Neurofibromatosis Pain Is in the Membrane. Focus on “Sensory Neurons from Nf1 Haploinsufficient Mice Exhibit Increased Excitability”

Robert W. Gereau IV
Washington University Pain Center and Department of Anesthesiology, Washington University School of Medicine, St Louis, Missouri

Neurofibromatosis type 1 (NF1) is a relatively common genetic disease that is associated with a variety of neurologic complications. In addition to irregularities such as the formation of neurofibromas and neurofibrosarcomas, NF1 patients also suffer increased incidence of chronic pain (Creange et al. 1999; Wolkenstein et al. 2001). In this issue of the Journal of Neurophysiology (p. 3670-3676), Cynthia Hingtgen and her colleagues at the Stark Neurosciences Research Institute of the Indiana University School of Medicine describe changes in the physiology of nociceptive sensory neurons that may help explain this increased pain perception in NF1 patients (Wang et al. 2005).

NF1 is an autosomal dominant condition that results from an inactivating mutation in the NF1 gene, which encodes the neurofibromin protein. Neurofibromin is a GTPase-activating protein (GAP) for the Ras class of small molecular weight G proteins. Thus in NF1, there is decreased Ras-GAP activity, and a consequent increase in active Ras (Ras-GTP). It is this increase in active Ras that is thought to underlie the neurological complications of NF1, although little is known about the mechanisms that underlie the increased pain sensitivity in NF1.

Wang et al. (2005) show that a subset of small-diameter DRG neurons that are presumed to be nociceptive show increased excitability in Nf1 +/− mice compared with similar neurons prepared from wild-type mice. Thus neurons from Nf1 +/− mice have lowered firing thresholds, require less current injection to elicit an action potential (decreased rheobase), and fire more action potentials in response to a given depolarization than similar capsaicin-sensitive DRG neurons from wild-type mice. All of these changes would result in an increase in the firing of these nociceptors in response to a given receptor potential, such as elicited by touch or heat. This is an exciting finding suggesting that altered nociceptor excitability might underlie the enhanced pain sensitivity seen in NF1 patients.

In addition to the changes described in the preceding text, Wang et al. show that nerve growth factor (NGF), which sensitizes this population of nociceptive DRG neurons in wild-type mice, does not have an effect on excitability of nociceptors in Nf1 +/− mice. This suggests that NGF sensitizes nociceptors via a mechanism that overlaps with the sensitization of nociceptors caused by the lack of neurofibromin. This mechanism is presumed to involve increased Ras activity, as the NF1 mutation increases active Ras, and NGF stimulates Ras and elicits multiple effects in DRG neurons via the Ras pathway. How might increased Ras activity lead to increased excitability of nociceptors? There are several possibilities, involving both transcription-dependent and posttranslational mechanisms. For example, NGF, acting via the Ras pathway, has been shown to lead to downregulation of K+ channels and increased expression of the noxious heat-sensing protein, TRPV1, an effect that was mimicked by overexpression of active Ras (Bron et al. 2003). However, acute administration of NGF can lead to the rapid development of pain hypersensitivity, an effect that occurs too quickly to be mediated by alterations in ion channel expression (Shu and Mendell 1999). This effect may be mediated by alteration of a variety of ion channels. For example, NGF-dependent modulation of tetrodotoxin-resistant (TTX-R) sodium channels and delayed rectifier potassium channels has been observed in nociceptive DRG neurons (Zhang et al. 2002), and NGF and Ras activation leads to increased voltage-gated calcium channel activity in these cells (Fitzgerald and Dolphin 1997). Any of these effects could lead to nociceptor sensitization and could underlie the sensitization of nociceptors observed in Nf1 +/− mice. However, the modulation of TTX-R and delayed rectifier channels in response to NGF was shown to be mediated by ceramide signaling (Zhang et al. 2002), although the altered excitability observed in response to NGF was identical to that observed in the Nf1 +/− mice reported by Wang et al. (2005). This apparent discrepancy could be explained by Ras activation of sphingomyelinas or by Ras activation downstream of ceramide production. Alternatively, this may be due to similar downstream modulatory effects mediated by both ceramide- and Ras-dependent signaling, such as a modulation of TTX-R and/or delayed rectifier K+ channels.

While the results presented by Wang et al. argue for Ras-mediated increased excitability of nociceptors in Nf1 +/− mice that could explain the enhanced pain sensitivity in NF1 patients, there are several open questions that are worthy of future experimentation. First and foremost, the fact that NGF and Ras increase the expression of TRPV1 raises some questions regarding the results presented by Wang et al. Because NGF/Ras signaling increases capsaicin sensitivity (Ganju et al. 1998) and TRPV1 expression (Bron et al. 2003) in DRG neurons, it is conceivable that the neurons being studied in the Nf1 +/− mice, which are defined by their small diameter and capsaicin sensitivity, are not the same population of neurons being studied in wild-type mice. If TRPV1 expression is induced in a novel subset of neurons with lower rheobase and firing threshold, then this might explain the differences between wild-type and Nf1 +/− neurons observed in this study. Clarifying this will require a more extensive characterization of TRPV1 expression patterns in Nf1 +/− DRG neurons.

With this answer in hand, it will then be important to demonstrate whether the increased excitability of Nf1 +/−

Address for reprint requests and other correspondence: Washington University Pain Center and Department of Anesthesiology, Washington University School of Medicine, 660 S. Euclid Ave, St Louis, MO 63110 (E-mail: gereau@wustl.edu).

First Published August 10, 2005; doi:10.1152/jn.00862.2005.


www.jn.org 0022-3077/05 $8.00 Copyright © 2005 The American Physiological Society

3659
DRG neurons can be reduced by reducing Ras activity, perhaps using the expression of dominant-negative Ras as was done to show the role of Ras in the upregulation of TRPV1 by NGF (Bron et al. 2003). In addition, it will be interesting to identify the hierarchy of signaling involving NGF, ceramide, and Ras as well as to identify the critical downstream ion channel targets that underlie the peripheral sensitization mediated by NGF. This information gleaned from in vitro experiments could lead to in vivo studies that manipulate the key players to identify potential targets for the development of novel therapeutic strategies that will allow better management of pain in patients with NF1. Clearly, the report by Wang et al. has pointed the way to exciting new lines of investigation into the mechanisms of enhanced pain sensitivity seen in neurofibromatosis patients.

REFERENCES


