A communication from the immune system to the nervous system

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The mammalian immune system is ranked next to the nervous system in complexity. Both are involved in processing and responding to signals from the environment. The nervous system responds to a wider variety of stimuli and in a complex manner, made possible by its anatomy and higher-order interactions of the component cells. The immune system has traditionally been studied in isolation and was thought to be regulated only by interactions among its component cells. On the other hand, advantages of any cooperativity between the nervous system and the immune system would be several. Neuromodulation of the immune system has been the subject of much scientific investigation in the last fifteen years, and both feedback and feed-forward regulation of the immune system by the nervous system have been established. Research in this area, called psychoneuroimmunology, has been reviewed recently by Ader *et al.*[1] and Blalock[2]. There is much clinical and experimental literature concerning the effects of psychological states and stress in the modulation of immune function, and interactions among neural, endocrine and immune processes. Receptors for various neuropeptide hormones have been shown on immune cells, and activation and inhibition of lymphocytes by different neuropeptide hormones have been tested *in vitro*. The *in vitro* production of neuropeptides by immune cells has also been shown. However, a physiologically functional communication from the immune system to the nervous system was yet to be established.

Stein *et al.*[3], in their recent study designed to investigate pain under stress, show a functional communication from the immune system to the nervous system. In experiments with rats the opioids β-endorphin and [Met]enkephalin were shown to be produced by immunocytes at localized areas of experimentally induced inflammation. The opioids are induced by an external stimulus (cold-water swim). These opioids, by their interaction with opioid receptors at peripheral terminals of primary afferent neurons, bring about antinociception (nociception is the sensation of pain).

Nociception is measured by the paw pressure threshold (PPT) value[4]. A blunt wedge-shaped piston with tip diameter 1.75 mm was used to apply incremental pressure (in steps of 16 g sec^{-1}) to the dorsal aspect of the hind paw of experimental rats. The pressure necessary to cause the animal to attempt removal or remove its paw from the test apparatus was taken as PPT.

After a cold-water swim at 1–2°C for 1 minute, the PPT value increased significantly on the inflamed paw. The increase was dose-dependently blocked by prior local, but not by systemic, administration of naloxone, a classical opioid antagonist[5], and anti-id-14, a monoclonal antibody which acts as a functional antagonist at opioid receptors. Opioid receptors were visualized in non-inflamed and inflamed paws by immunocytochemistry. Immunostaining of opioid peptides in subcutaneous tissue revealed macrophages, monocytes, mast cells, lymphocytes and plasma cells staining for β-endorphin in inflamed but not in non-inflamed tissue. Pretreatment of animals with cyclosporin A, a suppressor of immune function, led to blocking of cold-water-swim-induced antinociception in inflamed paws. From the above it is clear that the release of opioids by the immunocytes acts as a signal to decrease the sensation of pain. Thus a physiologically functional communication from the immune system to the nervous system is evident.

Earlier studies have shown the *in vitro* production of opioids by immunocytes[6]. Receptors for these have been shown on lymphocytes, and the latter are stimulated to proliferate in the presence of opioids *in vitro*. The production of opioids by immunocytes leading to antinociception may also be a proliferative stimulus *in vivo* in the inflamed tissue under further stress.

Inter-cell signalling necessarily depends on secreted molecules and their receptors and is a universal feature all along the phylogenetic spectrum. If one considers the views of Roth *et al.*[7], it is possible to explain the evolutionary basis for the communication between immune and nervous cells. They have considered the possibility that the molecules of intercellular communication, including neuropeptides and their receptors, are very ancient and predate the evolutionary origins of the metazoans and vertebrates in which the immune and nervous systems are seen. Neuropeptides and their receptors are also highly conserved in evolution and are present also in unicellular organisms and plants apart from animal tissues[8–10]. The existence of such conserved molecules allows functional communication between diverse cells in an organism and the formation of cooperative networks.

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