Austin Journal of Anesthesia and Analgesia

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Austin Publishing Group

Short Communication

Opioid Receptors in the Skin

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Received: October 26, 2018; **Accepted:** November 06, 2018; **Published:** November 13, 2018

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Most research has focused on opioid receptors residing in the central nervous system. Last decade researchers however found such receptors present in the nerve endings up in the epidermis (the nociceptors), keratinocytes and immunocompetent cells (e.g. mast cells and the Langerhans cells). This is important, as it suggests that in specific cases topical treatment with opiate agonists could contribute in the treatment of peripheral neuropathic pain syndromes.

Opioid receptors are metabotropic membrane receptors and are subdivided in three major subtypes: μ opioid receptors (MOR), δ opioid receptors (DOR) and κ opioid receptors (KOR). The endogenous ligands which inhibit nociception are the endorphins and enkephalins for MOR and DOR and the dynorphins for KOR [1,2]. MOR, KOR and in lesser extend DOR are found at the peptidergic sensory nerve endings [3,4]. DOR are exclusively found on axons and nerve ending of unmyelinated C-fibers [5]. Opioid receptors are furthermore expressed on skin cells, such as melanocytes, hair follicle epithelium, fibroblasts, keratinocytes, bone, joint tissue and immune cells [1,6].

On activation the opioid receptors couple to inhibitory G-proteins (Gi/o) and inhibit cyclic adenosine monophosphate (cAMP) production and/or directly interact with ion channels, such as K^+ and Ca^{2+} channels in the membrane [7]. This leads to reduced action potential propagation, and decreased release of excitatory pro-inflammatory neuropeptides [1].

Peripheral inflammation induces increased synthesis, axonal transport and accumulation of peripheral opioid receptors at the peripheral sensory nerve endings. It also triggers migration of opioid containing immune cells [1]. Inflammation further enhances sprouting of sensory nerve endings, which also leads to increased number of peripheral opioid receptors [2]. The decrease in tissue pH due to inflammation results in increasing opioid agonist efficacy [2,8]. The heightened expression of receptors depends on the receptor type and on the duration of inflammation. In case of MOR, inflammation increases MOR density per neuron and the number of neurons expressing MOR, while the affinity of opioid agonists to MOR remains unchanged [1,9]. MOR mRNA displays a biphasic up-regulation pattern (at 2h and 96h) and KOR mRNA has a peak at 12h, though DOR mRNA concentration remains unchanged [10].

Within peripheral inflamed tissue close associations between opioid-containing immune cells and peripheral afferent nerve endings has been observed [11]. Lymphocytes that have been activated by inflammatory factors can express opioid peptides. Immune cells accumulating around injured nerves and/or tissue contain around 35% opioid peptides, which are released upon stimulation by noradrenaline, corticotrophin-releasing factor and by pro-inflammatory cytokines, such as tumor necrosis factor α and interleukin 1β [1]. Analgesia is thus achieved when activated immune cells are present at the injured site. In early phases of inflammation, granulocytes (especially neutrophils) are the major opioid-containing leukocytes, whereas in later stages of inflammation, monocytes or macrophages and lymphocytes (especially activated T and B cells) predominate containing opioids [11]. Furthermore, inflammation increases the expression of opioid peptides within these cells [11]. Inhibiting the migration of memory type T cells into inflamed tissue results in reduced numbers of β-endorphin-containing cells, a reduced concentration of β-endorphin in inflamed tissue and reduced peripheral analgesia [12]. This seems in line with the fact that immunosuppression is associated with increased pain in patients [12]. Moreover, immunosuppression results in decreased lymphocyte numbers as well as decreased effects of analgesic compounds in animal models [12].

In neuropathic pain expression of all types of opioid receptor mRNA was found to be decreased [13]. This might be a result of the chronic state of neuropathic pain. Given the fact that opioid receptors are present in the various tissues of the skin, topical treatment with creams containing opioids, for instance loperamide, might be a promising inroad in the treatment of neuropathic pain.

Conflict of Interest

Authors are patent holders of two patents related to the topical formulations of phenytoin in the treatment of pain: Topical Phenytoin for Use in the Treatment of Peripheral Neuropathic Pain and Topical Pharmaceutical Composition Containing Phenytoin and a (Co-) Analgesic for the Treatment of Chronic Pain.

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Citation: Kopsky DJ and Keppel Hesselink JM. Opioid Receptors in the Skin. Austin J Anesthesia and Analgesia. 2018; 6(2): 1074.

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Austin J Anesthesia and Analgesia - Volume 6 Issue 2 - 2018
ISSN : 2381-893X | www.austinpublishinggroup.com

Citation: Kopsky DJ and Keppel Hesselink JM. Opioid Receptors in the Skin. Austin J Anesthesia and Analgesia. 2018; 6(2): 1074.