Literature Review

Clinical Relevance of Central and Peripheral Prostaglandins in Postoperative Pain

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"These concerns are significant given that this decade has been dedicated by the U.S. Congress as the 'Decade of Pain Control and Research,' and too little attention has been directed at preventing chronic pain from surgical trauma."

Surgical incision leads to cell disruption and subsequent intracellular release of phospholipids and a state of widespread inflammation depending on the degree of surgical trauma. Enzymatic action on phospholipids results in the release of prostanoids at the site of injury [Figure 1] that sensitizes the nociceptors to mechanical stimuli (primary hyperalgesia) and also to several chemical mediators such as prostanoids, bradykinin and nerve growth factor. The chemical mediators may be the cause for secondary hyperalgesia, and continued peripheral sensitization leads to central pain sensitization. One of the prostanoids, PGE_2, is the predominant mediator of both peripheral and central pain sensitization.[1] Spinal cord sensitization with surgical persistent pain is believed to have striking similarities in brain (hippocampal) mechanisms of memory and synaptic plasticity.[2]

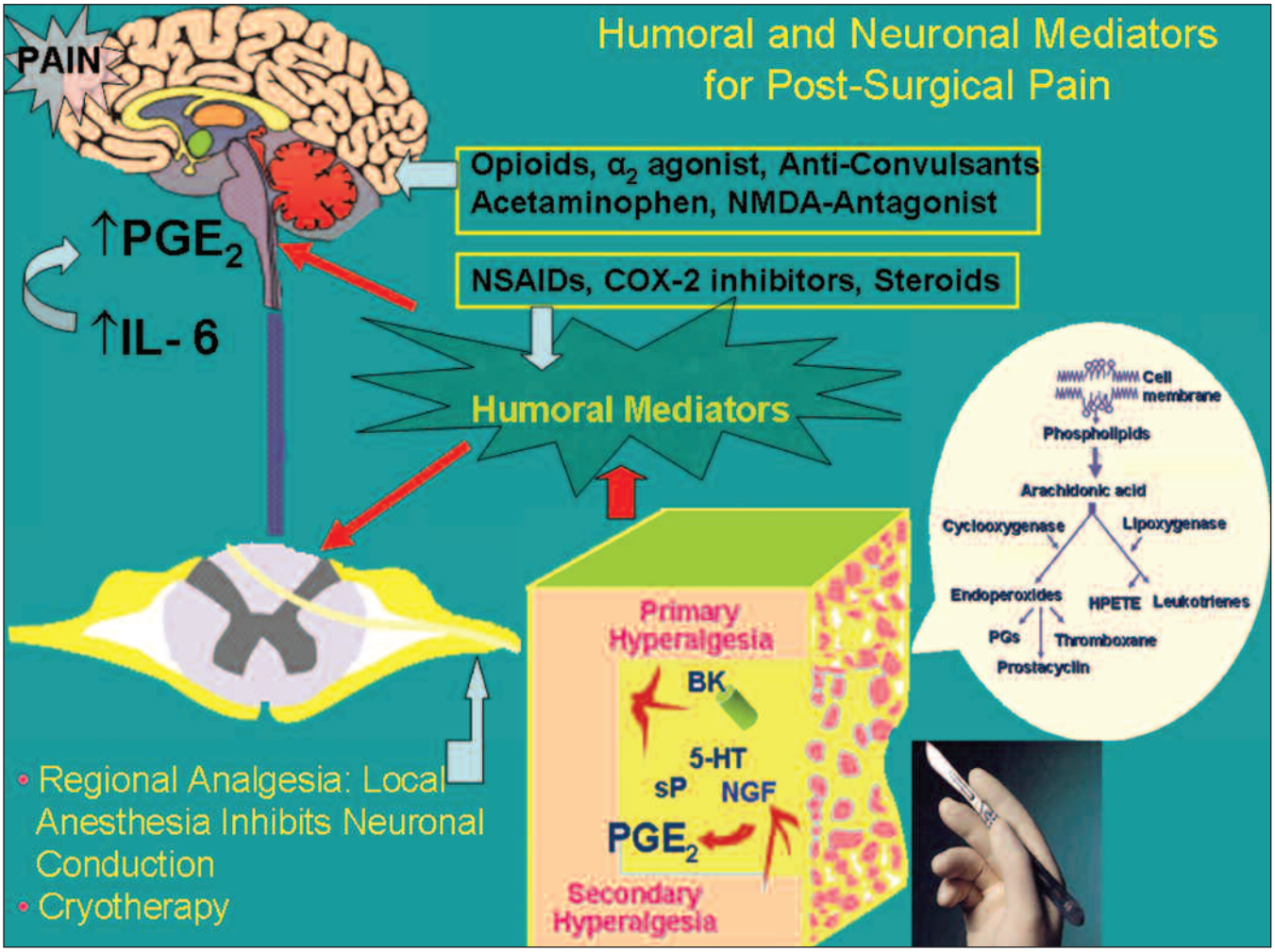
Peripheral inflammation induces a widespread increase in cyclooxygenase-2 (COX-2) and PGE_2 in the central nervous system (CNS). The inflammatory component of surgical pain is the stimulus that, in the absence of any peripheral nerve damage, drives acute postoperative pain until the surgical wound has healed. If a focus of ongoing inflammation persists, so will the pain.[3] Increased levels of PGE_2 in the brain (from the amygdala) have been demonstrated from preclinical surgical models.[4] Based on preclinical studies, it was postulated that these events were activated by the pro-inflammatory mediator IL-1.[5] In preclinical studies of postsurgical pain states, peripheral nerve blockade provided analgesia to the affected extremity but did not prevent the up-regulation of COX-2 in the CNS.[6] Recent studies in patients undergoing major surgery under spinal anesthesia and analgesia have now demonstrated that CSF PGE_2 is increased in the perioperative period.[7,8] In addition it is hypothesized that the major pro-inflammatory mediator in CNS in humans during surgery is IL-6[7] and not IL-1,[5] as suggested initially in the preclinical studies.

The question often posed by the practicing anesthesiologist is the clinical relevance of studies that report measurements of inflammatory mediators. In recent clinical studies, reduction in CSF PGE_2 values have been found to be correlated with reduced postoperative pain scores and opioid consumption.[7-8] In addition a positive correlation exists between poor function recovery and increased surgical site (tissue) PGE_2 concentration.[7] There is evidence that COX-1 is mainly responsible for the PGE_2 production at the surgical site in the early postoperative phase and that the local induction of COX-2 accounts for the enhanced PGE_2 release.[9,10]

As stated above, IL-6 may be the pro-inflammatory stimulator for CSF PGE_2 in humans. Higher CSF IL-6 in the immediate postoperative period has been shown to cause increased sleep disturbances.[7] Previous studies have demonstrated that the serum and surgical tissue levels of IL-6 are proportional to the amount of surgical trauma.[11] Once the biochemical mediators of physiological responses (pain, sleep, physical activity) are identified, receptor-specific pharmacological agents can be discovered, devoid of adverse effects.

With the current COX-2 inhibitor controversy surrounding cardiovascular safety, there is intense interest in newer pharmacological agents that target specific receptors (EP-receptors).[12] In addition, with the growing body of literature supporting the up-regulation of CSF PGE_2 in the CNS during surgical trauma and inflammation,[4-8] the role of COX-2-specific inhibitors that pharmacologi-

Figure 1



cally act at the neuroaxial region following systemic administration or that can be delivered via the spinal route needs to be investigated.

Nationally there is an increase in the use of regional anesthesia and analgesia for surgery and postoperative pain. Recent preclinical data demonstrate that anesthesia with propofol suppresses central PGE_2 compared with spinal anesthetic[13]; however, this needs to be confirmed in humans. The neuronal blockade providing surgical anesthesia does not prevent the local inflammatory mediators released from incision to up-regulate the noxious mediators (humoral-response) in the CNS, probably via systemic circulation. Randomized trials comparing general anesthesia to general anesthesia, plus peripheral nerve blocks have demonstrated superior immediate postoperative analgesia but no difference in the cytokine responses to surgery and long-term outcome.[14] Therefore regional anesthesia and analgesia combined with a multimodal pharmacological approach, which leads to the suppression of inflammatory mediators to surgery, is of essence for improved perioperative pain control to our patients, which can lead to improved outcome. This improved long-term outcome has been demonstrated in studies where a multimodal approach has been utilized.[15] In addition, appropriate therapeutic management of acute postoperative pain can reduce the incidence of chronic pain syndromes from developing after surgery.[3] These chronic pain syndromes can be debilitating for patients, and treatment is often challenging and expensive. These concerns are significant given that this decade has been dedicated by the U.S. Congress as the "Decade of Pain Control and Research," and too little attention has been directed at preventing chronic pain from surgical trauma.

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