G. B. West Memorial Prize

Leukocytes and neurogenic inflammation

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Abstract—Neurogenic inflammation is caused by the release of substance P and CGRP from sensory nerves, which stimulates microvascular plasma extravasation and vasodilatation. There is now an increasing body of evidence supporting a role for these neuropeptides in the control of the immune response, in addition to their local inflammatory effects. Indirectly, their ability to increase blood flow allows them to potentiate immunocyte accumulation. They are also able to directly affect immunocytes through cell surface receptors. Substance P has a general stimulatory role, activating immunocytes and enhancing their activities (e.g. cytokine and antibody production). CGRP plays a more subdued role, tailoring the immune response to particular pathogens. Recent evidence suggests that some immunocytes may even be able to synthesise and release neuropeptides. Overall, an increasingly complex system of neuropeptide control of the immune system is apparent, potentially providing novel therapeutic targets.

Key words: Neurogenic inflammation; substance P; CGRP; macrophage; neutrophil; lymphocyte.

1. NEUROGENIC INFLAMMATION

The neurogenic inflammatory response occurs as a result of neuropeptide release from the peripheral terminals of stimulated primary afferent neurones (mainly C and Aδ fibres). The major neuropeptides involved are considered to be substance P (SP) and calcitonin gene-related peptide (CGRP) (Lundberg et al., 1985; Maggi, 1995a). It is established that SP acts to increase microvascular permeability, allowing the exudation of plasma proteins from the blood vessels into the tissues (Lembeck and Holzer, 1979; Lembeck et al., 1992). CGRP is a potent vasodilator (Gamse and Saria, 1987; Escott and Brain, 1993) and potentiates the oedema response to SP (Brain and Williams, 1989). Together, the release of SP and CGRP in the skin leads to the classical inflammatory triple response of vasodilatation followed by wheal and flare. Neurogenic inflammation is thought to be a component of
several disorders and diseases, ranging from urticaria (Hernanz et al., 1989) and psoriasis (Naukkarien et al., 1989) in the skin, to migraine, asthma, and rheumatoid arthritis (Scott et al., 1994; Maggi, 1995a; Geppetti and Holzer, 1996; Brain and Cambridge, 1996). The precise roles of CGRP and SP in these conditions have yet to be elucidated, as in many cases (e.g. CGRP in migraine, SP in psoriasis) their involvement has been deduced purely from elevated plasma concentrations, so the evidence remains circumstantial.

At first it was believed that the only functions of SP and CGRP were their pro-inflammatory contributions to neurogenic inflammation. An increasing number of studies linking these peptides to a variety of other functions — developmental, physiological and pathological — has changed this perspective. If SP can have such diverse effects as control of digestion and modulation of pain transmission, and CGRP can regulate the formation of the neuromuscular junction, then why shouldn’t they additionally play a role in modulation of the immune response?

Initially a role for the neuropeptides as immunomodulators was thought to be unlikely. It was argued that the immune system was an independent process: antigens could stimulate the immune cells to proliferate, produce antibodies, attack foreign bodies, etc., all in isolation from other signals during in vitro studies. However, it has now become apparent that a variety of other factors (e.g. eicosanoids, nitric oxide) released from non-immune cells (e.g. endothelial cells, smooth muscle cells) are able to modulate and initiate immune responses. An increasingly complex system of controls imposed by sources not generally considered to be part of the immune system is evident. In light of this, and their diversity of function, it is attractive to suggest that neuropeptides also exert their own influences on the immune system. A variety of studies examining their effects on leukocytes have been carried out to test this hypothesis. The results are sometimes contradictory, but they point to the existence of another level of control for the activity of lymphocytes, macrophages and other immune cell types.

2. SUBSTANCE P

SP is an undecapeptide of the tachykinin family, a group of peptides which share a common COOH-terminal pentapeptide sequence: Phe-X-Gly-Leu-Met-NH$_2$ (X = a Phe or Val residue). The mammalian tachykinins are commonly referred to as neurokinins, as they are primarily expressed within neurons. However, this has led to some confusion as they are not only expressed in neuronal cells, but also found in some endothelial cells and immunocytes. The other two members of this family are the decapetides neurokinin A (NKA) and neurokinin B (NKB). They are derived from two prototachykinin (PPT) genes, PPT-A, which encodes SP and NKA, and PPT-B which encodes NKB, and primarily synthesised within neurons. The newly synthesised neurokinins are stored within secretory granules until the cells are activated.