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Insights into the Contribution of Voltage-Gated Sodium Channel 1.7 to Paclitaxel-Induced Neuropathy

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Review of Li et al.

Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of antineoplastic treatments, such as paclitaxel (for review, see Mekhail and Markman, 2005). Paclitaxel exerts its effects by promoting tubulin assembly and preventing microtubule depolymerization, hence inhibiting cell division and causing cell death. Unfortunately, the effects are not restricted to tumor cells, and numbness, tingling, mechanical/thermal allodynia, and burning pain develop in ~70% of treated patients (for review, see Seretny et al., 2014). Because no effective treatment prevents or relieves this kind of neuropathic pain, dose reduction or treatment cessation is required. Even after the discontinuation of therapy, however, symptoms can persist for months.

Animal models of paclitaxel-induced peripheral neuropathy show signs of mechanical allodynia and hyperalgesia, cold allodynia, and heat hyperalgesia that last up to 30 d (Polomano et al., 2001). Dissociated dorsal root ganglion (DRG) neurons from paclitaxel-treated rats show spontaneous activity that is not found in control animals (Zhang and Dougherty, 2014; Li et al. 2017). In addition, DRG neurons in paclitaxel-treated rats have higher-than-normal levels of mRNA and protein for voltage-gated sodium channel $Na_v1.7$ (Zhang and Dougherty, 2014; Xia et al., 2016). Notably, subcutaneous administration of low doses of tetrodotoxin (which blocks $Na_v1.1$–1.4, $Na_v1.6$, and $Na_v1.7$) reduced the development of mechanical and cold allodynia in paclitaxel-treated mice (Nieto et al., 2008). Moreover, minocycline (a broad-spectrum tetracycline antibiotic) protects against neuropathy in taxol-treated rats (Boyette-Davis et al., 2011) and is thought to exert its effects through inhibition of sodium channels in primary afferents (Kim et al., 2011).

In a study recently published in *The Journal of Neuroscience*, Li et al. (2018) extended previous work by elucidating the specific types of DRG nociceptive neurons that show elevated expression of $Na_v1.7$ after paclitaxel treatment. They also asked whether the function of these channels is also potentiated and assessed the contribution of the channels to mechanical hypersensitivity accompanying CIPN in rats. Finally, they obtained DRGs from patients with painful cancer-related neuropathy to further explore the role of $Na_v1.7$ in the development of hyperexcitability and its possible role in neuropathy in humans.

To address these questions, they induced peripheral neuropathy in rats by injecting paclitaxel intraperitoneally on 4 nonconsecutive days. Consistent with previous work (Xia et al., 2016), paclitaxel treatment increased the level of $Na_v1.7$ protein. This increase was found to be restricted to small- and medium-size nociceptive DRG neurons (mainly in peptidergic neurons, but also, to a lesser degree, in nonpeptidergic cells). The increased expression lasted for up to 14 d after the first injection, and thereafter started to decline despite persistent neuropathy. The authors also demonstrated that paclitaxel significantly increased the expression of $Na_v1.7$ channel at the central terminals of nociceptive fibers in the spinal cord (Li et al., 2018).

Whole-cell recordings of small-size neurons (putative nociceptors) from DRG cultures from paclitaxel-treated rats revealed an increase in $Na_v1.7$ current density. These currents also became activated at more hyperpolarized membrane potential in paclitaxel-treated neurons than in control neurons (Li et al., 2018). This increased current likely contributed to the development of spontaneous activity, which was found in 30% of the recorded nociceptors. Indeed, the specific $Na_v1.7$ blocker Pro-TxII abolished the current and the spontaneous activity.

It is likely that the development of spontaneous activity contributes to paclitaxel-induced neuropathic pain (Zhang and Dougherty, 2014; Li et al. 2017). Therefore, Li et al. (2018) explored

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whether the increase of the $Na_v1.7$ channel is responsible for the mechanical hyperalgesia that developed after paclitaxel treatment. They found that intrathecal administration of Pro-TxII, either before paclitaxel treatment or after neuropathy was stablished, reduced mechanical hyperalgesia. This is in contrast with earlier studies that had failed to demonstrate attenuation of mechanical hyperalgesia in paclitaxel-treated rats after local DRG $Na_v1.7$ blockade with a specific antibody (Xia et al., 2016). It may be that the blocking of peripheral channels is not sufficient to reduce hyperalgesia given that, as mentioned above, Li et al. (2018) detected increased expression of $Na_v1.7$ in the spinal cord. But this would be inconsistent with a role of $Na_v1.7$ channels in the cell body and the primary afferent.

Next, Li et al. (2018) investigated the mechanisms by which paclitaxel increases $Na_v1.7$ expression. Previous work indicated that paclitaxel treatment increased the expression of toll-like receptor 4 (TLR4) and its downstream signaling protein myeloid differentiation primary response 88 (MyD88; Li et al., 2014). Therefore, Li et al. (2018) asked whether signaling via the TLR4–MyD88–MAPK pathway altered $Na_v1.7$ expression. Indeed, LPS-RS (lipopolysaccharide from the photosynthetic bacterium *Rhodobacter sphaeroides*; a TLR4 antagonist) decreased $Na_v1.7$ channel expression in DRGs from neuropathic rats. This is consistent with the attenuation of mechanical hypersensitivity observed in knock-out TLR4 mice after cisplatin treatment (Park et al., 2014). Previous studies also suggested that paclitaxel-induced activation of TLR4 leads to increased expression and release of TNF-α in satellite glial cells (Wu et al., 2015), and that high levels of TNF-α are associated with an increase in $Na_v1.7$ channel in DRGs in rats with diabetic neuropathy (Huang et al., 2014). Thus, this might also contribute to $Na_v1.7$ channel upregulation in paclitaxel-induced neuropathy.

Larger-than-normal $Na_v1.7$ currents have also been described in patients treated with paclitaxel (Chang et al., 2018). Li et al. (2018) obtained DRGs from three patients with cancer-related neuropathies and confirmed by immunohistochemistry that $Na_v1.7$ was present in half of the nociceptors. Remarkably, the increased expression of $Na_v1.7$ was restricted to the DRGs that innervated painful dermatomes. Moreover, spontaneous activity, which was recorded only in neurons dissociated from DRGs that innervated painful dermatomes, was abolished by Pro-TxII. Essentially, the authors demonstrated that, like CIPN rats, nociceptors from patients with cancer-related neuropathies of different etiologies are sensitized and discharge at membrane potentials at which nociceptors are usually silent due to an overexpression of $Na_v1.7$.

In summary, Li et al. (2018) showed increased expression and function of the $Na_v1.7$ channel in rat and human DRG nociceptors, and that this increase in expression seems to contribute to neuropathic pain symptoms. The finding that blocking $Na_v1.7$ reduces paclitaxel-induced neuropathy is somewhat surprising, given that $Na_v1.7$ expression declines to baseline levels after 14 d even when neuropathy persists at least for 1 more week (Li et al. 2014). But spontaneously active nociceptors are considered an indicator of peripheral sensitization, which can potentiate central sensitization. This might explain how a transient upregulation of $Na_v1.7$ contributes to longer-lasting sensitivity. On the other hand, these results may indicate that other mechanisms contribute to CIPN. One likely contributor is the T-type calcium channel, the specific blockade of which has also been shown to prevent mechanical hypersensitivity in paclitaxel-treated rats (Li et al., 2017). TRPV4 (transient receptor potential cation channel subfamily V member 4) channels may also play a role, given that antisense oligodeoxinucleotides against these channels abolished mechanical hyperalgesia induced by taxol (Alessandri-Haber et al., 2004). Thus, although the study by Li et al. (2018) advocates for $Na_v1.7$ channels as a target to limit CIPN symptoms, the effectiveness of such treatments might be limited, because of the involvement of other ion channels. Furthermore, it is likely that these findings cannot be extrapolated to all neuropathies with different origins, given that, for example, mechanical hypersensitivity is independent of $Na_v1.7$ in oxaliplatin-induced neuropathy (Minett et al. 2014).

Because genetic variants of $Na_v1.7$ channels are associated with pain syndromes, several Na_v blockers are being tested in clinical trials to treat chronic pain conditions (for review, see Emery et al., 2016). Unfortunately, these trials have shown little promise and demand further study. Not only synthetic drugs but also several natural toxins have considerable therapeutic effects by blocking Na_v channels; however, their specificity and side effects limit their use. Nevertheless, the search for specific $Na_v1.7$ antagonists opens up the possibility of finding more adequate treatments to limit the positive symptoms of patients with different neuropathies.

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