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Review

Opioids, sensory systems and chronic pain

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ABSTRACT

Opioids are the oldest and most potent drugs for the treatment of severe pain. Their clinical application is undisputed in acute pain (e.g. associated with trauma or surgery) but their long-term use in chronic pain has met increasing scrutiny. Therefore, this article will review sensory mechanisms related to opioid analgesia and side effects with a special emphasis on chronic pain. Central and peripheral sites of analgesic actions and side effects, as well as conventional and novel opioid compounds will be discussed. Since pain is a complex bio-psycho-social phenomenon, non-pharmacological considerations important for the understanding of opioid analgesic efficacy are also included. Finally, examples of challenging clinical situations such as the perioperative management of patients receiving long-term opioid treatment are illustrated.

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1. Chronic pain

1.1. Basic concepts

1.1.1. Excitatory mechanisms

Pain may be roughly divided into two broad categories: physiological and pathological pain. Physiological (acute, nociceptive) pain is an essential early warning sign that usually elicits reflex withdrawal and thereby promotes survival by protecting the organism from (further) injury. In contrast, pathological (e.g. neuropathic) pain is an expression of the maladaptive operation of the nervous system; it is pain as a disease (Woolf, 2004). Physiological pain is mediated by a sensory system consisting of primary afferent neurons, spinal interneurons and ascending tracts, and several supraspinal areas. Trigeminal and dorsal root ganglia (DRG) give rise to high-threshold Aδ- and C-fibers innervating peripheral tissues (skin, muscles, joints, viscera). These specialized primary afferent neurons, also called nociceptors, transduce noxious stimuli into action potentials and conduct them to the dorsal horn of the spinal cord (Fig. 1). When peripheral tissue is damaged, primary afferent neurons are sensitized and/or directly activated by a variety of thermal, mechanical and/or chemical stimuli. Examples are protons, sympathetic amines, adenosine triphosphate (ATP), glutamate, neuropeptides (calcitonin gene-related peptide, substance P), nerve growth factor, prostanoids, bradykinin, proinflammatory cytokines and/or chemokines (Rittner et al., 2008; Stein, 2012; Woolf and Ma, 2007). Many of these agents lead to opening (gating) of cation channels in the neuronal membrane. Such channels include the capsaicin-, proton- and heat-sensitive transient-receptor-potential-vanilloid-1 (TRPV1), or the ATP-gated purinergic $P2X_3$ receptor. This gating produces an inward current of Na^+ and Ca^{++} ions into the peripheral nociceptor terminal. If this depolarizing current is sufficient to activate voltage-gated Na^+ channels (e.g. $Na_v1.8$), they too will open, further depolarizing the membrane and initiating a burst of action potentials that are then conducted along the sensory axon to the dorsal horn of the spinal cord (Wood, 2007; Woolf and Ma, 2007). Thereafter these impulses are transmitted to spinal neurons, brainstem, thalamus and cortex (Schaible, 2007; Tracey and Mantyh, 2007).

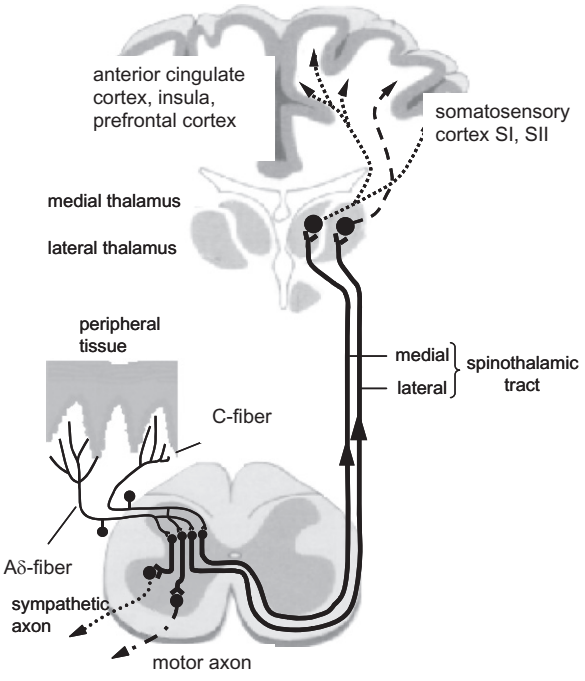

Fig. 1. Nociceptive pathways, adapted from Brack et al. (2006). For details see text.

Transmission of input from nociceptors to spinal neurons that project to the brain is mediated by direct monosynaptic contact or through multiple excitatory or inhibitory interneurons. The central terminals of nociceptors contain excitatory transmitters such as glutamate, substance P and neurotrophic factors. These activate postsynaptic *N*-methyl-D-aspartate (NMDA), neurokinin (NK_1) and tyrosine kinase receptors, respectively. Repeated nociceptor stimulation can sensitize both peripheral and central neurons (activity-dependent plasticity). In spinal neurons such a progressive increase of output in response to persistent nociceptor excitation has been termed "wind-up". Later, sensitization can be sustained by transcriptional changes in the expression of genes coding for various neuropeptides, transmitters, ion channels, receptors and signaling molecules (transcription-dependent plasticity) in both nociceptors and spinal neurons. Important examples include the NMDA receptor, cyclooxygenase-2 (COX-2), Ca^{++} and Na^+ channels, cytokines and chemokines expressed by neurons and/or glial cells (Basbaum et al., 2009). In addition, physical rearrangement of neuronal circuits by apoptosis, nerve growth and sprouting occurs in the peripheral and central nervous system (Schaible, 2007; Woolf, 2004).

1.1.2. Inhibitory mechanisms

Concurrent with the events described above, powerful endogenous mechanisms counteracting pain unfold both in the periphery and in the central nervous system. In injured tissue this occurs by interactions between leukocyte-derived opioid peptides and peripheral nociceptor terminals carrying opioid receptors (Stein et al., 1990, 2003; Stein and Machelska, 2011) and/or by anti-inflammatory cytokines (Rittner et al., 2008). Inflammation of peripheral tissue leads to increased expression, axonal transport and enhanced G-protein coupling of opioid receptors in DRG neurons as well as enhanced permeability of the perineurium. These phenomena are dependent on sensory neuron electrical activity, production of proinflammatory mediators, and the presence of nerve growth factor within the inflamed tissue (Cayla et al., 2012; Mousa et al., 2007a; Rittner et al., 2009b; Stein, 2012; Stein and Machelska, 2011). In parallel, opioid peptide-containing immune cells extravasate and accumulate in the inflamed tissue. These cells upregulate the gene expression of opioid peptide precursors and the enzymatic machinery for their processing into functionally active peptides (Busch-Dienstfertig et al., 2012; Mousa et al., 2004; Sitte et al., 2007). In response to stress, catecholamines, corticotropin releasing factor, cytokines, chemokines or bacteria, leukocytes secrete opioids, which then activate peripheral opioid receptors and produce analgesia by inhibiting the excitability of nociceptors, the release of excitatory neuropeptides, or both (Rittner et al., 2009a; Stein and Machelska, 2011) (Fig. 2). The clinical relevance of these mechanisms has been shown in studies demonstrating that patients with knee joint inflammation express opioid peptides in immune cells and opioid receptors on sensory nerve terminals within synovial tissue (Mousa et al., 2007b; Stein et al., 1993). After knee surgery pain and analgesic consumption was enhanced by blocking the interaction between the endogenous opioids and their receptors with intraarticular naloxone or adrenergic antagonists (Kager et al., 2011; Stein et al., 1993), and was diminished by stimulating opioid secretion (Likar et al., 2007).

In the spinal cord, inhibition is mediated by the release of opioids, GABA or glycine from interneurons, which activate presynaptic opioid- and/or GABA-receptors on central nociceptor terminals to reduce excitatory transmitter release. In addition, the opening of postsynaptic K^+ or Cl^- channels by opioids or GABA, respectively, evokes hyperpolarizing inhibitory potentials in dorsal horn neurons. During ongoing nociceptive stimulation spinal interneurons upregulate gene expression and production

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