



- **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).

- 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 (PKC α , β I and β II), 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) TNF α , 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].

REFERENCES

1. Brennan, T. J. Pathophysiology of postoperative pain. *Pain* 2011; 152, S33.
2. Pogatzki-Zahn, E. M., Zahn, P. K., & Brennan, T. J. Postoperative pain--clinical implications of basic research. *Best practice & research clinical anaesthesiology* 2007; 21, 3–13.
3. Deumens R, Steyaert A, Forget P, Schubert M, Lavand'homme P, Hermans E, De Kock M. Prevention of chronic postoperative pain: cellular, molecular, and clinical insights for mechanism-based treatment approaches. *Prog Neurobiol.* 2013;104:1-37.
4. Dahl JB, Kehlet H. Postoperative pain and its management. In: McMahon SB, Koltzenburg M, editors. *Wall and Melzack's textbook of pain.* Elsevier Churchill Livingstone; 2006. p 635–51.

5. Pogatzki EM, Gebhart GF, Brennan TJ. Characterization of A-delta- and C-fibers innervating the plantar rat hindpaw one day after an incision. *J Neurophysiol* 2002;87:721–31.
6. Spofford, C. M., & Brennan, T. J. Gene expression in skin, muscle, and dorsal root ganglion after plantar incision in the rat. *Anesthesiology* 2012;117, 161–172.
7. Carvalho B, Clark DJ, Angst MS. Local and systemic release of cytokines, nerve growth factor, prostaglandin E2, and substance P in incisional wounds and serum following cesarean delivery. *J Pain* 2008;9:650–7.
8. Kido, K., Gautam, M., Benson, C. J., Gu, H., & Brennan, T. J. Effect of deep tissue incision on pH responses of afferent fibers and dorsal root ganglia innervating muscle. *Anesthesiology* 2013; 119, 1186–1197.
9. Xu, J., & Brennan, T. J. The pathophysiology of acute pain: animal models. *Current opinion in Anaesthesiology* 2011; 24, 508–514.
10. Carreira, E. U., Carregaro, V., Teixeira, M. M., Moriconi, A., Aramini, A., Verri, W. A., Ferreira, S. H., Cunha, F. Q., & Cunha, T. M. Neutrophils recruited by CXCR1/2 signalling mediate post-incisional pain. *European Journal of Pain* 2013;17: 654–663.
11. Sahbaie, P., Li, X., Shi, X., & Clark, J. D. Roles of Gr-1+ leukocytes in postincisional nociceptive sensitization and inflammation. *Anesthesiology*;2012;117, 602–612.
12. Fragiadakis GK, Gaudillière B, Ganio EA, Aghaepour N, Tingle M, Nolan GP, Angst MS. Patient-specific Immune States before Surgery Are Strong Correlates of Surgical Recovery. *Anesthesiology* 2015;123(6):1241-55.
13. Martinez V, Ben Ammar S, Judet T, Bouhassira D, Chauvin M, Fletcher D. Risk factors predictive of chronic postsurgical neuropathic pain: the value of the iliac crest bone harvest model. *Pain* 2012;153(7):1478-1483.
14. Vandermeulen EP, Brennan TJ. Alterations in ascending dorsal horn neurons by a surgical incision in the rat foot. *Anesthesiology* 2000;93:1294–302.
15. Zahn, P. K., Pogatzki-Zahn, E. M., & Brennan, T. J. Spinal administration of MK-801 and NBQX demonstrates NMDA-independent dorsal horn sensitization in incisional pain. *Pain* 2005;114, 499–510.
16. Wang, Y., Wu, J., Guo, R., Zhao, Y., Zhang, M., Chen, Z., Wu, A., & Yue, Y. (2013). Surgical incision induces phosphorylation of AMPA receptor GluR1 subunits at Serine-831 sites and GluR1 trafficking in spinal cord dorsal horn via a protein kinase C γ -dependent mechanism. *Neuroscience* 2013;240, 361–370.
17. Guo, R., Zhao, Y., Zhang, M., Wang, Y., Shi, R., Liu, Y., Xu, J., Wu, A., Yue, Y., Wu, J., Guan, Y., & Wang, Y. (2014). Down-regulation of Stargazin inhibits the enhanced surface delivery of α -amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor GluR1 subunit in rat dorsal horn and ameliorates postoperative pain. *Anesthesiology* 2014;121, 609–619.
18. Hayashida K1, DeGoes S, Curry R, Eisenach JC. Gabapentin activates spinal noradrenergic activity in rats and humans and reduces hypersensitivity after surgery. *Anesthesiology*. 2007;106(3):557-62.
19. Reichl S, Segelcke D, Keller V, Jonas R, Boecker A, Wenk M, Evers D, Zahn PK, Pogatzki-Zahn EM. Activation of glial glutamate transporter via MAPK p38 prevents enhanced and long-lasting non-evoked resting pain after surgical incision in rats. *Neuropharmacology* 2016;105:607-17.
20. Reichl S, Augustin M, Zahn PK, Pogatzki-Zahn EM. Peripheral and spinal GABAergic regulation of incisional pain in rats. *Pain*. 2012;153(1):129-41.
21. Terman GW1, Eastman CL, Chavkin C. Mu opiates inhibit long-term potentiation induction in the spinal cord slice. *J Neurophysiol*. 2001;85(2):485-94.
22. Drdla-Schutting R1, Benrath J, Wunderbaldinger G, Sandkühler J. Erasure of a spinal memory trace of pain by a brief, high-dose opioid administration. *Science*. 2012;335(6065):235-8.
23. Guignard B1, Bossard AE, Coste C, Sessler DI, Lebrault C, Alfonsi P, Fletcher D, Chauvin M. Acute opioid tolerance: intraoperative remifentanyl increases postoperative pain and morphine requirement. *Anesthesiology*. 2000;93(2):409-17.
24. Gu, X., Wu, X., Liu, Y., Cui, S., & Ma, Z. (2009). Tyrosine phosphorylation of the N-Methyl-D-Aspartate receptor 2B subunit in spinal cord contributes to remifentanyl-induced postoperative hyperalgesia: the preventive effect of ketamine. *Molecular pain* 2009;5, 76.

AUTHORS

Timothy J. Brennan, MD, PhD
Samir Gergis Professor and Vice Chair for Research
Interim Director Acute Pain Service
Department of Anesthesia
Roy J. and Lucile A. Carver School of Medicine
University of Iowa
Iowa City, Iowa

Esther Pogatzki-Zahn, Prof. Dr.med.
Department of Anesthesiology, Intensive Care and Pain Medicine
University Hospital Muenster
Albert-Schweitzer-Campus
Muenster, Germany

REVIEWERS

Gregory Terman, MD, PhD
Professor, Department of Anesthesiology and Pain Medicine and the Graduate Program in Neuroscience
University of Washington
Director, Acute Pain Service, University of Washington Medical Center
Seattle, Washington, USA

Patrick Tighe, MD, MS
Associate Professor of Anesthesiology
Program Director, Perioperative Analytics Group
Acute and Perioperative Pain Medicine Faculty
Department of Anesthesiology
University of Florida
Gainesville, Florida, USA

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