Anesthesiology 2010; 112:511–3

Preclinical Research on Persistent Postsurgical Pain

What We Don't Know, but Should Start Studying

What Exactly Is Persistent Postsurgical Pain?

After surgical interventions, of skin, bone, or soft tissues, patients require analgesic therapy because they experience ongoing pain or are sensitive to incident, normally nonpainful stimulation. The intensity and duration of postsurgical pain vary, but with uncomplicated wound healing, the pain typically shows progressive attenuation. However, some patients experience deep pain or pain referred to the dermatomes that correspond to the operated organ, which persists for months or even years.[1] The nature and properties of persistent postsurgical pain are poorly characterized. Descriptions of postsurgical pain often do not differentiate between spontaneous pain and pain that is dependent on external stimulation, for example, clothing that touches the skin near the scar. We do not know whether there is a distinct transition period between acute and chronic pain or whether the chronic condition constitutes merely an extension of perioperative pain. Are the mechanisms responsible for sustained pain the same as those underlying acute postsurgical pain, or does, in this subgroup of patients, the trauma associated with the surgical intervention provoke different changes in sensory processing?

Potential Mechanisms

Surgery causes the release of inflammatory mediators, such as prostaglandins and cytokines,[2] that activate and sensitize primary sensory afferents. Peripheral sensitization and facilitation of synaptic transmission in the central nervous system normally resolve over time and afferent input is likely to decrease during wound healing. However, in some cases, inflammation may persist. For example, tension-reduced hernia repair with a prosthetic mesh generates a marked inflammatory response around the synthetic material that outlasts the healing of the superficial wound.[3] Surgical interventions such as thoracotomy or bunionectomy are also often accompanied by varying degrees of stretch or severing of peripheral nerves, risking the development of neuropathic pain. Sustained ectopic activity of primary sensory afferents and changes in spinal inhibition and facilitation may result. Persistent inflammation and nerve injury may lead to changes in gene expression, a phenotypical shift of primary sensory neurons, and activation of peripheral immune and glial cells, all contributing to lasting pain. Combinations of inflammatory and neuropathic mechanisms are likely to occur, for example, after removal of a herniated intervertebral disk or visceral surgery.

Do We Have Valid Preclinical Models?

To develop strategies for the prevention and treatment of persistent pain after surgery, we need preclinical models that replicate the complexity of the human condition. Only valid surrogate models of pain will provide the mechanistic insight necessary to identify risk factors for chronic pain, improve their management, and compare the efficacy of symptomatic *versus* disease-modifying therapies. Most preclinical studies rely on rodent models. They have been created using interventions similar to surgery in humans, for example, incisions of skin and muscles.[4] In general, these models are used to examine the consequences of wounding on primary afferent activity and characterize rapid changes in signal transduction, including peripheral sensitization of nociceptors. Incision models are useful for determining the efficacy of pharmacologic treatment during the early postsurgical phase. Although not typically associated with long-term changes, incisional injury indeed predisposes both neonate[5] and adult animals[6] to enhanced pain sensitivity when a second injury is applied several weeks later.

Subcutaneous, intramuscular, or intraarticular injections of irritants such as formalin or complete Freund's adjuvant induce inflammation associated with transient pain-related

Accepted for publication November 20, 2009. Dr. Scholz is receiving grant support from the National Institute of Neurological Disorders and Stroke (NINDS) (Bethesda, Maryland) and GlaxoSmithKline (London, United Kingdom). Dr. Scholz has received speaker's fees from GlaxoSmithKline and Pfizer (New York, New York) and grant support from Pfizer and Pharmacia (Peapack, New Jersey). The grant support from Pharmacia was provided through the Quality Care Research Fund of the Academic Medicine and Managed Care Forum. Dr. Scholz has acted as a consultant for GlaxoSmithKline and Pfizer and has served on an advisory board for Pfizer. Dr. Yaksh is receiving grant support from the NINDS and the National Institute on Drug Abuse (Bethesda, Maryland). Dr. Yaksh has received speaker's fees from Amylin (San Diego, California), InSet (Mount Olive, New Jersey), and Johnson & Johnson (Langhorne, Pennsylvania). He has undertaken contract work with Abbott (Abbott Park, Illinois) and Ironwood (Cambridge, Massachusetts), served as a consultant for Neuroadjuvants (Salt Lake City, Utah), and serves on the advisory board for Solace (Cambridge, Massachusetts).

Timothy J. Brennan, Ph.D., M.D., served as Handling Editor for this article.

behavior (present for minutes to days).[7] Models of inflammatory pain are therefore used to study the short-term consequences of surgery on sensory function and pain. Longer-lasting behavioral changes (persisting for weeks to months) are observed in models of nerve injury, including partial or complete ligation, transection, or neurectomy of cranial (trigeminal), peripheral or spinal nerves, or nerve roots. Nerve injury provokes neural and immune changes that differ from those observed in models of acute postsurgical pain or inflammation; in fact, exposure of a nerve by skin and muscle incision is a standard control procedure for experimental nerve lesions. Redistribution of the voltage-gated sodium channel subunit Nav1.8, which is predominantly expressed in nociceptors, and microglial activation in the ipsilateral dorsal horn of the spinal cord are examples of nerve injury-induced changes that contribute to the development of neuropathic pain but seem not to be involved in the induction of pain-like behavior after skin and muscle incision.[8,9] Nerve injury models are valuable tools for studying the consequences of surgical interventions that carry a risk for intraoperative nerve lesion. Such nerve lesions are likely to promote the development of persistent pain because they provoke long-term changes, for example, altered gene expression in the dorsal root ganglia and the spinal cord, central sensitization, and transsynaptic neurodegeneration.

Preclinical models of postsurgical pain, whether acute or persisting, have face validity because they produce increased withdrawal responses to calibrated mechanical or thermal stimulation that are reminiscent of pain elicited by normally nonpainful stimuli (allodynia) and increased sensitivity to painful stimuli (hyperalgesia), both common features of postoperative pain in humans. Assessing spontaneous pain in rats or mice, the two species most frequently used, is difficult, but presumptive parameters of spontaneous pain such as changes in exploratory behavior, vocalization, and conditioned place preference should be considered in the evaluation of animal models.[10,11] Veterinarians are routinely required to monitor pain in their patients after surgical interventions that are no less complex than those performed on humans. Reports of postsurgical pain in, for example, dogs or horses and guidelines developed for pain assessment in these species[12] are valuable yet underutilized resources for improving the design of preclinical research on pain after surgery.

What We Should Start Studying

First, studies on the prevention of persistent pain need to be distinguished from those focusing on preemptive or short-term perioperative analgesia. Preclinical models involving long-term neurobiologic and behavioral changes must reflect a time course that exceeds the duration of wound healing. Although we hesitate to specify an interval, 14–21 days after surgery would seem to be minimal. Second, analgesic treatment applied long enough to prevent the transition from acute to chronic pain—if the two processes can be separated and are not independent of each other—needs to be distinguished from disease-modifying interventions aimed to block, for example, central sensitization or the immune response to nerve injury. Third, timing of intervention is crucial. Drugs delivered before and early after surgery are preemptive if they reduce perioperative pain, and preventive if they block the development of sustained pain. Treatment initiated later after the surgical intervention may reverse persistent pain and prevent a relapse if the reversal is sustained beyond the pharmacokinetic activity of the drug at its molecular target.

Conclusion

Chronic pain after surgery is likely to result from a complex combination of mechanisms, and the relative contribution of each of these mechanisms to the persistence of pain will differ between surgical procedures. Most preclinical studies on postsurgical pain have focused on the immediate perioperative period. To make progress, we must characterize these models with respect to the sequence of associated inflammatory or neuropathic changes and their potential to induce sustained pain. Testing pain-related behavior should include withdrawal responses after stimulation and parameters of spontaneous pain to validate animal models against the phenotypes of postsurgical pain in humans. Ultimately, validation will require similar treatment success or failure in the surrogate model and the human condition, and the ability to predict treatment efficacy in humans. Genetic factors, gender, and age have an effect on the risk for developing chronic pain and should therefore be evaluated.[13,14] The epidemiologic significance of chronic pain after surgery is enormous. Successful prevention and effective management will depend on the identification of targets for disease-modifying intervention rather than analgesia alone.

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ANESTHESIOLOGY REFLECTIONS

Antique Chinese Diagnostic Dolls

For centuries, traditional Chinese physicians observed the *Nei Ching* by conducting "pulse diagnosis" on superficial and then deep pulsations at three discrete locations along the course of first the right and then the left radial pulses of their female patients. However, by the 1700s until as recently as the 1950s, Chinese social conventions were discouraging such cross-gender contact between strangers. So to preserve their modesty, aristocratic ladies—or their maid servants—would localize symptoms by pointing to corresponding sites on ivory figurines (*such as the copies above, courtesy of the Wood Library-Museum*). Such diagnostic dolls were typically naked except for shoes and often earrings, bracelets, or flower bouquets. When not in use, most statuettes reclined upon mahogany beds. (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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