REGULATION OF SPLENIC LYMPHOCYTE ACTIVITY BY THE HYPOTHALAMIC-SYMPATHETIC NERVOUS SYSTEM IN THE RAT : THE HYPOTHALAMIC ACTIVE SITE AND PEPTIDES

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It has been recognized that peripheral immune functions are modified by the central nervous system through both the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, as typically exemplified by immunosuppression induced by various types of stressors. In the present study, to investigate the possible role of the active sites and regulatory factors in the hypothalamus during stress situations, I examined splenic lymphocyte proliferation after electrical stimulation of the hypothalamus or intracerebroventricular (icv) injection of some peptides in rats. Particularly, I focused on the role of sympathetic nervous system in the hypothalamic regulation of splenic lymphocyte activity.

1) To investigate the role of the hypothalamus in the control of peripheral immune functions, I examined the effect of electrical stimulation of some hypothalamic regions on the mitogenic activity (ConA response) of splenic lymphocytes in rats. Stimulation of the ventromedial hypothalamus (VMH) showed a remarkable decrease in the ConA response, whereas stimulation of other hypothalamic regions including the paraventricular nucleus did not show any significant effects. A similar suppressive effect of VMH stimulation was also found in adrenalectomized rats, suggesting a minor role of the adrenocortical system in mediating the VMH-effect on spleen. In contrast, pretreatment with a ganglionic blocking agent, chlorisondamine, or a β-adrenergic receptor antagonist, propranolol, or surgical severing of the splenic nerves reversed the suppressive effect of VMH stimulation. These results indicate that VMH stimulation suppresses the C on A response through the activation of sympathetic nerves via the β-adrenergic pathway.

2) The VMH is known as a region where various neuropeptides and their receptors are present. In an attempt to determine which factors activate the VMH, next, the effects of intracranial administration of some peptides on splenic lymphocyte proliferation were examined in rats. Urocortin is a recently identified 40-amino acid peptide homologous to fish urotensin and mammalian corticotropin-releasing hormone (CRH). Leptin is one of the key afferent signals that regulate food intake and energy expenditure by acting on specific receptors in the VMH. To assess the possible role of urocortin and leptin, the

effects of icv administration of these peptides on C on A response were examined. Icv injection of urocortin or leptin produced a marked decrease in C on A response. The suppressive effect of both urocortin and leptin was abolished by pretreatment with chlorisondamine or propranolol, but not by adrenalectomy. The suppressive effect of leptin was completely abolished either by surgical severing of the splenic nerves or by icv injection of an antibody against CRH, but only partially by an anti-urocortin antibody. Additionally, the suppressive effect of urocortin was prevented by the anti-CRH antibody, while that of CRH was not prevented by the anti-urocortin antibody. These results suggest that urocortin, CRH and leptin are important neuropeptides involved in the hypothalamic control of peripheral immune functions such as stress-induced immunosuppression. The suppressive effect of leptin is mediated through the activation of the CRH (urocortin)-sympathetic nervous system.

3) To elucidate possible involvement of leptin, CRH and urocortin in the stress-induced immunosuppression, the effects of respective antibodies on splenic lymphocyte proliferation after footshock stress were examined. Icv injection of an antibody against CRH completely abolished the stress-induced suppression of the C on A response. However, antibodies against leptin and urocortin showed no effect. Moreover, the serum leptin level was decreased by immobilization and footshock stress. These results suggest that the central CRH, but not urocortin and leptin, is a factor regulating the peripheral immune activity through sympathetic nerve activation under stress-conditions.

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SYMPATHETIC REGULATION OF HEPATIC INTERLEUKIN EXPRESSION DURING NON-INVASIVE STRESS

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IL-1 and IL-6 are the major cytokines produced in the liver, which are involved in some specific responses in this organ during the acute phase of inflammation. Recently, evidence has accumulated suggesting that the production of IL-1 and IL-6 is also increased during various non-invasive stress such as immobilization and exercise. In this thesis, to