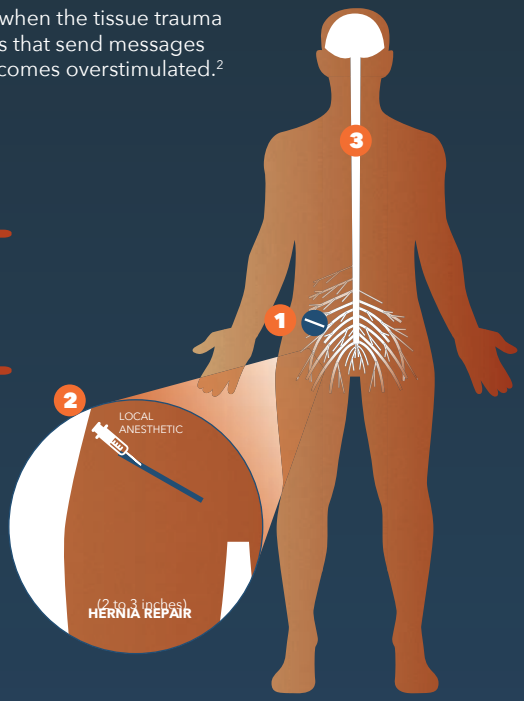
IMAGINE WHAT LONGER PAIN RELIEF MIGHT LOOK LIKE

HERON THERAPEUTICS

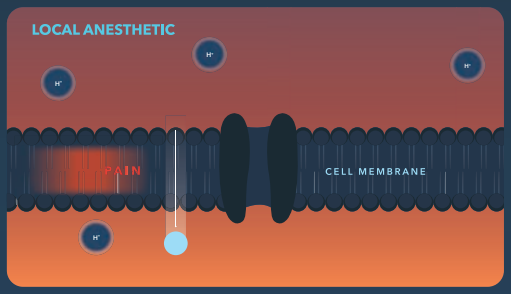
HOW LOCAL ANESTHETICS WORK TO BLOCK PAIN SIGNALS POSTSURGERY

Patients experience their most severe postsurgical pain in the first 72 hours.[1]

1. Nociceptive pain is caused by the cutting of tissues and nerve fibers during surgery.[2]
2. The inflammatory process increases acidity at the surgical site. Inflammatory pain increases sensitivity to the affected area and encourages patients to reduce movement of, or contact with, the injury until repair is complete to minimize further damage.[2,3]
3. Neuropathic pain is caused when the tissue trauma overloads the pain receptors that send messages to the spinal cord, which becomes overstimulated.[2]



Local anesthetics such as bupivacaine work by stopping pain at the source. Unfortunately, generic local anesthetics are not designed to provide pain relief beyond 8 to 12 hours. Longer-acting local anesthetics exhibit limited and inconsistent efficacy beyond 24 hours in part because the inflammatory process inhibits their ability to penetrate the nerve cell membrane.[3-6]

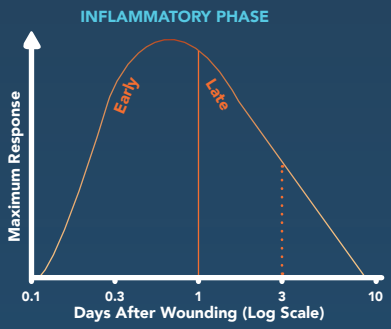


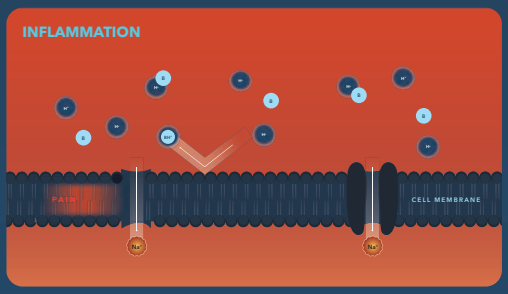
Bupivacaine must be in its un-ionized form to penetrate nerve cell membranes and stop pain at the site of injury. Once inside the nerve cell, the bupivacaine becomes ionized. Now in its active form, it can effectively block the voltage-gated sodium ion channels, preventing pain signals from propagating along the nerve cell.[4]

THE INFLAMMATORY PROCESS CAUSED BY TISSUE INJURY DURING SURGERY CAN INHIBIT BUPIVACAINE FROM PENETRATING THE NERVE CELL MEMBRANE, LIMITING ITS EFFICACY.[3]

HOW INFLAMMATION INHIBITS THE EFFICACY OF BUPIVACAINE

The inflammatory phase is a normal component of the wound-healing process and occurs regardless of whether the injury was caused by trauma or precise tissue disruption, such as surgery.[2,7]





As the inflammatory process unfolds, the wound site becomes increasingly acidic. This acidity causes more bupivacaine to become ionized, preventing it from entering the nerve cell. Because the ionized bupivacaine molecules cannot penetrate the nerve cell membrane, they are unable to block the pain signals from propagating at the surgical site and traveling to the brain.[3]

Inflammation reaches its peak around 24 hours following surgery but remains relatively high through the first 72 hours following surgery.[7]

References: 1. Svensson I, Sjöström B, Haljamäe H. Assessment of pain experiences after elective surgery. *J Pain Symptom Manage.* 2000;20(3):193-201. doi:10.1016/S0885-3924(00)00174-3. **2.** Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med.* 2004;140(6):441-451. doi:10.7326/0003-4819-140-8-200404200-00010. **3.** Becker DE, Reed KL. Essentials of local anesthetic pharmacology. *Anesth Prog.* 2006;53(3):98-109. doi:10.2344/0003-3006(2006)53[98:EOLAP]2.0.CO;2. **4.** Berde CB, Strichartz GR. Local anesthetics. In: Miller RD, Cohen NH, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, eds. *Miller's Anesthesia.* Vol 2. 8th ed. Philadelphia, PA: Saunders; 2015:1012-1054.e4. **5.** Carvalho B, Clark DJ, Yeomans DC, Angst MS. Continuous subcutaneous instillation of bupivacaine compared to saline reduces interleukin 10 and increases substance P in surgical wounds after cesarean delivery. *Anesth Analg.* 2010;111(6):1452-1459. doi:10.1213/ANE.0b013e3181f579de. **6.** Kim J, Burke SM, Kryzanski JT, et al. The role of liposomal bupivacaine in reduction of postoperative pain after transforaminal lumbar interbody fusion: a clinical study. *World Neurosurg.* 2016;91:460-467. doi:10.1016/j.wneu.2016.04.058. **7.** Enoch S, Leaper DJ. Basic science of wound healing. *Surgery (Oxford).* 2008;26(2):31-37. doi:10.1016/j.mpsur.2007.11.005. doi:10.1177/0022034509359125.