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Opioids affect inflammation and the immune system

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Neurogenic inflammation, with its associated hyperalgesia, is linked to release of neuropeptide mediators including substance P, calcitonin gene-related peptide and corticotrophin-releasing factor. The release of substance P may be modified by opioid receptors on afferent nerve terminals. It is known to be a major mediator of neurogenic inflammation in synovia and is implicated in lymphocyte proliferation and arthritic bone changes. However, opioids may inhibit plasma extravasation and appear to decrease substance P release.

Opioid peptides are found in inflamed tissues, released early by interleukin-1 and later by a corticotrophin-releasing factor effect. Opioids appear to interact with interleukins and may act as signalling molecules between immunologically active cells. Endogenous opioids tend to stimulate and exogenous opioids tend to suppress the immune system; information from infections in opioid addicts suggests that this has clinical significance.

Thus, the effect of opioids in modifying the peripheral inflammatory response indicates an analgesic potential at peripheral afferent receptors.

Introduction

Morphine and other opioids have traditionally been thought to act as analgesics centrally, with effects at peripheral receptors accounting for wide-ranging adverse effects such as constipation and itching. Many opioid receptors have been found on immune cells, nerve endings, gut and other tissues, but until recently the nature of their roles and actions has been uncertain.

Opioids are known to act on peripheral receptors, rapidly decreasing the propagation of action potentials along afferent C and A delta fibres; they also diminish the release of excitatory transmitters such as substance P from primary afferent neuronal endings, resulting in analgesia. Other peripheral actions include important neuroendocrine and immunological functions, which are reviewed here. Peripheral actions of opioids, particularly their possible role in inflammatory mechanisms, have increasing clinical implications.[1]

Neurogenic inflammation and pain

Primary afferents and sympathetic postganglionic neurone terminals have been shown to release inflammatory mediators, causing neurogenic inflammation.[2–5] This results in processes, including plasma extravasation, that play a critical

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role in conditions such as asthma, airway hyper-reactivity, inflammatory bowel disease and arthritis.

In tissue damage a wide variety of neuropeptides are released from local primary afferents. These include substance P (SP), calcitonin gene-related peptide (CGRP), somatostatin, galanin, neurokinin-A, vasoactive intestinal peptide, cholecystokinin (CCK) and corticotropin-releasing factor (CRF); others from sympathetic post-ganglionic neurones, such as prostaglandins, purines and neuropeptide Y, also appear to be involved.[6–9] These neuropeptides interact with locally released bradykinin, serotonin, potassium and hydrogen ions to sensitize nociceptors and cause further vasodilatation and plasma extravasation, leading to the classic signs of redness, pain and swelling.[10]

In the spinal cord, released CGRP competes with SP for enzymatic breakdown, causing free SP to diffuse more widely in the dorsal horn and thereby sensitizing afferent pathways.[10] Incrementally raised levels of SP and excitatory amino acids in the dorsal horn eventually cause activation of *N*-methyl-D-aspartate (NMDA) receptors and hence prolonged hyperalgesia.[11] This latter then become independent of peripheral input.[12] Opioids acting on peripheral afferent receptors inhibit SP release[13,14] and, therefore, modulate the potential changes in the dorsal horn wide dynamic range neurones, possibly preventing long lasting or permanent changes in function.

SP is synthesized in the dorsal root ganglia (DRG) and axonally transported to tissues such as skin, tooth pulp and viscera.[15] In patients with rheumatoid arthritis, SP causes prostaglandin E_2 and collagenase to be released from intra-articular cells, and can induce interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor (TNF) release from monocytes.[16] Three tachykinin receptors (NK_1, NK_2 and NK_3) have been identified, with SP acting mainly at NK_1. Sendide, a newly identified peptide that is a potent antagonist of NK_1, has been investigated in animals as a spinally administered analgesic for inflammatory pain.[17]

Nerve growth factor (NGF), which has a trophic action on the developing central nervous system (CNS), appears to function as an inflammatory mediator in adults with persistent pain states.[18] Tissue levels rise within hours of injury and produce hyperalgesia by increasing nociceptor sensitivity.[19] NGF, which can be produced from mast cells, also induces mast cell degranulation and causes thermal and mechanical hyperalgesia. The rapid onset of thermal hyperalgesia is prevented by pretreatment with kappa-selective opioid antagonists, but not by mu and delta opioid antagonists, indicating a role for kappa opioid receptors in the generation of pain of inflammatory origin.[20] NGF is bound and taken up by retrograde axonal transport to stimulate production of SP and CGRP through gene expression, which leads in turn to central sensitization.[21–23]

Specific NGF receptors on lymphocytes, especially B cells, allow NGF to have an immunoregulatory effect upon cytokine action.[24] These NGF-mediated mechanisms suggest that a highly selective NGF antagonist could, theoretically, be an effective analgesic and anti-inflammatory agent.[25]

Neurogenic inflammation in asthma, arthritis and migraine

Asthma and bronchial hyper-reactivity involve bronchoconstriction, vasodilatation, increased vascular permeability and mucous secretion. In asthmatics, damage to bronchial epithelium may expose sensory nerves and decrease the amounts of neuropeptide-degrading enzymes from epithelial cells. Thus, neuropeptides released by a local reflex result in increased inflammation.[5] SP immunoreactive neurones in the respiratory tract are known to be mainly of vagal sensory origin.[26]

In inflammatory bowel disease, parasympathetic dysfunction may result from neuropeptide release from sensory nerve terminals.[3]

In arthritis, SP promotes the chemotaxis of lymphocyte cells into joints, activates synovial neutrophils and macrophages, stimulates lymphocyte proliferation, induces pro-inflammatory cytokine release and stimulates phagocytosis.[27]

Experimental intra-articular infusion of SP results in decreased bone density, cartilage and bone destruction, and periosteal new bone for-

mation as typically seen in arthritis.[28] The concentration of enkephalinase, which metabolizes SP and other neuropeptides, is five- to tenfold higher in synovial fluid in arthritis than in the serum, reflecting the intensity of the inflammatory process.[16]

A migraine crisis may be triggered via neurogenic inflammation; the neurotransmitter endothelin acts directly and indirectly via SP, CGRP and catecholamine release to cause vasodilatation and pain.[29] In psoriasis, beta-endorphins in the skin are also increased, suggesting a neuropeptide-generated inflammation.[30]

Role of opioids in neurogenic inflammation

The mu-selective agonists inhibit primary afferent-dependent plasma extravasation, and delta- and kappa-selective opioids inhibit bradykinin-stimulated plasma extravasation.[31,32] Morphine inhibits cigarette smoke-induced airways exudate.[33] Opioids have been shown in animal studies to inhibit plasma extravasation into the trachea and bronchi[34] and into inflamed joints.[31,35]

Opioids block the vasodilatation and increased vasopermeability of arthritis[13] caused by SP release. Beta-endorphins can stimulate neutrophil chemotaxis and activate leucocyte oxidative mechanisms, while morphine has been shown to inhibit aggregation of granulocytes and secretion of thromboxane B_2.[34] Thus, opioids may have anti-inflammatory properties.[36]

Illness-induced hyperalgesia

Increasing evidence suggests that peripheral immune signals activate central pathways, which in turn produce an illness response.[37] Evolutionarily, hyperalgesia may be adaptive to protect wounds and healing fractures, and to minimize energy expenditure. The vagus nerve appears to be a major route whereby immune system cytokines communicate directly with the brain.[38]

In tissue damage, IL-1 triggers mast cell and nerve terminal SP release and, subsequently, TNF, IL-6 and further IL-1 production.[27,39] In the rat, systemic TNF, IL-6 and IL-1 promote paw hyperalgesia in the absence of inflammation.[40] In contrast, in the presence of inflammation, the local injection of IL-1 and CRF produce potent nociceptor inactivation by immunosuppression and the release of opioid receptor agonists.[41]

IL-1 and CRF are important in peripheral opioid analgesia; they are both capable of releasing endogenous opioid from immune cells and decreasing pain when locally administered to inflamed tissue[42] (Figure 1). Opioid receptors expressed in DRG are present on peripheral sensory nerve terminals in both inflamed and healthy tissue. However, high concentrations of endogenous opioid peptides are found only in inflamed tissue because they are synthesized and released from immune cells.[43,44] CRF and IL-1 stimulate this opioid release from immune cells, thereby resulting in anti-nociception.[41,45] IL-1 levels peak early in inflamed tissue, whereas local CRF levels rise gradually and trigger opioid release. Through negative feedback, opioids regulate the production of several interleukins and block immune cell responses to TNF and SP. Thus, analgesia from morphine may result from an immune function as well as by the known direct neuronal action[27] (Figure 2).

Opioids in inflammatory pain

In pain associated with inflammation, the analgesic effect of morphine may be due to a peripheral action and also enhancement of its spinal effects by decreasing CCK levels. CCK has been shown to reduce the analgesic effect of opioids on mu-receptors at a number of CNS sites and is involved in the development of tolerance.[46] Within hours of inflammation, activity increases in nonopioid inhibitory pathways involving gamma-amino-butyric acid (GABA) receptors and alpha-2 autoreceptors, causing a reduction in NMDA-driven excitability.[47,48]

In conventional therapy, opioids are delivered systemically or spinally to obtain CNS concentrations the levels of which are unlikely to affect the peripheral inflammatory processes. Ongoing 'firing' from the periphery may explain why, after initially successful spinal analgesia, some patients still experience pain.

Opioids as neuroimmune transmitters

Much interest has focused on the role of opioids in the relationships between the immune and nervous systems.[49] All lymphocytes are capable of producing endorphin-like substances.[50] T lymphocytes accumulate preproenkephalin mRNA on activation; enkephalins, released by activated T cells in an immune response act as lymphokines

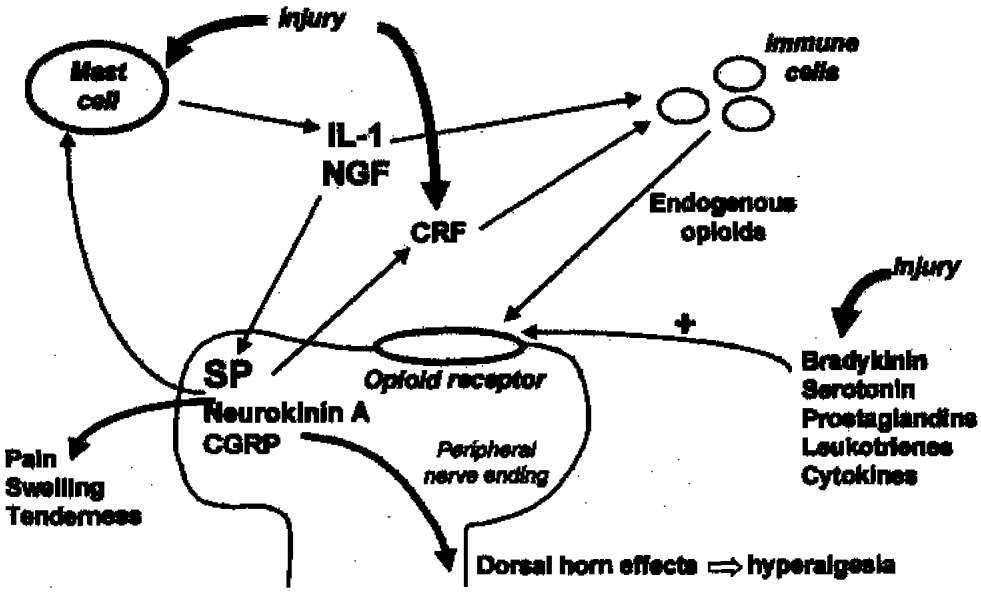

Figure 1 Sensitization of peripheral opioid receptors in inflammation

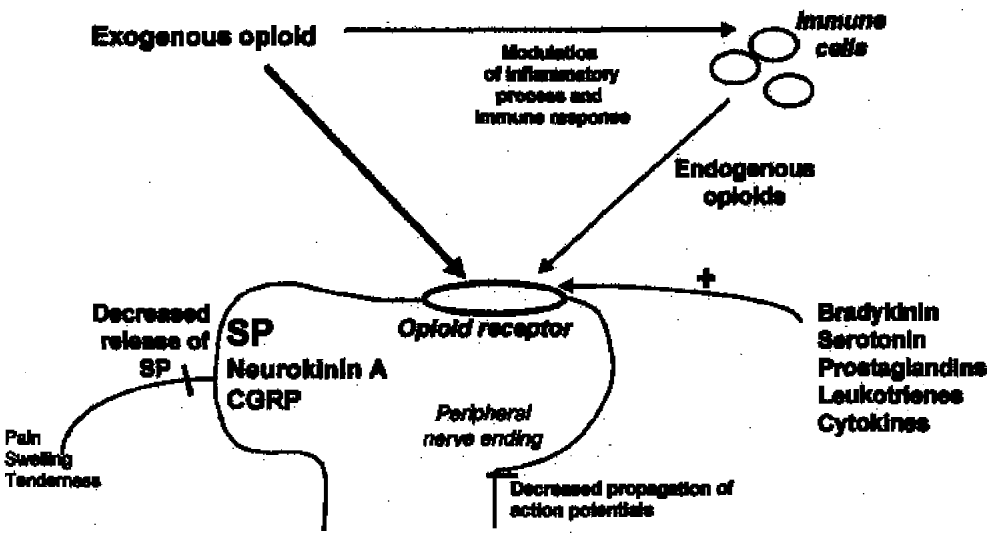

Figure 2 Action of exogenous peripheral opioids in inflammation

to attract lymphocytes to the damaged tissue and signal between the immune and neuroendocrine systems.[42,51]

Opioids and the immune system

Opioid peptides can regulate T-lymphocyte proliferation and cytotoxic activity of natural killer (NK) cells, suppress antibody production by human lymphocytes and bind to the terminal complex of complement.[52–54] In general, exogenous opioids tend to suppress, while endogenous opioids often stimulate the immune system; the positive or negative modulation of immune cells depends on the opioid, its dose and the route of administration.[55] Most, but not all, of these immunoregulatory effects are blocked by opioid antagonists.[56] Morphine impairs granulocyte aggregation and suppresses intracellular killing mechanisms in activated monocytes.[49] Specific high-affinity mu-3 opioid receptors have been found on human monocytes and endogenous opioids have been found to counteract the stimulatory effect of TNF alpha and IL-1 alpha on these cells. Morphine appears to decrease the immune response by lowering chemotaxis and cell adherence, but the effects of different endogenous opioids are complex and paradoxical.[57,58] Thus, enkephalins and endorphins appear to modulate immune responses and may become therapeutically important.[59]

The effects of opioid agonists and antagonists on immune function vary. In animals, the administration of morphine is associated with alterations in a number of immune parameters such as NK activity, proliferation of lymphocytes, antibody production and the production of interferon.[60] For example, NK cell activity generally appears to be suppressed by morphine, but the effect depends on the route of administration.[61] A recent animal study showed that activation of opioid receptors within the CNS was required for the acute administration of morphine to alter NK-cell activity.[60]

In summary, opioids appear directly to affect immune cell function, but their specific role is poorly understood.[55]

Opioids and oncogenesis

Opioid binding sites and intracellular opioid peptides have been found in small cell lung carcinoma, L-4 thymoma and lymphoma.[52,62,63] Naltrexone, a selective mu-antagonist, modulates tumour response in animals inoculated with neuroblastoma cells; low-dose naltrexone prolongs survival but high doses shorten survival time.[64] Endogenous opioids and opioid receptors may affect tumour growth through immunomodulation and a direct autocrine effect on different receptor subtypes.[52,57]

Opioids as immunomodifiers

Chronic morphine ingestion leads to suppressed lymphocyte and macrophage function. Heroin addicts, in the absence of HIV infection, show an increased susceptibility to infection with decreased T-lymphocyte and NK-cell activity and impaired antibody generation.[65,66] Poor nutrition however, may possibly, play a greater role than any opioid effect.

Pain and the immune system

Immune system function appears to be involved in intrinsic mechanisms of pain control, suggesting that pain associated with cancer and AIDS may be related to immunosuppression.[41–43] Pain is prevalent in men with HIV and increases with disease progression.[67–71] Chronic pain *per se* may influence immune function; patients with chronic pain (complex regional pain syndrome I, whiplash syndrome) have immunological changes including an increase in inducer T cells and a decrease in suppressor T cells and helper cells.[72]

The future

Physiological approaches to pain control have included the activation of endogenous opioid production and release from immune cells.[41,42] CRF may be the prototype of a new generation of analgesics that release local endogenous opioids in injured tissues.[43,73] IL-1B peptide

analogues antagonize IL-1-induced hyperalgesia and may present the key to new analgesics in inflammatory pain.[74] Theoretically, a highly selective NGF antagonist should be an effective analgesic and anti-inflammatory agent,[25] although the multiplicity of roles of NGF in nerve cell function makes this unlikely. The new bradykinin receptor antagonists may represent a more feasible drug template.[19]

Peripherally-acting opioid analgesics may hold the key to analgesia because opioids appear to be dynamic signalling molecules that are produced and involved in regulating immune responses.[49]

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