- **FACT SHEET No. 3**

Pathophysiology of Acute Postoperative Pain

Decades of research have established that acute pain after surgery has a distinct pathophysiology that reflects peripheral and central sensitization as well as humoral factors contributing to pain at rest and during movement. This can impair functionality and often culminates in delayed recovery [1,2,3].

Nociceptor activation, sensitization, and hyperalgesia:

Surgical tissue trauma leads to nociceptor activation and sensitization. As a result, individuals suffer ongoing pain at rest and increased responses to stimuli at the site of injury (primary hyperalgesia) [4,5].

- Different surgical procedures (including debridement for acute burn care) involve distinct organs and specific tissue within and adjacent to them, creating a variety of patterns of nociceptor sensitization and differences in the quality, location, and intensity of postoperative pain.
- Mediators released locally and systemically during and after surgery that contribute to nociceptor sensitization include: prostaglandins, interleukins, cytokines and neurotrophins (e.g. nerve growth factor (NGF), glial-derived neurotrophic factor (GDNF), neurotrophin (NT)-3, NT-5, and brain-derived neurotrophic factor (BDNF)) [6,7].
- Decreased tissue pH and oxygen tension, and increased lactate concentration, persist at the surgical site for several days. These responses may contribute to peripheral sensitization (e.g., muscle C-fibers) and spontaneous pain behavior following an incision. Acid-sensing ion channels (e.g. ASIC3) likely transduce this ischemic-like signal (1,8,9).
- Peripheral neutrophilic granulocytes (NGs) contribute to peripheral sensitization and pain after surgical incision (10,11). Endogenous CD14+ monocyte responses (e.g., via the TLR4 signaling pathway) are associated with differences in the time course of postsurgical pain (12).

IASP brings together scientists, clinicians, health-care providers, and policymakers to stimulate and support the study of pain and translate that knowledge into improved pain relief worldwide.

- Nerves may be injured during surgery and hence discharge spontaneously. Spontaneous action potentials in damaged nerves may account for qualitative features of neuropathic pain that may be present early in the postoperative period and can evolve into chronic neuropathic pain [13].

Central sensitization during acute postoperative pain:

- Noxious input during and after surgery can enhance the responses of nociceptive neurons in the CNS (central sensitization) thereby amplifying pain intensity [14].
- The magnitude of central sensitization depends on many factors, including the location of the operative site and the extent of the injury.
- α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-receptor mediated spinal sensitization contributes to pain and hyperalgesia after incision [15].
    - Phosphorylation of the AMPA receptor GluR1 subunit at Serine-831 via protein kinase C gamma (PKC)γ, but not other conventional PKC isoforms (PKCα, βI and βII), leads to an increase trafficking of Ca2+ permeable AMPA receptors in the neuronal plasma membrane [16].
    - GluR1 is upregulated in the spinal cord ipsilateral to an incision via stargazin, a transmembrane AMPA receptor regulatory protein [17].
- Other molecules involved in central sensitization after surgical incision involve phosphorylated extracellular signal-regulated kinases (ERK) 1/2, BDNF, Tumor necrosis factor) TNFα, iNOS, mitogen-activated protein kinase phosphatase (MKP)3, monoamine oxidase (MAO) B, toll-like receptor (TLR) 4 receptor and cyclooxygenase (COX) 2 (among others).
- Spinal inhibitory mechanisms may be able to prevent central sensitization after surgery, for example via spinal α-adrenoceptors, γ-Aminobutyric acid (GABA) -receptors, or enhanced Glutamate transporters, among other mechanisms [18,19,20].
- Opioids modulate central sensitization in complex ways. Some in-vitro studies indicate that opioids can inhibit sensitization of nociceptive pain pathways (21,22]. Clinical studies suggest that opioids actually amplify pain transmission [23]; one mechanism may be, for example, ketamine-sensitive phosphorylation of spinal NMDA receptors (NR2B at Tyr1472)[24].

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