David S. Warner, M.D., Editor

Testing the Link between Sympathetic Efferent and Sensory Afferent Fibers in Neuropathic Pain

Srinivasa N. Raja, M.D.,* Rolf-Detlef Treede, M.D., Ph.D.†

Systemic α-adrenergic Blockade with Phentolamine: A Diagnostic Test for Sympathetically Maintained Pain. By S. N. Raja, R. D. Treede, K. D. Davis, and J. N. Campbell. ANESTHESIOLOGY 1991; 74:691–8. Reprinted with permission.

ABSTRACT:

The diagnosis of sympathetically maintained pain (SMP) is typically established by assessment of pain relief during local anesthetic blockade of the sympathetic ganglia that innervate the painful body part. To determine if systemic α-adrenergic blockade with phentolamine can be used to diagnose SMP, we compared the effects on pain of local anesthetic sympathetic ganglion blocks (LASB) and phentolamine blocks (PhB) in 20 patients with chronic pain and hyperalgesia that were suspected to be sympathetically maintained. The blocks were done inrandom order on separate days. Patients rated the intensity of ongoing and stimulus-evoked pain every 5 min before, during, and after the LASB and PhB. Patients and the investigator assessing pain levels were blinded to the time of intravenous administration of phentolamine (total dose 25–35 mg). The pain relief achieved by LASB and PhB correlated closely ($r = 0.84$), and there was no significant difference in the maximum pain relief achieved with the two blocks ($t = 0.19$, $P > 0.8$). Nine patients experienced a greater than 50% relief of pain and hyperalgesia from both LASB and PhB and were considered to have a clinically significant component of SMP. We conclude that α-adrenergic blockade with intravenous phentolamine is a sensitive alternative test to identify patients with SMP.

AT the 2000 spring meeting of the editorial board of ANESTHESIOLOGY, Dr. Michael Todd, then editor-in-chief of ANESTHESIOLOGY, and the board members were brainstorming ideas to enhance the journal's educational value to the readers in the new millennium. I suggested a new

* Professor of Anesthesiology and Professor of Neurology, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University, School of Medicine, Baltimore, Maryland. † Professor, Chair of Neurophysiology, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany.

Received from the Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland, and the Department of Neurophysiology, University of Heidelberg, Mannheim, Germany. Submitted for publication March 6, 2012. Accepted for publication March 29, 2012. Supported by grant no. NS-26363 from the National Institutes of Health, Bethesda, Maryland (to Dr. Raja). Figure 2 was prepared by Annemarie B. Johnson, C.M.I., Medical Illustrator, Wake Forest University School of Medicine Creative Communications, Wake Forest University Medical Center, Winston-Salem, North Carolina.

Address correspondence to Dr. Raja: Division of Pain Medicine, Department of Anesthesiology/CCM, Johns Hopkins University, 292 Osler, 600 N. Wolfe Street, Baltimore, Maryland 21287. sraja2@jhmi.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

 Anesthesiology 2012; 117:173–7

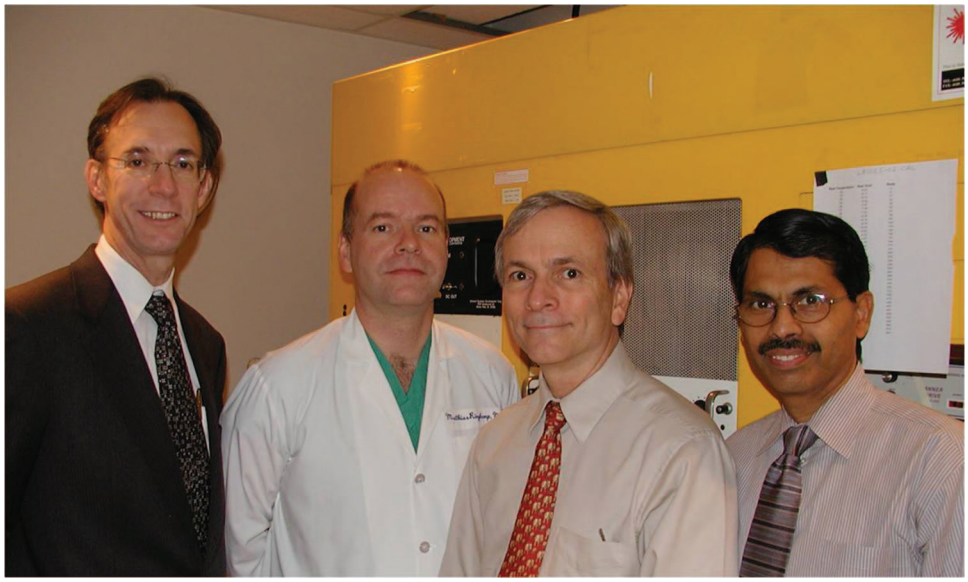

Fig. 1. Srinivasa N. Raja with his mentors and coinvestigators: James N. Campbell, Matthias Ringkamp, Richard A. Meyer, and Srinivasa Raja (left to right). Campbell and Meyer were Raja's mentors who introduced him to pain research and peripheral nerve neurophysiology. The team collaborated for nearly three decades. Ringkamp has been a coinvestigator for more than 10 yr on several of the experimental, behavioral, and neurophysiological studies examining the role of the sympathetic nervous system in neuropathic pain states. In the background is the feedback-controlled laser thermal stimulator that has been used in many of the correlative psychophysical studies in humans and neurophysiological experiments in primates to understand the peripheral signaling of pain.

section that could highlight publications related to anesthesiology, critical care medicine, and pain that are regarded as classics because of their scientific or clinical impact. During the subsequent 6 yr as editor of this Classic Papers Revisited section, I had the pleasure of corresponding with several giants in our field who graciously contributed insightful articles to the section, despite many being in the midst of their retirement. Recently, I was pleasantly surprised to receive an invitation from Dr. David Warner to contribute an article to this section on our paper published two decades ago in this journal.[1] It was, however, not without a bit of trepidation that I accepted the invitation, for during the early years, more than 50% of the authors who were invited to contribute an article for this section passed away within a year of having their manuscript published.

From Bench to Bedside Research

After my residency in anesthesiology at the University of Washington, Seattle, under the chairmanships of Drs. John Bonica and Thomas Hornbein, I was fortunate to be offered a postdoctoral research position by Dr. Robert Epstein at the University of Virginia, Charlottesville, in 1979. My introduction to research and neurophysiology in the laboratory of Dr. Patrice Guyenet (professor of pharmacology) was studying the mechanisms of action of phencyclidine (angel dust) and its derivative, ketamine, on the central nervous system. In 1981, I joined the faculty at Johns Hopkins and was introduced to pain research by my mentors Richard Meyer and James Campbell in the Department of Neurosurgery (fig. 1). During the first several years of our research, we focused on understanding the peripheral signaling of pain from the skin under normal conditions and after acute injury by using neurophysiologic studies in primates and parallel psychophysical studies in humans.[2] Subsequently, we examined the altered pain signaling that occurred after injury to nerves.

Clinically, in addition to working in the operating rooms, I was consulting in the pain center, where I managed patients with chronic pain disorders. Dr. Campbell, a neurosurgeon who specialized in peripheral nerve disorders, was primarily treating patients who developed pain after peripheral nerve injuries. Many of these patients suffered from the typical burning pain or "causalgia," a syndrome described first by Weir Mitchell in Civil War soldiers who had received gunshot wounds to nerves. Patients with causalgia (now termed complex regional pain syndrome 2, or CRPS-2) and reflex sympathetic dystrophy (RSD, now termed CRPS-1) were referred for diagnostic sympathetic ganglion blocks. A block that produced significant pain relief was considered to be a prognostic indicator for surgical sympathetic ganglionectomy. Although historically, sympathetic ganglion blocks and/or sympathectomy were used empirically to treat these patients, the mechanisms by which the sympathetic efferent system influenced the pain-signaling afferent system were still unclear.

Around the same time, I was sharing a recent publication related to my laboratory work on altered pain signaling from injured nerves with my wife, an internist, as my 5- and 7-yr-

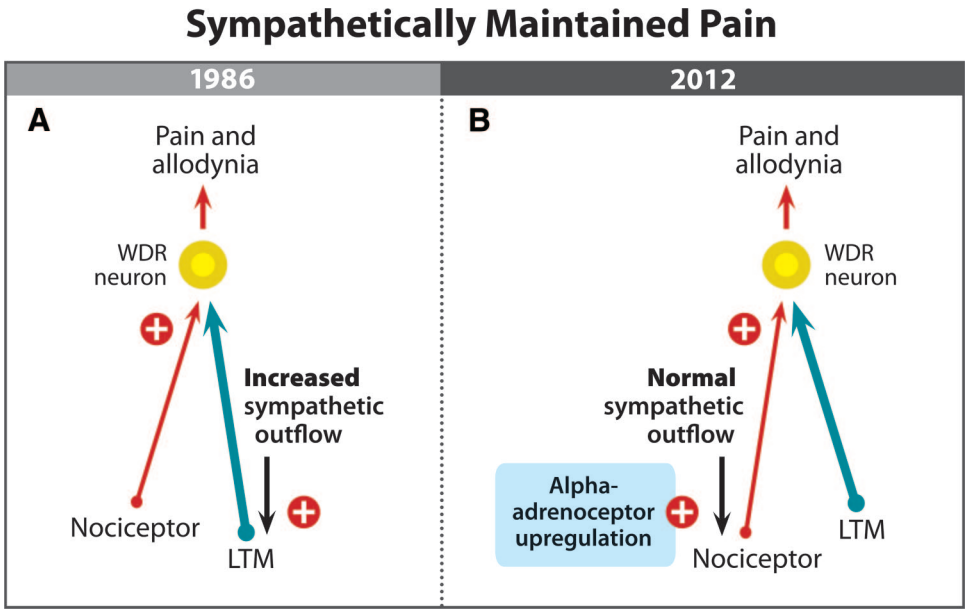

Fig. 2. Models representing the mechanism of sympathetically maintained pain (SMP). (*A*) The original hypotheses proposed by William Roberts.[3] Roberts proposed that the sympathetic efferent activity was enhanced in SMP and that the ongoing pain in chronic SMP was mediated by activity in low-threshold, myelinated mechanoreceptors, the result of sympathetic efferent actions on myelinated, mechanoreceptor afferents or on afferent fibers ending in a neuroma. (*B*) Revised hypotheses based on our studies and those of several other investigators. Subsequent studies indicate that the sympathetic outflow is not enhanced in SMP, but that α-adrenoceptors are enhanced on nociceptors and blood vessels in the periphery. The ongoing activity in nociceptors results in sensitization of wide-dynamic range neurons in the spinal cord. Activation of low-threshold mechanoreceptors converging on sensitized WDR cells results in allodynia (pain to normally innocuous stimuli). LTM = low-threshold mechanoreceptors; WDR = wide-dynamic range.

old daughters looked on. After patiently listening to me, my little one innocently asked, "Does this mean your patients are going to feel much better?" This humbling and provocative question, despite being from a 5-yr-old, prompted me to step back and examine the translational relevance of our work and motivated me to carry out subsequent studies with more direct application to patient care. The late 1980s was an intellectually stimulating time in the Meyer and Campbell laboratory, which comprised an international team of bright and inquisitive visiting scientists and postdoctoral fellows. Rolf-Detlef Treede, a physiologist from Germany, and Karen Davis, who had just completed her graduate work at the University of Toronto, Canada, were part of our team and were interested in studying patients with chronic pain. In subsequent brainstorming sessions, we agreed that the plasticity of the nervous system and the role of sympathetic efferents in the mechanisms of neuropathic pain would be worth careful investigation in patients and later in animal models.

Pain and the Sympathetic Nervous System

In 1986, William Roberts presented a provocative hypothesis on the neurologic basis for causalgia and painful neuromas in a review paper.[3] Roberts coined the term "sympathetically maintained pains" (SMP) for the neuropathic pain states in which the sympathetic nervous system plays a critical role in the pain mechanism. Based on studies in experimental animals, he postulated that the nerve injury-induced activity in nociceptors resulted in sensitization of spinal wide-dynamic-range neurons. He went on to suggest that ongoing pain in chronic SMP was mediated by activity in low-threshold, myelinated mechanoreceptors, the result of sympathetic efferent actions on mechanoreceptors or on afferent fibers ending in a neuroma. Based on observations that the sympathetic activation of wide-dynamic-range neurons was abolished by subcutaneous injection of local anesthetic and by intravenous injection of the α-adrenergic blocker, phentolamine, Roberts suggested that the sympathetic activation of wide-dynamic-range neurons was mediated by an α-adrenergic mechanism in the periphery (fig. 2A).[4]

We decided to compare the effects of a sympathetic ganglion block and the intravenous administration of phentolamine on ongoing and stimulus-evoked pain in a group of patients suspected to have SMP. Phentolamine mesylate was available clinically as a screening tool for the diagnosis of pheochromocytoma before laboratory tests were available for measuring urinary and plasma catecholamines, and for the management of hypertensive crises during surgical removal of the tumor. We found that phentolamine was able to reduce both ongoing pain and hyperalgesia in patients with SMP. We also observed a close correlation between the pain relief achieved by α-adrenergic blockade and that achieved by sympathetic local anesthetic block. These findings led us to conclude that the pain in SMP may be the result of activation of peripheral α-adrenoceptors.[1] Moreover, since local anesthetic

sympathetic blocks may be associated with false positive results caused by placebo responses and the systemic effects of local anesthetics, we suggested that intravenous administration of phentolamine could be a sensitive alternative test for patients with RSD and causalgia who had an SMP.

The results of our study were first presented in 1990 at the VI[th] World Congress on Pain in Adelaide, Australia. At the same meeting, Staffan Arnér from the Department of Anaesthesiology and Intensive Care, Karolinska Hospital, Stockholm, Sweden, independently reported his observations on the use of intravenous phentolamine as a diagnostic and prognostic test in patients with RSD. Arnér observed that subjects who experienced transient relief of their pain after intravenous phentolamine administration were very likely to respond favorably to subsequent sympatholytic treatment with intravenous regional guanethidine.[5] In follow-up studies, we were able to demonstrate that with an infusion of phentolamine, cutaneous temperature changes similar to those observed with local anesthetic sympathetic ganglion blockade could be achieved, suggesting a nearly complete blockade of peripheral sympathetic function.[6]

The possibility that sympathetic mechanisms may contribute to CRPS was supported by the observation that autonomic reflexes evoked by forehead cooling or by being startled resulted in increased pain and more intense vasoconstriction in the symptomatic limb.[7] Based on subsequent studies in patients with SMP and in amputees with stump and phantom pain, we and others have postulated that a direct interaction between norepinephrine and sensory afferent fibers results in activity of nociceptors, possibly because of development of α-adrenergic sensitivity after injury, and is involved in the maintenance of central sensitization.[8–11] Additional studies in which clonidine was applied topically suggested that SMP is mediated *via* α_1-adrenoceptors located in the affected tissue.[12] In elegant studies conducted more recently by Baron *et al.*, sympathetic vasoconstrictor tone of CRPS patients was manipulated by core temperature warming or cooling.[13] The intensity of spontaneous pain and the spatial distribution of mechanical dynamic and punctate hyperalgesia were greater during high sympathetic activity than during low activity, suggesting a pathologic interaction between sympathetic and afferent neurons within the skin. Additional studies indicated that sympathetic-afferent coupling in the deep somatic tissues may also play an important role in the pathophysiology of SMP. Catecholamine assays in patients with RSD demonstrated that the levels of venous norepinephrine were not increased in the affected limbs compared with those in the control extremity.[14] Hence, SMP was not because of hyperactivity of sympathetic efferents but is a result of receptor supersensitivity, probably caused by overexpression of α-adrenoceptors on primary afferents (fig. 2B). When catecholamines are released during stress, this peripheral receptor supersensitivity may lead to hyperalgesia instead of the usual centrally mediated analgesia.[15]

Bedside to Bench Translation

The clinical observations of an interaction between adrenoceptors and sensory afferents stimulated us and many others to further examine the sites, mechanisms of interaction, and adrenoceptors involved by using animal models of partial nerve injury and nerve transection-induced neuroma. In animal models of spinal nerve injury, sprouting of sympathetic fibers in the dorsal root ganglion of the injured segment was observed and this sprouting has been postulated to play an important role in the development and maintenance of SMP.[16,17] Neurophysiologic studies showed that afferents that originate from a neuroma as well as uninjured cutaneous C-fiber nociceptors innervating skin that has been partially denervated by spinal nerve ligation acquire abnormal properties, including spontaneous activity and α-adrenergic sensitivity.[18,19] In animal models of neuropathic pain, behavioral signs of mechanical allodynia and ectopic discharges of injured afferents were in part mediated by mechanisms involving both α_1- and α_2-adrenoceptors.[20,21] These studies indicate that α-adrenoceptor-mediated sympathetic-sensory coupling after nerve injury occurs not only in the peripheral target tissue, but also at the nerve injury site and at the level of the sensory cell soma in the dorsal root ganglion.

The Challenge: Bridging Basic Science and the Clinic

We have pondered why our study in a relatively small number of patients has been listed among the 50 most-cited articles during the last 25 yr in anesthesia-focused journals.[22] We believe that the study has been a catalyst that has kindled the interest of several investigators to examine the pathophysiologic, cellular, and molecular mechanisms of sensory-sympathetic coupling in neuropathic pain states. In addition, the study served as an impetus for the use of drug infusions as diagnostic, prognostic, and therapeutic tools in the management of chronic pain.[23] Moreover, we believe that the study raised awareness of the potential for local anesthetic blocks to give false positive results when used for the diagnosis and treatment of pain. Another contributing factor may be that, even two decades later, the therapeutic relevance of the sympathetic-sensory interactions observed in humans and in animal models of neuropathic pain remains controversial. As indicated above, several lines of evidence from preclinical studies suggest that the sympathetic efferent and the sensory afferent systems are linked by α-adrenergic mechanisms. However, the role of sympathetic blockade as a therapeutic tool in patients with CRPS and other neuropathic pain remains uncertain. For example, a double-blind, double-dummy, placebo-controlled crossover study in children with CRPS indicated that lumbar sympathetic block with lidocaine reduced ongoing pain and allodynia significantly more than did intravenous injection of lidocaine.[24] A more recent observational study, however, showed that only 31% of patients with CRPS had a good or excellent response to

sympathetic blockade and that the response could not be predicted by any symptom or sign.[25]

It is becoming increasingly evident that neuropathic pain is mediated or maintained by the sympathetic nervous system in only a subset of patients and that the interaction between sympathetic efferent fibers and the somatosensory afferent fibers is dynamic, changing throughout the course of the disease state. Although we have improved our understanding of the mechanisms of sympathetic-afferent coupling, the challenge has been the same since the times of Mitchell, Leriche, or Bonica: how to best identify and manage the patients who are likely to respond to interrupting the link between the sympathetic efferent and the sensory afferent systems.[26]

References

1. Raja SN, Treede RD, Davis KD, Campbell JN: Systemic α-adrenergic blockade with phentolamine: A diagnostic test for sympathetically maintained pain. ANESTHESIOLOGY 1991; 74: 691–8
2. Raja SN, Meyer RA, Campbell JN: Peripheral mechanisms of somatic pain. ANESTHESIOLOGY 1988; 68:571–90
3. Roberts WJ: A hypothesis on the physiological basis for causalgia and related pains. Pain 1986; 24:297–311
4. Roberts WJ, Foglesong ME: Spinal recordings suggest that wide-dynamic-range neurons mediate sympathetically maintained pain. Pain 1988; 34:289–304
5. Arnér S: Intravenous phentolamine test: Diagnostic and prognostic use in reflex sympathetic dystrophy. Pain 1991; 46: 17–22
6. Raja SN, Turnquist JL, Meleka S, Campbell JN: Monitoring adequacy of α-adrenoceptor blockade following systemic phentolamine administration. Pain 1996; 64:197–204
7. Drummond PD, Finch PM, Skipworth S, Blockey P: Pain increases during sympathetic arousal in patients with complex regional pain syndrome. Neurology 2001; 57:1296–303
8. Treede RD, Davis KD, Campbell JN, Raja SN: The plasticity of cutaneous hyperalgesia during sympathetic ganglion blockade in patients with neuropathic pain. Brain 1992; 115(Pt 2): 607–21
9. Ali Z, Raja SN, Wesselmann U, Fuchs PN, Meyer RA, Campbell JN: Intradermal injection of norepinephrine evokes pain in patients with sympathetically maintained pain. Pain 2000; 88:161–8
10. Lin EE, Horasek S, Agarwal S, Wu CL, Raja SN: Local administration of norepinephrine in the stump evokes dose-dependent pain in amputees. Clin J Pain 2006; 22:482–6
11. Torebjörk E, Wahren L, Wallin G, Hallin R, Koltzenburg M: Noradrenaline-evoked pain in neuralgia. Pain 1995; 63:11–20
12. Davis KD, Treede RD, Raja SN, Meyer RA, Campbell JN: Topical application of clonidine relieves hyperalgesia in patients with sympathetically maintained pain. Pain 1991; 47: 309–17
13. Baron R, Schattschneider J, Binder A, Siebrecht D, Wasner G: Relation between sympathetic vasoconstrictor activity and pain and hyperalgesia in complex regional pain syndromes: A case-control study. Lancet 2002; 359:1655–60
14. Drummond PD, Finch PM, Smythe GA: Reflex sympathetic dystrophy: The significance of differing plasma catecholamine concentrations in affected and unaffected limbs. Brain 1991; 114(Pt 5):2025–36
15. Donello JE, Guan Y, Tian M, Cheevers CV, Alcantara M, Cabrera S, Raja SN, Gil DW: A peripheral adrenoceptor-mediated sympathetic mechanism can transform stress-induced analgesia into hyperalgesia. ANESTHESIOLOGY 2011; 114: 1403–16
16. McLachlan EM, Jänig W, Devor M, Michaelis M: Peripheral nerve injury triggers noradrenergic sprouting within dorsal root ganglia. Nature 1993; 363:543–6
17. Chung K, Lee BH, Yoon YW, Chung JM: Sympathetic sprouting in the dorsal root ganglia of the injured peripheral nerve in a rat neuropathic pain model. J Comp Neurol 1996; 376: 241–52
18. Michaelis M, Devor M, Jänig W: Sympathetic modulation of activity in rat dorsal root ganglion neurons changes over time following peripheral nerve injury. J Neurophysiol 1996; 76:753–63
19. Ali Z, Ringkamp M, Hartke TV, Chien HF, Flavahan NA, Campbell JN, Meyer RA: Uninjured C-fiber nociceptors develop spontaneous activity and α-adrenergic sensitivity following L_6 spinal nerve ligation in monkey. J Neurophysiol 1999; 81:455–66
20. Lee DH, Liu X, Kim HT, Chung K, Chung JM: Receptor subtype mediating the adrenergic sensitivity of pain behavior and ectopic discharges in neuropathic Lewis rats. J Neurophysiol 1999; 81:2226–33
21. Birder LA, Perl ER: Expression of α_2-adrenergic receptors in rat primary afferent neurones after peripheral nerve injury or inflammation. J Physiol 1999; 515(Pt 2):533–42
22. Terajima K, Aneman A: Citation classics in anaesthesia and pain journals: A literature review in the era of the internet. Acta Anaesthesiol Scand 2003; 47:655–63
23. Dellemijn PL, Vanneste JA: Randomised double-blind active-placebo-controlled crossover trial of intravenous fentanyl in neuropathic pain. Lancet 1997; 349:753–8
24. Meier PM, Zurakowski D, Berde CB, Sethna NF: Lumbar sympathetic blockade in children with complex regional pain syndromes: A double blind placebo-controlled crossover trial. ANESTHESIOLOGY 2009; 111:372–80
25. van Eijs F, Geurts J, van Kleef M, Faber CG, Perez RS, Kessels AG, Van Zundert J: Predictors of pain relieving response to sympathetic blockade in complex regional pain syndrome type 1. ANESTHESIOLOGY 2012; 116:113–21
26. Sethna NF, Berde CB: Sympathetic nerve blocks, pragmatic trials, and responder analysis. ANESTHESIOLOGY 2012; 116: 12–4