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Neuropeptides: Active Participants in Regulation of Immune Responses in the CNS and Periphery

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Although traditionally the nervous and the immune systems have been considered to be independent, in the last two decades it has become apparent that they are linked through a strong bidirectional connection. Both systems produce soluble mediators such as cytokines, chemokines, neuropeptides and neurotransmitters, and share receptors for these molecules that allow them to respond in a specific manner. However, since the biological functions of the two systems are quite different, the soluble mediators have unique consequences in cells of the nervous and immune system.

Anatomical and functional studies established the existence of several pathways connecting the CNS with the immune system in the periphery. The first to be identified, the hypothalamus-pituitary-adrenal axis (HPA axis) has been well characterized in numerous studies [reviewed in (Sternberg, 2006)]. A cholinergic anti-inflammatory pathway involving the efferent vagus and innate immune cells, primarily splenic and liver macrophages, was shown recently to play a major role in preventing the detrimental effects of proinflammatory cytokine release in sepsis, endotoxemia, and other inflammatory conditions [reviewed in (Tracey, 2007)]. In addition, neuroimmune interactions occur through peripheral nerve fibers innervating the lymphoid organs, and are mediated by neurotransmitters and neuropeptides [reviewed in (Ganea, 2007; Gonzalez-Rey et al., 2007; Kin and Sanders, 2006)].

Most studies related to the anatomical link between the CNS and the immune system, were based on the identification of various types of innervation in thymus, spleen and lymph nodes. However, this represents a serious limitation, since effector immune cells, both for innate responses (macrophages, dendritic cells, monocytes) and adaptive immune responses (T and B lymphocytes) are located mostly outside the classical immune organs. Therefore, the autonomic and sensory innervation in skin, gut and lungs – major homing sites for effector immune cells, plays as important a role in controlling the immune response as in spleen and lymph nodes.

A second consideration that has to be taken into account is the fact that in certain conditions immune cells themselves express and secrete neuropeptides/neurotransmitters, in a mirror image of CNS glial cells producing cytokines and chemokines. Does this mean a return to the concept of independent nervous and immune systems? On the contrary, what it means is that depending on the circumstance, two separate sources for cytokines/chemokines operate in the CNS, *i.e.* immune cells and activated glial cells, and in a similar fashion, two sources for

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neuropeptides/neurotransmitters function in the periphery, *i.e.* the innervation and activated immune cells. A third neuropeptide source is provided by the HPA axis, as some neuropeptides are released as hormones or prohormones and arrive in the lymphoid organs via the circulation.

Regardless of their exact *in vivo* origin, neuropeptides have been shown in a number of studies to affect both innate and adaptive immune responses, with significant consequences for anti-microbial, anti-viral and autoimmune responses, raising the possibility of their use as future therapeutic agents. Since the number of immunoregulatory neuropeptides is quite large, the present series consists of a limited selection of manuscripts reporting original, primary data that are representative of immunomodulatory neuropeptides in physiological and pathological conditions.

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