin-dependent) diabetes mellitus and provides a unique opportunity to study the immune process leading to beta-cell destruction (41). This model is very useful because it offers the possibility to conduct well-controlled studies with precise immune and neuroendocrine endpoints and is particularly relevant to studies of lymphocyte distribution and homing because the progressive infiltration of pancreatic islets by lymphocytes is characteristic of the inflammatory process that leads to clinical diabetes. Adoptive transfer studies have shown that the homing of T cytotoxic/suppressor lymphocytes (CD8+) to the pancreas is mediated in part by CD4 cells, however more research is needed to clarify the role of adhesion and homing receptors (42). Thus, lymphocyte-lymphocyte interactions are essential events in the development of diabetes, and elucidation of the mechanisms of the adhesion and homing receptors involved in these processes will lead to greater understanding of this disease, and to the development of treatment interventions.

Infection with human immunodeficiency virus (HIV) is associated with spontaneous LFA-1-dependent fusion of infected lymphoid and myeloid cells (i.e., syncytium formation) (43). HIV infection can also lead to severe neuroendocrine disease. Levels of cortisol are often elevated in some HIV+ patients, while others have circulating cortisol levels lower than the normal range (44). This could be an outcome of HIV-induced adrenopathy resulting from cytomegalovirus opportunistic infection. Twenty four-hour circulating levels of two adrenocortical androgen steroids, dehydroepiandrosterone and its sulfate derivative, are significantly lower in HIV + patients compared to control subjects. The circadian fluxes in these three steroids are flattened in HIV disease, as well as diurnal patterns of circulating CD4 cells (45).

Taken together, these findings, obtained from varied models of clinical research, support the hypothesis that the interaction between the neuroendocrine and immune systems is physiologically relevant and pathologically significant, particularly in the context of lymphocyte adhesion and distribution.

CONCLUSIONS

There is a strong connection between physical and mental health. The field of psychoneuroimmunology seeks to define and characterize the interactions between the environment, the brain, the hormonal system, and resistance to disease. Intense research has been focused on the interaction between neurons and immune cells.

The interaction between the endocrinal system and immune cells is present in diverse situations. For example, in healthy subjects, fluctuations in plasma levels of cortisol are in a negative phase relationship to those of immune cells. When cortisol levels are higher (mid-morning), the number of immune cells is lower. Studies suggest that this interrelationship does not occur in HIV+ patients. These relationships may also be disrupted in certain groups of psychiatric patients, in the elderly, or in normal subjects following strenuous exercise or psycho-emotional stress. However, in humans, lymphocyte subsets in the blood do not necessarily mirror lymphocyte distribution in other immune compartments. Therefore, further research should be continued in this field to improve the understanding of lymphocyte homing in neuroimmunology.

Conflict of interest

The authors declare that they have no conflict of interest.

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