Published in final edited form as:
Curr Opin Anaesthesiol. 2011 October ; 24(5): 508–514. doi:10.1097/ACO.0b013e32834a50d8.

The Pathophysiology of Acute Pain: Animal Models

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Abstract

Purpose of review—Trauma, surgery and burns are three common clinical scenarios that are associated with significant acute pain. This review describes the pathophysiology of acute pain utilizing three preclinical models: surgery, burn, and fracture.

Recent findings—In general, there is greater interest directed toward peripheral mediators of acute pain. Studies indicate that treatment against nerve growth factor, interleukins, and ischemic-like mediators may provide valuable avenues for treatment of acute pain. By targeting the periphery, analgesic therapies may be reduced side effects.

Summary—Peripheral mediators of acute pain will vary depending upon the type of injury. Treatment aimed toward those mediators specific to the injury could improve acute pain management in the future. It will be important to translate these findings into clinical trials in the future.

Keywords

Incision; fracture; burn; nociception; hyperalgesia

Introduction

Surgery, burn injury and fracture can lead to severe acute pain. Adequate pain control is a key priority for patients to start early rehabilitation, which is crucial for restoring function and reducing morbidity and mortality after these acute events [1-3]. The effectiveness of these currently utilized analgesic therapies is often limited [4] and these treatments can, in some cases, have deleterious side effects. Thus, novel analgesics without side effects are needed for pain after these injuries; furthermore, a better understanding of pain caused by these acute events is needed to guide development new therapeutic approaches.

Animal models of fracture pain

Two preclinical animal models of fracture pain have recently been developed in rodents, a closed femur fracture pain model in mouse and rat [5, 6] and a closed tibia fracture pain model in mouse [7]. These two models are adapted from common fracture models, which have been used for studies of bone reconstruction and bone healing [8, 9].

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In the femur fracture model, fracture induced spontaneous pain-related behaviors including flinching and guarding [5, 10]. These behaviors were sustained through approximately 18 days after fracture. Fracture-induced pain was also assessed by measuring movement-evoked flinching and guarding [10]. Similar to the time-course of spontaneous behaviors, movement-evoked flinching and guarding peaked at day 2 post-fracture, decreased gradually and continued through day 18 post-fracture (Fig. 1). Compared to spontaneous behaviors, these behaviors evoked by movement were significantly greater in magnitude and appear to mirror exacerbated pain experienced by patients when they utilize their fractured limb [11]. In addition, reduced ability to bear weight on the fractured limb was also observed in this model [5, 12].

In the tibia fracture model, guarding behavior was observed as well [7]. This spontaneous pain-related behavior peaked immediately after tibial fracture (2 hr post-fracture) and remained evident until 7 days afterwards. In contrast to the femur fracture pain model, spontaneous flinching was not observed following tibial fracture. Tibial fracture-induced pain was also assessed by measuring responses of animals to mechanical and heat stimuli. Both mechanical and heat nociceptive behaviors were the greatest immediately after fracture and sustained for 7 days.

These animal models of fracture pain have been further validated with existing analgesics effective in treating pain in patients experiencing fracture. If analgesics used in patients also reduce pain-related behaviors in these models, it suggests similar pathophysiology between patients with fracture and the models. Administration of morphine dose-dependently reduced spontaneous flinching and guarding and also improved weight bearing on the fractured limb [5]. On day 1 or day 2 following tibial fracture, both morphine and ketoprofen, a non-selective cyclooxygenase −1 and −2 inhibitor, attenuated spontaneous pain-related behaviors as well as mechanical and heat nociception [7].

Animal models of burn pain

Several preclinical animal models have been developed to study underlying mechanisms of burn injury-induced pain. To prepare these models, varied thermal injury parameters (temperature range and burn duration), injury sites and thermal devices were utilized and, consequently, generated differential pain-related behaviors. All burns were performed while animals underwent general anesthesia. A mild burn injury (52.5 ± 1.0 °C for 45 sec) at the rat plantar hindpaw with a hot plate induced consistent but short-lasting primary heat hyperalgesia which was present only at 30 min post-injury [13, 14]. No evident primary mechanical hyperalgesia was observed. Outside the mild burn area, secondary mechanical hyperalgesia peaked at 30 to 60 min post-injury and gradually resolved in 3 hours. Secondary heat hyperalgesia did not develop. Finally, Wang et al. established another model of burn pain by immersing the dorsal part of rat hindpaw into a hot water bath (85 °C for 12 sec) and measured behavioral responses at the uninjured plantar side [15]. Such a burn injury induced profound secondary mechanical and heat hyperalgesia which were apparent by day 1 post-injury and sustained throughout the next 7 days.

Primary mechanical hyperalgesia at the burn site (procedural pain) is the most intense type of pain in burn patients [16, 17]. In an effort to develop an animal model exhibiting burn-induced primary mechanical hyperalgesia, Summer et al. [18] used a thermal probe with fine temperature control (52.5 ± 0.1 °C for 45 sec). In this model, a 60% reduction in mechanical withdrawal threshold at the injured site was observed at 30 min post-injury. This primary hypersensitivity peaked at day 3 and persisted throughout the 7-day study. Profound primary mechanical hyperalgesia was also present in a model developed more recently by Chang et al. [19]. In this model, the rat plantar hindpaw was placed on a hot plate at 85.0 ± 0.5 °C for

15 sec. Primary mechanical hyperalgesia was observed 1 day after injury and persisted for the entire duration of the 8-week study (Fig. 2).

Mechanisms of burn pain

Peripheral and spinal mechanisms underlying burn pain have been investigated using these preclinical animal models. The cannabinoid receptor (CB) was recently reported as a therapeutic target that could be utilized in the future for the treatment of burn pain [20]. Local injection of cannabinoid receptor agonists into the burn injury site at the rat hindpaw dose-dependently reversed both primary mechanical and heat hyperalgesia. Such antinociceptive action was largely blunted when the CB agonist was co-injected with a CB1 antagonist, but not when the CB agonist was co-injected with CB2 antagonist.

Burn-induced nociception is also mediated by nerve growth factor (NGF) and its cognate receptor, the tyrosine kinase A (TrkA) pathway. Following a large burn injury (25% of total body surface), NGF was upregulated in healing skin and the occurrence of systemic hyperalgesia by the injury was prevented with anti-NGF treatment [21]. Burn-induced hyperalgesia was also attenuated by down-regulation of TrkA in primary sensory neurons with antisense oligodeoxynucleotides (ODN) [18].

The pathogenesis of burn pain also involves an inflammatory component. In burn-injured tissue, a sustained local increase of interleukin-6 (IL-6) was observed for 6 days [22]. Disruption of IL-6 signaling by knocking down glycoprotein (gp130), the signal transducing subunit of IL-6 receptor, in primary sensory neurons with antisense ODN or by functional blocking the cytokine with anti-IL-6 antibodies attenuated burn-induced hyperalgesia.

In the spinal cord, burn injury induced microglial activation as evidenced by increased cell density of microglia in the spinal dorsal horn and enhanced phosphorylation of p38 MAPK (P-p38 MAPK), which was predominantly localized to microglia [19, 23]. Suppression of glial p38 MAPK activation with a specific inhibitor (SB203580 and SD-282) or minocycline suppressed the development of hyperalgesia after burn injury [23, 24], suggesting a contribution of spinal microglia to the development of burn pain.

Animal model of postoperative pain

Several rodent models have been developed for studying the pathophysiology of postoperative pain. Among them, the plantar incision model has been most widely used [25]. This model is produced by a simple incision that includes skin, fascia and deep muscle tissue at the plantar side of rat hindpaw under general anesthesia. Following the plantar incision, animals exhibited non-evoked guarding behavior, a posture noted after hindpaw incision. It peaked immediately after incision (4hr post-incision) and resolved within 3-4 days. Non-evoked guarding likely correlates to pain at rest in patients after surgery. An incision in rat plantar hindpaw also induced hyperalgesia to mechanical and heat stimulation [26]. The greatest level of primary mechanical and heat hyperalgesia was present early after incision (2 hr post-incision). Primary mechanical hyperalgesia usually resolved within 5-6 days after incision, whereas primary heat hyperalgesia tended to last longer and returned to pre-incision level over 7-10 days. In addition, secondary mechanical hyperalgesia, but not secondary heat hyperalgesia, was observed in the plantar incision model [26].

Pain-related behaviors in the plantar incision model could be differentially inhibited by systemic morphine at doses similar to those applied in human postoperative pain studies [27]. Non-evoked guarding was most responsive to morphine and could be attenuated by a dose of 0.03 mg/kg. Greater doses were needed to reduce primary mechanical (1 mg/kg) and heat (0.3 mg/kg) hyperalgesia.

Other types of surgical procedures have been employed to model postoperative pain in animals. In comparison to the plantar incision model involving an incision in glabrous skin, a hairy-skin incision model was developed by making an incision in skin on the back of rats [28]. Mechanical hypersensitivity was induced at sites both close and distant to the incision in this model. To focus on secondary hyperalgesia, a rat gastrocnemius incision model involved an incision in the rat posterior hindlimb and behavioral responses were measured from the ipsilateral hindpaw [29, 30]. Abdominal surgery models including ovariohysterectomy and subcostal incision model closely mimicked surgical procedures to patients [31, 32]. These models possessed apparent clinical relevance and also included visceral injury component. Prolonged tissue retraction is a common practice in clinical surgeries. It was involved two animal models, postthoracotomy pain model and skin/muscle incision and retraction (SMIR) model [33, 34]. Incision in tissue followed by prolonged retraction induced long-lasting pain-related behaviors (approximately 20 to 40 days) in these two models.

Mechanisms of postoperative pain

Based on the plantar incision model, a series of studies using behavioral and neurophysiological approaches have enriched our understanding of the etiology of postoperative pain. Incision in rat plantar hindpaw induced hyperexcitability of both primary afferent nociceptors and nociceptive neurons in the spinal cord [35-41]. These processes of peripheral and central sensitization are believed to be the neural basis of postoperative pain. Spontaneous activity in pain transmission pathways was significantly increased following incision [35-40]. This elevation in neuronal spontaneous activity correlated the occurrence of non-evoked guarding behavior. Further, increased spontaneous activity in spinal dorsal horn neurons could be reversed by infiltration of local anesthetic into the incised tissue, indicating that peripheral inputs drove the neuronal hyperexcitability at the spinal level [38-40].

More recent studies have closely examined the specific contribution of different tissues to pain-related behaviors and neuronal hyperexcitability after incision. Incised deep tissue (fascia and muscle) rather than skin had a predominant role in the genesis of non-evoked guarding and spontaneous activity in nociceptors (Fig. 3) and nociceptive transmitting dorsal horn neurons, whereas incision in skin alone was sufficient to induce mechanical and heat hyperalgesia [39, 42]. Such differential contributions to incisional pain by cutaneous versus deep tissue have also been indicated by human studies [43-46].

Several mediators of incisional pain have been suggested based on preclinical studies. Incision in plantar hindpaw induced a decrease in tissue pH (lowest pH = 6.8) and an increase in lactate concentration (peak = 5 mM) locally for several days [47, 48]. These changes in local chemicals paralleled pain-related behaviors after incision. In addition, nociceptors in incised tissue exhibited greater sensitivity to lactic acid compared to those in intact tissue [36, 49]. Together, it suggests that an ischemic-like signal contributes to pain caused by incisions.

NGF is another component of the local chemical environment, which can sensitize nociceptive nerve endings surrounding the incision site. An increase of NGF expression in injured tissue occurred within hours after incision and returned to baseline in approximately 7 days [50-52]. Fibroblasts and Schwann cells adjacent to the incision were sources of NGF [51, 52]. Treatment of anti-NGF antibody dose-dependently attenuated non-evoked guarding [50]. Anti-NGF also induced moderate inhibition of heat hyperalgesia but had no effect on mechanical responses of incised hindpaw.

The transient receptor potential vanilloid 1 (TRPV1) receptor is considered a molecular integrator of various nociceptive stimuli. In incision-induced pathological conditions, blockade of TRPV1 with an antagonist (AMG0347) only exerted moderate inhibition of heat hyperalgesia and did not affect guarding or mechanical responses [27]. Similar findings were observed in TRPV1 knockout mice when incision was made in the mouse plantar hindpaw [53].

Although the TRPV1 receptor itself does not appear to be a key mediator of postoperative pain, TRPV1 expressing nociceptors are likely the critical afferents transmitting postoperative pain. Treatment of dilute capsaicin (0.025-0.10%), a specific activator of TRPV1, attenuated non-evoked guarding in a dose-dependent manner [54]. It also inhibited heat hyperalgesia but did not alter hypersensitivity to mechanical stimulation. Further studies suggested that capsaicin at low concentrations might selectively affect nociceptive transducing pathways since it interfered with chemo- and heat sensitivity, but not mechanosensitivity of C-nociceptors [55].

Conclusion

Several preclinical animal models for surgery, fracture and burn pain have been developed and exhibit different forms of pain-related behaviors. The complex mechanisms underlying pain in these models may include inflammatory, ischemic and neuropathic components. Key mediators contributing to the pathogenesis of pain after these acute injuries like NGF, cannabinoids, IL-6, ischemic mediators and TRPV1 containing afferents are being explored at both the peripheral and spinal levels.

Acknowledgments

This work was supported by the Department of Anesthesia at the University of Iowa and by National Institutes of Health, Bethesda, Maryland grant GM-55831 Nociception from Deep Muscle Incision to T.J.B.

T.J.B. currently is a consultant for Cubist Pharmaceuticals. He has served as a consultant in the past for PainReform, Xenon Pharmaceuticals, Covidian, AnaptysBio, Trevena, Inc., and Angiochem. T.J.B. has served on the Pfizer Advisory Board in the past. T.J.B. has current grants from Hydra Biosciences and Ironwood Pharmaceuticals. He has an ongoing grant with Galleon Pharmaceuticals. He has received grants in the past from Kai Pharmaceuticals and Adynxx, Inc.

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Key points

* Optimizing preclinical animal pain models is critical for elucidating the pathophysiology of acute pain.

* In contrast to chronic pain models induced by chemicals or nerve ligations, clinically relevant injuries are utilized to model acute pain preclinically.

* Different types of acute tissue injury can result in specific patterns of pain-related behaviors in these rodent models.

* Non-evoked ongoing pain is an important, overlooked component of acute pain and is likely transmitted by increased spontaneous activity in nociceptive pathways.

* Peripheral sensitization appears to make a major contribution to the development of acute pain and several key targets in the periphery have been suggested.

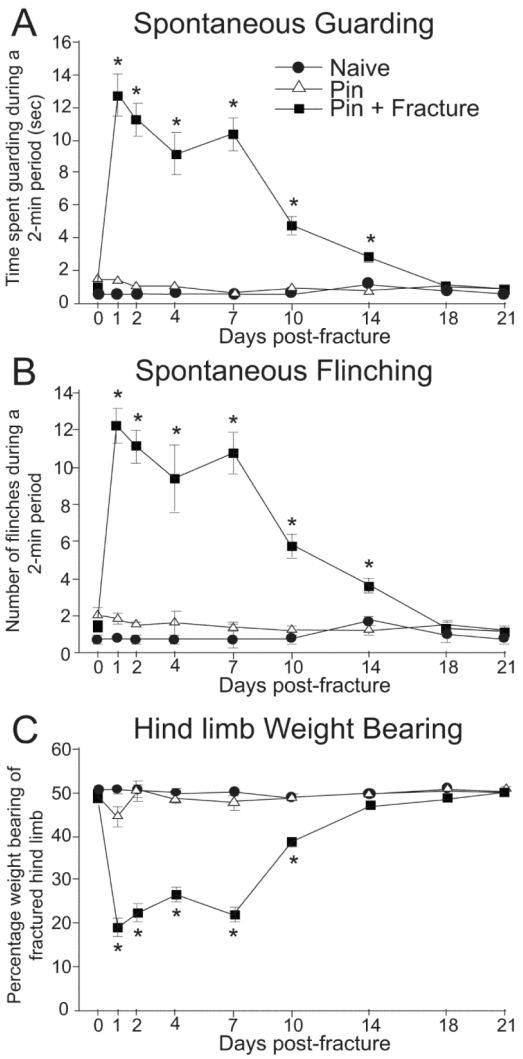

Fig. 1.

Guarding, flinching and weight bearing in female rats after closed fracture of the femur. Three groups of rats were studied, naïve, those with a pin in the femur only, and those with a pin plus a fracture. P <0.05 vs. pin. There is no difference between naïve and pin rats. Reprinted with permission from Freeman K, Koewler N, Jimenez-Andrade J, et al. A Fracture Pain Model in the Rat: Adaptation of a Closed Femur Fracture Model to Study Skeletal Pain. Anesthesiology 108(3), 477.

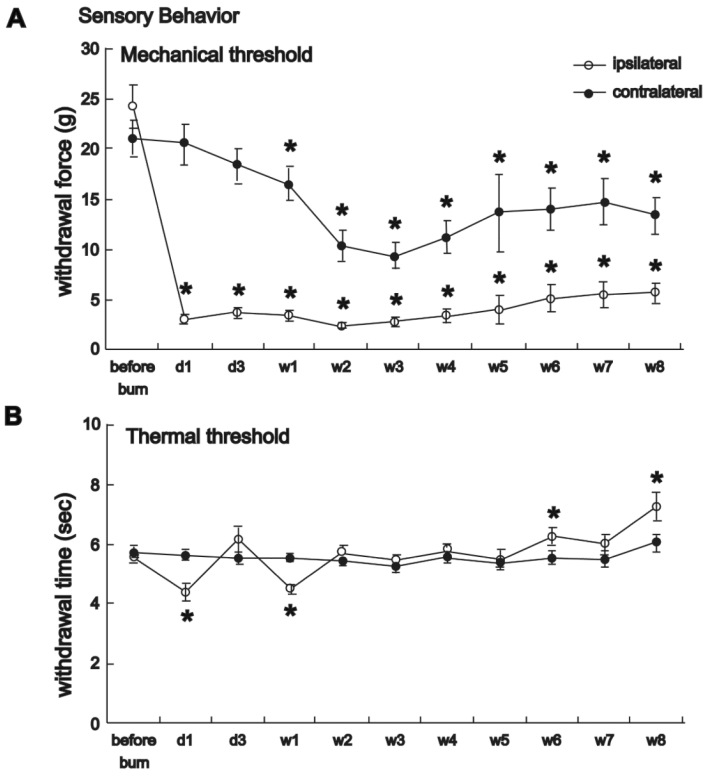

Fig. 2.

Behavioral studies after surface burn. A. Time course of mechanical withdrawal threshold in a burn injury model. Mechanical hyperalgesia persisted through 8 weeks. Hyperalgesia was also evident in the non-injured contralateral paw. B. Heat hyperalgesia was transient, only apparent one day and one week after surface burn. Data are graphed as mean ± standard error of the mean. * $P < 0.05$ after injury, compared to before injury. D=day; W=week. Reprinted from The Journal of Pain, 11(2), Chang Y-W, Tan A, Saab C, Waxman S, Unilateral Focal Burn Injury Is Followed by Long-Lasting Bilateral Allodynia and Neuronal Hyperexcitability in Spinal Cord Dorsal Horn, 121, Copyright 2010, with permission from Elsevier.

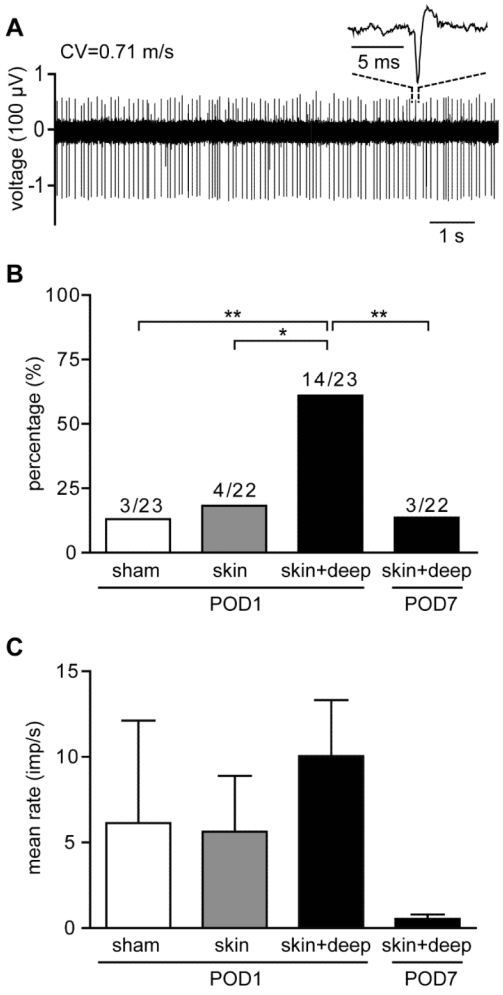

Fig. 3.

Spontaneous activity of afferent fibers in 4 groups: one day after sham procedure, one day after skin, or one day after skin plus deep tissue incision, and 7 days after skin plus deep tissue incision. (A) Digitized oscilloscope trace of action potentials (inset is a representative single action potential) of a C-nociceptor 1 day after skin plus deep tissue incision. (B) Percentage of afferents with spontaneous activity in the 4 groups. (C) Comparison of average activity among the 4 groups. Imp = impulse. * $P < 0.5$, ** $P < 0.01$ versus sham. Reprinted with permission from Freeman K, Koewler N, Jimenez-Andrade J, et al. A Fracture Pain Model in the Rat: Adaptation of a Closed Femur Fracture Model to Study Skeletal Pain. Anesthesiology 108(3), 477. Reprinted with permission from Xu J, Brennan TJ. Guarding Pain and Spontaneous Activity of Nociceptors after Skin versus Skin Plus Deep Tissue Incision. Anesthesiology 108(3), 477.