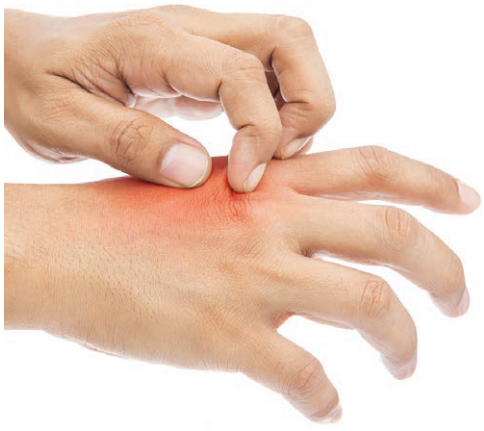
Central Sensitization, *N*-methyl-D-aspartate Receptors, and Human Experimental Pain Models

Bridging the Gap between Target Discovery and Drug Development

Srinivasa N. Raja, M.D., Eellan Sivanesan, M.D., Yun Guan, M.D., Ph.D.

The best available pharmacologic therapies for chronic pain leave much to be desired in terms of both effectiveness and tolerability. Additionally, the opioid epidemic that currently ravages the United States has highlighted an unmet need and spurred the urgent search for safer and more effective analgesics. Researchers are now working to develop targeted therapies based on advances in our understanding of the molecular mechanisms and pathophysiology of acute and chronic pain. One such mechanism is the concept of "central sensitization," a key component of postinjury pain hypersensitivity that was proposed over three and a half decades ago.[1,2] Intense noxious inputs induce a prolonged state of neuronal hyperexcitability in the central nervous system, particularly in the spinal dorsal horn. Among the neurochemical mechanisms that contribute to this central sensitization, activation of the *N*-methyl-D-aspartate (NMDA) receptor plays a pivotal role,[3] and NMDA antagonists were proposed as potential analgesics.[4] However, no new drugs targeting this site have shown beneficial clinical effects or been approved for pain treatment in decades. Hence, there is renewed interest in utilizing clinically available drugs of this class, such as ketamine and dextromethorphan, for pain management. In this issue of Anesthesiology, Martin *et al.*[5] use a human freeze injury model of cutaneous hypersensitivity to demonstrate that the noncompetitive NMDA antagonist dextromethorphan decreases both primary (at the site of tissue injury) and secondary (outside the injury site) hyperalgesia—surrogate measures of peripheral and central sensitization. These observations raise the intriguing question of whether human pain models can facilitate the translation of mechanism-based targets identified in animal models to clinically effective drugs.



"[Can] human pain models… facilitate the translation of mechanism-based targets identified in animal models to clinically effective drugs[?]"

The NMDA receptor is a membrane-bound, voltage-dependent ion channel that is widely distributed in the central nervous system and also expressed on primary sensory neurons. The role of NMDA receptors in the induction and maintenance of central sensitization and pathologic pain conditions has been well established in animal models.[3,6,7] These preclinical findings provide the scientific premise for testing NMDA antagonists as potential analgesics for treating perioperative pain and certain chronic pain states.

Central sensitization presents as amplification of sensory inputs and is characterized by allodynia, secondary hyperalgesia, and temporal summation or wind-up. It is normally an adaptive, self-limiting process to facilitate healing from injury. However, prolonged central sensitization is maladaptive and may lead to chronic pain.[2] In certain chronic pain states (*e.g.*, neuropathic pain), the central nervous system hypersensitivity may be triggered and maintained by ongoing activity from the nerve injury site. In other widespread chronic pain conditions (*e.g.*, fibromyalgia, irritable bowel syndrome, temporomandibular disease), the central activation and maintenance mechanisms may be autonomous and independent of peripheral input.

Unfortunately, the substantial advances in our understanding of the mechanisms involved in central sensitization have not translated to new pain treatments. The arduous

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This editorial accompanies the article on p. 356.

Accepted for publication April 3, 2019. From the Department of Anesthesiology and Critical Care Medicine (S.N.R., E.S., Y.G.), and the Department of Neurological Surgery (Y.G.), Johns Hopkins University, School of Medicine, Baltimore, Maryland.

 Anesthesiology 2019; 131:233–5. DOI: 10.1097/ALN.0000000000002808

<zdoi>; DOI: 10.1097/ALN.0000000000002808

journey from novel target identification in animal models to the development of a clinically effective drug is long, expensive, and risky. Many promising drug candidates for pain have failed in clinical trials owing to either a lack of analgesic effect or off-target actions. This history has led to an ongoing debate on the utility of animal models and the use of evoked pain as an outcome measure in the development of clinical analgesic drugs. Proof-of-concept studies in humans have been developed in an attempt to reduce the risks of failure during the translational process from bench to bedside. These early studies in human experimental models of prolonged but reversible pain and central sensitization are being explored as a possible bridge on the path to drug development.[8] Several models of hyperalgesia that use a variety of nociceptive inputs, including electrical, chemical (capsaicin, hypertonic saline), and thermal (hot, cold), have been established to help uncover pain mechanisms and predict the clinical effects of pharmacologic agents.[9,10]

In the freeze injury hyperalgesia model used by Martin *et al.*, certain approaches and results are worth highlighting.[5] Most earlier studies in human pain models evaluated the effects of a single drug dose. In this study, the effects of a 30-mg dose of dextromethorphan as well as repeated doses over a 24-h period were compared to placebo. Additionally, plasma concentrations of dextromethorphan and its metabolite, dextrorphan, were correlated with central and cognitive effects such as pupillary reactivity and repeated reaction time to visual stimuli. This approach allowed the authors to link the pharmacokinetic and pharmacodynamic aspects of the drug and its metabolite. Intriguingly, the authors observed conflicting effects of the drug and its metabolite on pupillary diameter. The effect of dextromethorphan on pupillary diameter was positively correlated with its plasma concentration, whereas the effect of dextrorphan was negatively correlated with its plasma concentration, suggesting that the actions of the drug and its metabolite differ. The investigators also observed that reaction time and the learning effect during repeated reaction time tests, but not motor response time, were impaired by dextromethorphan. These results are consistent with preclinical studies suggesting that learning and memory may be impaired by NMDA antagonists. Another important observation is that dextromethorphan decreased the primary and secondary hyperalgesia caused by mechanical pain stimuli but had no significant effect on pain from thermal stimuli. This modality selectivity is unlike that observed with μ-opioid agonists that attenuate pain evoked by both mechanical and thermal stimuli. Although previous reports suggest that hyperalgesia in the freeze-injury model is stable up to 72 h, Martin *et al.*[5] observed that the time course of hyperalgesia was variable and that only 50% of subjects showed evidence of central sensitization after day 1. These findings highlight the intersubject variability in human pain models and suggest that the ability to examine long-term antihyperalgesic effects of drugs may be limited.

To help answer the broader question of whether studies in human experimental models of pain are useful as predictors of a drug's clinical effect, it is worth examining how the observations of Martin *et al.*[5] are consistent with results of clinical trials with NMDA antagonists in different pain states associated with central sensitization. Ketamine, methadone, and dextromethorphan remain the most commonly used agents in the clinical arena. Their benefits have been examined in the postoperative period and in a host of chronic widespread pain states (*e.g.*, fibromyalgia, irritable bowel syndrome, temporomandibular disease) and central neuropathic pain conditions that may share a similar phenotype of central sensitization. A recent quantitative meta-analysis of 21 randomized controlled trials in which dextromethorphan was used in the perioperative period revealed a reduction in pain and decreased opioid consumption during the first 24 h without significant adverse effects.[11] The more widely used NMDA antagonist, ketamine, has also been shown to decrease postoperative pain when administered before, during, or after surgery, but it is associated with the adverse effects of hallucinations and nightmares. In contrast, studies that have examined the clinical effects and safety of dextromethorphan to enhance opioid analgesia and reduce opioid tolerance in patients with chronic pain have had mixed results. Three large multicenter trials failed to demonstrate any added clinical benefit of combining dextromethorphan and opioids.[12] These reports suggest that the human pain model used by Martin *et al.* may be more reflective of mechanisms involved in perioperative pain (peripheral sensitization that maintains the central sensitization) than of those involved in chronic pain where central sensitization may be independent of peripheral input.

In summary, human experimental pain models may be useful tools in early proof-of-concept studies to determine the efficacy, optimal dosing, and potential undesirable off-target effects of a drug and its metabolites. Additional sensory tests such as temporal summation and conditioned pain modulation may provide further insights into centrally mediated pain facilitation and pain inhibitory mechanisms. A critical evaluation of how well specific human pain models mimic clinical pain states mechanistically and pharmacologic studies correlate with results of human clinical trials will determine the utility of these models. Reports such as those by Martin *et al.*[5] may set the stage for the use of human experimental models to bridge the gap between target discovery and drug development for pain treatment.

Acknowledgments

The authors are grateful to Tina Doshi, M.D., Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland, for her critical review and feedback on the article, and Claire F. Levine, M.S., E.L.S., Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University, for her assistance in editing the article.

Research Support

This work was supported, in part, by grant Nos. NS26363 (to Dr. Raja) and NS70814 (to Dr. Guan) from the National Institutes of Health, Bethesda, Maryland.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Raja: sraja2@jhmi.edu

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