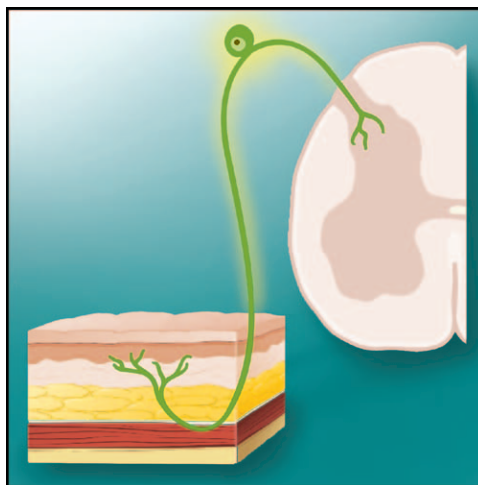


Is Chemotherapy-induced Peripheral Neuropathy More Than Just a Peripheral Nervous System Disorder?

Patrick M. Dougherty, Ph.D.

SENSORY dysfunction and pain are among the most common treatment-limiting factors and most distressing physical symptoms of patients receiving any of the most commonly used cancer chemotherapy treatments. Symptoms range from mild tingling to a painful burning paresthesia that is refractory to effective remedy. The incidence and severity of chemotherapy-induced pain is correlated with duration and dose such that nearly all patients experience discomfort by a third treatment cycle with vincristine, paclitaxel, bortezomib, cisplatin, or oxaliplatin and forces discontinuation of optimal therapy in up to half of patients. Treatment-related pain is, therefore, not only distressing, but also impacts survival. Symptoms also often persist long after treatment and so impact rehabilitation and the return to productivity. By far the majority of studies into the underlying mechanisms of chemotherapy-induced pain and dysesthesia have focused on those occurring in primary afferent nerves. Effects on dorsal root ganglion (DRG) neurons and distal nerve endings in particular have been the focus of many studies given that these are the neural tissues seemingly most directly affected by chemotherapy drugs due to their location outside the blood–brain barrier and the poor penetration of the majority of chemotherapy drugs into the central nervous system (CNS).¹ Indeed, this bias is reflected in the commonly accepted name for this condition, chemotherapy-induced peripheral neuropathy (CIPN). Yet, the work by Huang *et al.*² in this issue reveals that CIPN may in fact involve important effects mediated by chemotherapeutics directly in the CNS on spinal cord neurons.

Huang *et al.*² show that a single systemic (intraperitoneal) dose of 4.0 mg/kg of oxaliplatin induces signs of acute pain within 1 h after dosing in rats and that this was accompanied



“... these studies show that CNS effects of very low concentrations of chemotherapeutics can no longer be excluded as having potentially important roles in generating [chemotherapy-induced peripheral neuropathy].”

by increased spinal cord responses evoked by sciatic nerve stimulation. They then used a very sensitive detection method, inductively coupled mass spectrometry, to reveal that albeit small, nevertheless significant amounts of oxaliplatin penetrate into spinal cerebrospinal fluid after the systemic dose used in the behavioral studies. Direct application of this small dose of oxaliplatin onto the spinal cord by intrathecal injection reproduced both the behavioral signs of hyperalgesia and the enhanced evoked responses of the spinal cord to sciatic nerve stimulation. Neither effect was reproduced by injection of oxaliplatin directly into the skin of the hind paw at a concentration corresponding to the levels of oxaliplatin detected in this tissue using mass spectrometry after systemic dosing. Finally, the investigators provide data suggesting that oxaliplatin acts within the CNS to produce its effects by the induction and release of the chemokine CX3CL1.

The findings by Huang *et al.*² suggesting CNS effects are involved in producing pain evoked by chemotherapeutics are not without precedent as a recent article by Li *et al.*³ reported complementary findings on the chemotherapeutic paclitaxel. Paclitaxel, like oxaliplatin, although previously thought to not enter the CNS, does indeed penetrate into the CNS, albeit at very low concentrations, after systemic dosing that produces hyperalgesia in rats. Li *et al.*³ tested the direct effects of paclitaxel at this very low concentration on the physiologic responses of spinal cord neurons *in vitro*. They found that paclitaxel acts on Toll-like receptor 4 on spinal neurons to increase the signaling of the transient receptor potential vallinoid 1 channel and intrathecal transient receptor potential vallinoid 1 antagonists reduce paclitaxel-induced hyperalgesia in rats. Combined these studies show that CNS effects of very low concentrations

Image: A. Johnson.

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of chemotherapeutics can no longer be excluded as having potentially important roles in generating CIPN.

Although the work by Huang *et al.*² may underscore previously little studied mechanisms in CIPN, one should remain mindful that, as noted above, there are numerous studies showing effects of chemotherapy drugs on DRG neurons and distal nerve endings; the potential efficacy of altering signaling in these tissues in preventing or reversing CIPN is well documented. Indeed, based on the data shown in this issue, it cannot be excluded that the intrathecal dosing scheme used by Huang *et al.*² did in fact affect DRG neurons or their central terminals. It should also be noted that, whereas an acute pain syndrome characterized by arthralgia and myalgia is reported for paclitaxel, acute mechanically-evoked pain is not a commonly reported symptom after oxaliplatin treatment in humans. Rather, acute sensitivity to skin cooling is the most common sensory side effect for oxaliplatin. Thus, the work by Huang *et al.*² may reveal potentially important new mechanisms of CIPN, yet the full context of this work will require further investigation.

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Competing Interests

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