British Journal of Anaesthesia **111** (1): 80–8 (2013)
doi:10.1093/bja/aet153

BJA

Opioids and immune modulation: more questions than answers

M. Al-Hashimi, S. W. M. Scott, J. P. Thompson and D. G. Lambert*

Department of Cardiovascular Sciences, University of Leicester, Division of Anaesthesia, Critical Care and Pain Management, Leicester Royal Infirmary, Leicester, LE1 5WW, UK

* Corresponding author. E-mail: dgl3@le.ac.uk

Editor's key points

- There is increasing evidence for immunemodulatory effects of opioids.
- The precise sites of immune modulation are controversial and unclear.
- Urgent translational research is needed, as increasing numbers of people are on long-term opioids.

Summary. Opioid addicts are more likely to present with infections suggesting opioids are immune modulators. The potential sites/mechanism(s) for this modulation are controversial and on close inspection not well supported by the current literature. It has long been assumed that opioid-induced immune modulation occurs via a combination of direct actions on the immune cell itself, via the hypothalamic-pituitary-adrenal (HPA) axis, or both. Opioid receptors are classified as MOP (μ, mu), DOP (δ, delta), and KOP (κ, kappa)—classical naloxone sensitive receptors—or NOP (the receptor for nociceptin/orphanin FQ), which is naloxone insensitive. Opioids currently used in clinical practice predominantly target the MOP receptor. There do not appear to be classical opioid receptors present on immune cells. The evidence for HPA activation is also poor and shows some species dependence. Most opioids used clinically or as drugs of abuse do not target the NOP receptor. Other possible target sites for immune modulation include the sympathetic nervous system and central sites. We are currently unable to accurately define the cellular target for immune modulation and suggest further investigation is required. Based on the differences observed when comparing studies in laboratory animals and those performed in humans we suggest that further studies in the clinical setting are needed.

Keywords: HPA axis; immunomodulation; opioid receptors

The link between opioids and an alteration in host immune function is often referred to in the literature. The increased incidence of various local and systemic infections in introvenous drug users led to the conclusion that the causative link between i.v. drug abuse and infections could not be simply explained by the injection process being the route of infection, but that the opiates themselves were acting to modulate immune function. The increased incidence and severity of infections among opiate abusers was documented in the early 19th century with similar observations appearing in the literature as early as the mid 1500s when Professor Fallopious of Pisa recorded the death of a prisoner probably from malaria after experimental opium administration.[1] In 1950, Hussey and Katz published a landmark paper describing the growing list of infections associated with narcotic addiction.[2] As then, extensive research has been directed at investigating the immunomodulatory effects of opioids and mechanisms and the clinical significance of such effects.

Opioids can affect innate and adaptive immune function and their effects are summarized in Table 1.[3–28] In this review, we explore the possible mechanisms of immune modulation caused by opioids in the current literature. The evidence discussed in this article should be taken in the context of the diversity and complexity of the subject, immune function and the group of patients/cells/species in which those studies were conducted.

Immune regulation

The immune system is intricate and diverse; its main function is fighting infections in the host environment. Regulation of the immune system is very important and, when imbalanced, may result in either increased susceptibility to infections or autoimmune disease status. Immune regulation refers to the interactions between immune cells and mediators.[29] Immune regulation can be affected by any stimuli that can affect immune cell haemopoiesis, immune system component development, and antigen-antibody feedback mechanisms. Other factors that can affect immune regulation are neuroendocrine control, mental and physical stress, and genetic predisposition. There are numerous receptors on different populations of immune cells that interact with corticosteroids, insulin, growth hormones, β-adrenergic agonists, acetylcholine, and many others that may potentially affect immune function.[30]

A simplified representation of the immune cell generation process and the antigen-antibody immunity pathway is shown in Figure 1. The term 'immunemodulatory' refers to any endogenous or exogenous stimulus that can potentially

Table 1 Opioid effects on immunity. IL, interleukin; TNF-α, Tumour Necrosis Factor-Alpha; IFN-γ, Interferon-gamma; PBMC, Peripheral Blood Mononuclear Cell; NK, Natural Killer; LPS, Lipopolysaccharides; TFG-β, Transforming Growth Factor Beta; NF-κb, Nuclear Factor kappa Beta; AP-1, Activator Protein 1; NFAT, Nuclear factor of activated T-cells; Fc, fragment crystallisable region; HPA, Hypothalamic Pituitary Adrenal axis; ACTH, Adrenocorticotropic hormone; CRH, Corticotropin releasing hormone; LH, Luteinizing hormone

Adaptive immunity
↓ Splenic and thymic weight (rodents)[4–6]
↓ T cell viability and proliferative response
↓ T-helper cell function
↓ CD4/CD8 population *in vivo*
↓ IL1β, IL-2, TNF-α and IFN-γ (mouse splenocytes)
↓ Th1/Th2 ratio of T-helper cell population (PBMCs)[7]
↓ NK cell activity[8]
↓ Primary antibody response (B cells)[9]
↓ B cells mitogenic response to bacterial LPS[4 10 11]
↓ Macrophage activity[9]
↑ TFG-β1 and IL-10 (anti-inflammatory cytokines)[12]
↑ T cell apoptosis (NF-k β and AP-1/NFAT pathways)[13]
Inhibition of CD3/28 mAb induced IL-2 transcripts[14]
Innate immunity
↓ Number of macrophages available to fight infections[15]
↓ Leucocyte migration[16]
↓ Peritoneal macrophages phagocytosis
↓ Respiratory burst activity and chemotaxis[17]
Inhibition of Fc γ receptor mediated phagocytosis[18]
↓ Superoxide production from neutrophils and macrophages[19–21]
Alteration of IL-8 induced neutrophil chemotaxis[22 23]
↓ Neutrophil cytokines involved in wound healing[24]
↑ Apoptosis of macrophages impairing host defence barrier[25]
↓ Leucocytes endothelial adhesion (↓ intracellular adhesion molecules expression)[26 27]
Neuroendocrine system
↑ Growth hormone, prolactin, and thyroid stimulating hormone secretion in humans[28]
May affect the function of the HPA axis (ACTH and CRH) with risk of adrenal insufficiency[28]
↓ Sex hormones [LH and testosterone (hypogonadism)], oxytocin, and estradiol[28]

alter immune function by effects on the generation, function, and maturation of immune cells.

Classification of opioid receptors

Opioid receptors were first demonstrated in neural tissue in 1973 by Pert and Snyder[31] followed by the characterization of a range of endogenous opioid ligands.[32 33] Interestingly, the endomorphins were only identified as endogenous ligands for the MOP receptor in 1997.[34] Despite the long history describing the existence of endogenous opioid-binding sites, opioid receptors were only formally identified in 1992 by the pioneering work of Kieffer and colleagues[35] and Evans and colleagues[36], the crystal structures of all members of the opioid family were published in 2012.[37–40] There have been several attempts to classify the opioid receptors. Table 2 lists the current classification system for opioid receptors: MOP (μ, mu), DOP (δ, delta), and KOP (κ, kappa) for classical naloxone-sensitive receptors, and NOP for the non-classical nociceptin/orphanin FQ (N/OFQ) receptor, which is naloxone-insensitive. All of the classical opioid receptors are capable of producing analgesia along with variable side-effects including respiratory depression, tolerance, dependence, and immunosuppression.[41] Activation of the NOP receptor with its endogenous peptide ligand N/OFQ produces analgesia spinally and hyperalgesia/anti-opioid actions supraspinally. Unlike classical opioids, there is no respiratory depression and little evidence for tolerance/dependence with NOP receptor activation. NOP receptors are known to be located on immune cells.[42] In the literature, there are numerous reports of subtypes of the classical receptors (MOP, KOP, and DOP) but data from knockout experiments, where single receptor gene knockouts result in a complete loss of function, indicate that these proposed subtypes are unlikely to represent structurally distinct receptor proteins.[41] In addition, there is good evidence to support the simultaneous targeting of multiple opioid receptors to improve analgesia and adverse effect profiles.[43] Throughout the remainder of this article, we will use the MOP, DOP, KOP, and NOP terminology but in describing some of the older studies, other terminology (as in Table 2) will be used and qualified.

Some opioids cause more immunomodulation than others

Different opioids affect immune function differently depending on drug factors, host factors, and the duration of exposure.[44] A recent publication from the British Pain Society[45] states that 'patients must be aware of uncertainty regarding the long-term effects of opioids, particularly in relation to endocrine and immune function'. The practice guide also acknowledges the immune modulatory effects of opioids but states that buprenorphine has no impact on immune function.[45] Table 3[44 46–49] summarizes the immune modulatory effects of opioids in animal studies; these may not reflect responses in humans where the duration of exposure to opioids changes the observed degree of immune modulation. Some data suggest that the immune modulatory effects of different opioids depend more on their molecular structure than their interaction with the MOP receptor,[49] which might imply a non-opioid receptor site of action. However, in MOP knockout animals, no immune modulation is seen.[8 50 51] Clearly, inter-species variability is an important issue in studies of immune modulation (see below).

Potential sites of immunomodulation

The immune modulatory effects of opioids (Fig. 2) are often linked to central neuro-endocrine/neuro-paracrine and peripheral mechanisms; it has often been suggested that peripheral actions are mediated by MOP receptors on immunocytes,