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Perioperative analgesia: Ever-changing technology and pharmacology

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Our understanding of pain and its long-term implications have dramatically changed with the advent of advancements in molecular mechanisms involved in acute or postoperative pain and chronic pain. This better understanding has led to multiple pharmacologic advancements to better treat pain with minimal side effects. Currently, we are still struggling to find the right balance between all of the different modalities that we have at our leisure. In order to best take care of postoperative pain, we are improving patient satisfaction, decreasing hospital stays, and decreasing the development of long-term pain and its related complications. However, despite using a multimodal approach that includes newer technologies, we still have a long way to go before we can guarantee a pain-free postoperative course or a comfortable end for a terminally ill patient. These arms of anesthesiology are ever changing. Anesthesiologists have taken a leadership role in perioperative pain management and clinical research designed for the improvement of pain.

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Brief history and introduction

In ancient times, different substances such as cannabis, alcohol, and opium were used to treat pain. With regard to opium, ancient civilizations including Persia, Egypt, and Mesopotamia all cultivated it. The first documented use of opioids for medicinal purpose was documented in the 3rd century B.C. in Theophrastus, Sumerian, Babylonian, and Egyptian writings. In this regard, Egyptian Eber papyrus in 1552 B.C. advised the use of juice from the unripe poppy seedpod "to prevent the excessive crying of children". Since the introduction of opium for postoperative pain by James Moore in 1784, the use of opium and its derivatives has substantially increased. Morphine was developed in 1805 by Friedrich Serturner, a German pharmacist, followed by the development of the hypodermic needle a few decades later.

In 1898, Bayer launched a "non-addictive" alternative to opium and morphine, diacetylmorphine or heroin, which is German for hero. Currently, morphine is available in many forms, including epidural, intrathecal, intramuscular, rectal, intravenous (IV), and oral. Newer synthetic opioids offer more dosing routes and increased dispensing options. The first documented use of intrathecal morphine was in Japan by Katwatal in 1901; the first use of epidural morphine was in 1979 by Behar et al.; and the first combined use of morphine and a local anesthetic was documented in 1985 by Rucci et al. Henry Knowles Beecher (1904–1976) is considered the godfather of modern analgesia. During World War II, he published an article in *JAMA* about his experience with morphine in wounded soldiers. He also made a recommendation to use morphine at a dose of 10 mg every 6 h, intramuscularly.

Molecular mechanisms

Surgery causes tissue injury with subsequent release of multiple inflammatory mediators, including histamine, bradykinin, prostaglandins, serotonin, nerve growth factor, leukotrienes, and 5-hydroxytraptamine. These inflammatory mediators stimulate the release of neurotransmitters such as calcitonin gene-related peptide, substance P, and cholecystokinin. All these substances mediate or modulate numerous pain pathways and ultimately play a role in peripheral sensitization. This results in a decreased activation threshold and an increased basal rate of discharge. These mediators activate peripheral nociceptors and these impulses travel via A delta and C fibers and the synapses in lamina II and lamina V of the spinal cord [1,2].

In the spinal cord, the dorsal horn is the primary site for the integration of peripheral nociception and descending modulatory input (i.e., serotonin, norepinephrine, γ-aminobutyric acid, encephalin). Sophisticated modulating influences cause further transmission of nociceptive stimuli to higher brain centers through spinothalamic and spine reticular tracts, ultimately producing the perception of pain.

Lamina I responds to impulses from C fibers. Lamina V is responsible for fast synaptic transmission using neurotransmitters such as glutamate and aspartate, which bind and activate amino-3-hydroxyl-5-methyl-4-proprionic acid (AMPA) and kainate (KAR) receptors. Activation of AMPA and KAR receptors start the priming of N-methyl-D-aspartate (NMDA) receptors.

NMDA receptor activation in the spinal cord and higher brain centers, such as the anterior cingulate gyrus, the amygdala, and the rostroventral medulla, play an important role in central sensitization, along with other mechanisms and neurotransmitters. The hippocampus also is involved in long-term potentiation (LTP) of pain. In addition, the upregulation of cyclooxygenase 2 (COX2) and neurokinin receptor (NK1) in the spinal cord facilitate central sensitization. Studies have shown that noxious stimuli can produce new gene expression in the dorsal horn of the spinal cord within 1 h. Clinical studies also suggest that the intensity of acute postoperative pain is a significant predictor of chronic postoperative pain. LTP is a reversible process and hence amenable to treatment (e.g., transcription-independent process of sensitization). However, transcription-dependent sensitization can produce irreversible structural modifications in the central nervous system (CNS) [3–5].

Chronic postoperative pain and its implications

Chronic postoperative pain is an under-recognized entity, found in about 10–65% of postoperative patients, including those who have undergone limb amputations (30–83%), thoracotomy (22–67%), sternotomy (27%), and gall bladder surgery (up to 56%) [6].