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The Spine Journal 10 (2010) 733–735

THE SPINE JOURNAL

Commentary

Is there an antinociceptive role for peripheral brain-derived neurotrophic factor?

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Received 24 May 2010; accepted 1 June 2010

COMMENTARY ON: Tender GC, Li Y-Y, Cui J-G. Brain-derived neurotrophic factor redistribution in the dorsal root ganglia correlates with neuropathic pain inhibition after resiniferatoxin treatment. Spine J 2010:10:715–20 (*in this issue*).

Chronic pain has a high incidence and significant costs [1]. Treatments remain hindered by limited efficacy and/or side effects [2], and no clear understanding of the cellular mechanisms involved. Targeted destruction of specific neuronal populations can help define cellular mechanisms and may be an effective modality to treat pain. Ablating agents, such as saporin and resiniferatoxin (RTX), are used to target specific neuronal populations [3–5]. The capsaicin analog, RTX, selectively ablates neurons that express the vanilloid receptor-1 (VR1) via sustained Ca^{2+} influx [5–7]. The VR1 is a ligand-gated, nonspecific cation channel in small- and some medium-sized neurons in the dorsal root ganglion (DRG) [5]. The VR1 integrates nociceptive stimuli and is sensitive to heat, protons, capsaicin, bradykinin, nerve growth factor, and other stimuli [8]. Accordingly, VR1-positive neurons are involved in the development and/or maintenance of pain. Resiniferatoxin effectively abolishes thermal hyperalgesia and differentially attenuates mechanical allodynia in many pain models [5,9–11]. For example, intrathecal RTX is analgesic in a canine bone cancer model [9], and perineural application of RTX to the sciatic nerve prevents the development of inflammation-induced thermal, but not mechanical, hyperalgesia in the rat [5]. Previously, Tender et al. [10] showed that direct injection of RTX into lumbar DRGs reversed thermal hyperalgesia that was induced by a photochemical sciatic nerve injury but only partially mitigated mechanical allodynia. That finding provides a foundation for Tender's present study investigating brain-derived neurotrophic factor (BDNF) in RTX-mediated neuropathic pain suppression because BDNF is localized in small- and medium-sized DRG neurons [12–14].

Brain-derived neurotrophic factor is a peripherally derived modulator of sensory neurotransmission that promotes the survival, growth, and differentiation of neurons [15]. Several neurotrophins, including BDNF, are also involved in nociception and synaptic plasticity [15–19]. Brain-derived neurotrophic factor is endogenously produced in the periphery mainly by small unmyelinated neurons. It is packaged into dense core vesicles that undergo anterograde transport to presynaptic terminals in the dorsal horn of the spinal cord, where their release is stimulus dependent [15,20]. Peripheral stimulation of primary afferents causes release of BDNF at central synapses, where it acts through its high-affinity receptor, tyrosine kinase B, to sensitize excitatory transmission through the phosphorylation of glutamatergic postsynaptic receptors [15]. Brain-derived neurotrophic factor can also act presynaptically to increase excitatory neurotransmitter release in the dorsal horn. Inhibition of spinal BDNF-induced tyrosine kinase B activation through BDNF sequestration prevents pain development and abolishes existing pain [14,18,19]. Considering that BDNF release alters central synaptic efficacy based on peripheral stimuli, BDNF is a key regulator throughout the nervous system.

Painful peripheral insults directly and indirectly modify BDNF in the DRG and spinal cord. In neuropathic pain, expression of BDNF in neurons in the DRG shifts from its normal expression, which is primarily in small-diameter tyrosine kinase A–positive neurons, to expression in larger

DOI of original article: 10.1016/j.spinee.2010.03.029.

FDA device/drug status: not applicable.

Author disclosures: BAW (research support: investigator salary, Synthes; research support: staff/materials, Synthes; grants, Synthes).

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doi:10.1016/j.spinee.2010.06.004

diameter neurons, a shift that is also seen in inflammation [12,13,21,22]. This phenotypic shift suggests that a redistribution of BDNF in the DRG may influence cellular sensitization involved in pain. In fact, BDNF expression shifts from the smaller afferents of the joint capsule to the larger ones after facet joint inflammation [22]. Other groups have characterized BDNF expression after sciatic nerve transection [12,13,21], a neural trauma that produces behavioral sensitivity early after injury that is sustained for at least 3 weeks [23,24]. A phenotypic switch in neuronal expression of BDNF has been observed in those pain models similar to that described by Ohtori et al. [22] for the joint inflammation but was also accompanied by upregulation in the spinal cord as early as 1 day after injury [12,13,21]. That shift in BDNF expression from smaller- to larger-diameter neurons has been proposed to contribute to the initiation or maintenance of pain [12,13,22]. Spinal sensitization can also result from sprouting of the nonnociceptive large-diameter neurons into the superficial laminae of the dorsal horn, a region primarily associated with nociception [15,25–27]. Although many pain models demonstrate altered BDNF expression in the DRG and spinal cord, it remains unknown how these changes modulate pain. For this reason, using RTX to ablate the specific nociceptive neurons can provide mechanistic insight into the role of BDNF in sciatic nerve pain.

Tender et al. showed that direct injection of RTX in DRGs reversed thermal hyperalgesia and abolished mechanical allodynia induced by a photochemical sciatic nerve injury. Nerve injury alone increased BDNF expression in small and medium neurons in the DRG, whereas for RTX treatment given after injury, BDNF increased in large neurons [7]. Although they report upregulation of BDNF that is consistent with other studies of sciatic nerve injury, the increases in specific neuron populations is not consistent [12,13,21]. Also, this study reports expression in normal naive rats to be equally distributed among all neuron sizes, which is contrary to other reports in which BDNF expression is limited to mainly small- and medium-sized neurons [7,12,13,15,21,22]. This discrepancy in the basal response directly affects any conclusions because the changes in expression that are reported are relative to a potentially skewed and atypical basal BDNF response. The authors also found that in some cases after injury, allodynia was not induced, but BDNF expression was upregulated in large neurons and downregulated in the other neurons. Resiniferatoxin treatment of the allodynic rats that attenuated sensitivity also induced BDNF upregulation in large neurons and downregulation in the other neurons, suggesting a relationship between lack of sensitivity and such responses. But, it is unclear if that decrease in the nociceptive neurons is because of their ablation or an actual downregulation of BDNF. Because no data are provided describing BDNF expression in any of the neuronal populations in the DRG for vehicle treatment, it is difficult to interpret any of these findings.

Although RTX selectively destroys VR1-positive neurons, its effect on sensory neurons is dose dependent. In fact, these same authors reported that RTX given at a lower dose (0.8 μg) only partially attenuated mechanical allodynia [10]. They hypothesized that allodynia persisted despite RTX treatment because large-diameter Aβ-fibers had become nociceptive [10]. If there is indeed an Aβ-fiber component to nociception in this model as their previous work suggests, then it should also be present in their current report. Yet, they observed complete abolishment of mechanical allodynia using the higher dose [7], which may indicate a more widespread (and nonspecific) ablation of additional fiber populations. Pan et al. [27] reported damage to myelinated fibers in the sciatic nerve along with eliminated VR1-positive neurons after intraperitoneal injection of RTX in normal rats; although that finding may be because of systemic administration, it supports a potential nonspecific effect of RTX. Unfortunately, the BDNF responses for the lower RTX dose were not reported in the previous study [10], so it is not known if BDNF upregulation in large neurons is analgesic, or if it serves another function—perhaps promoting cell survival [28]. Neubert et al. [5] reported that at least 125 ng of RTX applied perineurally was needed to produce thermal hypoalgesia after peripheral inflammation, but that 250 ng only partially attenuated mechanical allodynia. Tender et al. [7,10] found that a fivefold higher dose was required to abolish allodynia, which may have abolished mechanical allodynia because of toxic effects on the large-diameter neurons. Taken together, all these studies highlight that RTX-mediated analgesia is dose dependent, and that the conclusions by Tender et al. should be viewed in that context.

The hypothesis that the shift in BDNF expression to large-sized neurons in the DRG after RTX is ‘‘analgesic’’ ignores recent insight into spinal contributions. Brain-derived neurotrophic factor is upregulated in both inflammatory and neuropathic pain models in the superficial dorsal horn, where afferents synapse, and also in deeper laminae [12,13,29]. Spinal BDNF modulates the excitability of neurons and contributes to central sensitization [15]; activated spinal microglia are also a source of BDNF. Intrathecal sequestration of BDNF abolishes injury-induced sensitivity, further supporting central BDNF as a regulator of sensitivity [14]. Because large-diameter neurons can sprout new connections to the superficial laminae of the spinal dorsal horn, they activate nociceptive pathways [15,25–27]. In this way, upregulation of BDNF in large neurons can be nociceptive. This sprouting could partially account for the Aβ-fiber contributions that Tender et al. [10] previously hypothesized in this model. Although peripheral modification of BDNF may be important in pain, it likely is not the only BDNF-related mechanism. Therefore, further investigations of central BDNF with RTX treatment are needed to determine its role in this and other models.

Despite some limitations in methodology, Tender’s investigation of the cellular effects of RTX treatment on

neuropathic pain raises several important considerations. Although the authors focused on the role of BDNF, they do acknowledge that other molecules likely play a role in nociceptive signaling in the nervous system, and that none act in isolation. Undoubtedly, defining how BDNF and other neurotrophins and neuromodulators regulate pain in specific cell populations is key to understanding chronic pain. Continued efforts are needed to determine the specific effects and specificity of higher doses of RTX, as well as to determine whether BDNF is exclusively nociceptive or antinociceptive, or some combination of both. Understanding that role will help develop potential treatments for both tissue healing and pain relief, as has been done with other neurotrophins [30].

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