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Research Report

Behavioral and electrophysiological studies in rats with cisplatin-induced chemoneuropathy

*Juan P. Cata, Han-Rong Weng, Patrick M. Dougherty**

The Department of Anesthesiology and Pain Medicine, The University of Texas-M.D. Anderson Cancer Center 1400 Holcombe Blvd., Unit 409 Houston, TX 77030, USA

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ABSTRACT

Neuropathy is the chief dose-limiting side effect associated with the major classes of frontline cancer therapy drugs. Here the changes in behavioral responses of rats to cutaneous mechanical and thermal stimuli occurring following treatment with cisplatin and the changes in spinal neurophysiology accompanying the development of chemotherapy-induced hyperalgesia were explored. Systemic treatment with cisplatin induced changes in both mechanical and thermal cutaneous sensory withdrawal thresholds of Sprague–Dawley rats. High doses of chemotherapy produced hypoalgesia whereas lower doses produced hyperalgesia. Follow-up neurophysiological studies in rats with chemotherapy-induced hyperalgesia revealed that deep spinal lamina wide dynamic range neurons had significantly higher spontaneous activity and longer afterdischarges to noxious mechanical stimuli than wide dynamic range neurons in control rats; cisplatin administration was also associated with longer afterdischarges and abnormal wind-up to transcutaneous electrical stimuli. The hyperexcitability observed during cisplatin-induced hyperalgesia is very similar to that observed in rats with hyperalgesia produced following treatment with other very diverse types of chemotherapeutic agents and similar to that observed following specific types of direct nerve injury.

1. Introduction

Cancer treatments are almost never given at the optimal dosages or schedules to kill cancer cells. Rather treatment protocols are governed by the necessity of limiting toxicities. Protective measures have been developed for two of the major complications of chemotherapy, bone marrow suppression and renal toxicity, but the third major toxicity, debilitating and painful neuropathy remains largely unmanageable (Alberts and Noel, 1995; Cavaletti et al., 1995; Quasthoff and Hartung, 2002). Neuropathy is the chief dose-limiting side effect associated with the major classes of frontline drugs, including the taxanes, the vinca alkaloids, and the platin-based drugs, that are used against all of the most common types of cancer. The survival of hundreds of thousands of patients each year is therefore at risk due to this problem. Moreover, the numbness, tingling, burning pain and sensory-motor impairments characteristic of chemoneuropathy is largely refractory to treatment and often persists as a chronic condition long after treatment, thus affecting the quality of life and return to productivity in many cancer survivors (Boogerd et al., 1990; Cata et al., 2004; Dougherty et al., 2004; Roefols et al., 1984).

A noteworthy clinical feature of chemo-related pain discovered by this laboratory is the consistency of symptoms among patients receiving very different types of agents. Patients complain of symptoms in identical distributions

* *Corresponding author*. Fax: +1 713 745 2956.
E-mail address: pdougherty@mdanderson.org (P.M. Dougherty).

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and describe these sensations with nearly identical word descriptors regardless of whether this was produced by treatment with taxanes, vinca alkaloids, or the proteosome inhibitor bortezomib. Quantitative sensory examination reveals nearly identical deficits in sensory function over all skin areas affected by symptoms (Cata et al., 2007; Dougherty et al., 2004; 2006). Models of chemoneuropathy in animals, like the clinical pain syndromes, are also remarkably similar in behavioral characteristics (Apfel et al., 1992; Barajon et al., 1996; Polomano et al., 2001; Tredici et al., 1998; Weng et al., 2003). Taxol and vincristine also induce essentially identical changes in the physiological properties of primary afferent fibers and spinal dorsal horn neurons. Animal models of cisplatin chemoneuropathy have been reported, but remain less well characterized than the taxane- and vinca-alkaloid models (Apfel et al., 1992; Authier et al., 2003; Bianchi et al., 2007). The platin compounds, most notably, cisplatin (*cis*-diaminedichloroplatinum II) are frontline treatments for many solid and hematologic neoplasms, including lung cancer, the number one cancer killer in the United States (Prestayko et al., 1979). Given the importance of not only understanding the toxicity of this key chemotherapeutic drug, but also of determining whether chemotherapy drugs as a general class show convergence in their mechanisms of neuropathic pain, the goal in this study was to explore the dosing regimen needed to induce cisplatin chemoneuropathy in rats and to determine the resulting physiological changes occurring in spinal neurons of animals with cisplatin-induced pain.

2. Results

2.1. *Behavioral experiments*

2.1.1. *Body weight changes*

Cisplatin treatment produces a failure to normally thrive in rats (Cavaletti et al., 1992; Garcia et al., 2008; Tredici et al., 1998). This was evidenced here by a reduced rate of weight gain in the three groups of cisplatin-treated rats during chemotherapy. Failure to gain weight was evident from day 1 of treatment in the animals receiving 0.5 and 1.0 mg/kg cisplatin and only showed increases similar to the control animals following day 3 of treatment. Saline rats showed a gain in weight of 8.6±1.0% over baseline in this interval whereas the rats receiving 0.5 mg/kg cisplatin showed a −3.±1.2% change in body weight and the rats receiving 1.0 mg/kg cisplatin had a −2.9±2.6% change in body weight ($p<0.01$) . The rats treated with 0.1 mg/kg cisplatin showed a modest increase in body weight (Day 3, 4.6±0.9%) that was not significantly different from controls but that was significantly different from the other cisplatin-treated groups ($p<0.001$). Cisplatin-treated rats resumed a positive rate of body weight increase once chemotherapy was discontinued, though the overall rate of gain remained less than that of saline-treated rats. The rate of change in body weight among the treatment groups was comparable from day 7 to the end of the experiment.

2.1.2. *Mechanical nociceptive thresholds*

Baseline mechanical nociceptive thresholds to von Frey filaments were similar among rats in the four treatment groups and these thresholds remained stable and without significant change throughout the experiment in the saline and 0.1 mg/kg cisplatin-treated animals. Rats treated with 0.5 mg/kg cisplatin showed a significant decrease in withdrawal threshold that was evident following the second day of treatment and this decrease persisted until day 7 of the experiment ($p<0.01$, Fig. 1). Mechanical withdrawal thresholds in these rats then showed recovery from day 7 reaching baseline levels by day 11. Repeated administration of 1.0 mg/kg of cisplatin did not induce increased responsiveness to the von Frey filaments, but rather produced a decrease in responsiveness such that animals were assigned cut-off response values from days 2 to 7 ($p<0.05$). Responses of rats to the mechanical stimuli gradually returned over the next week following chemotherapy such that normal response rates were observed by day 12.

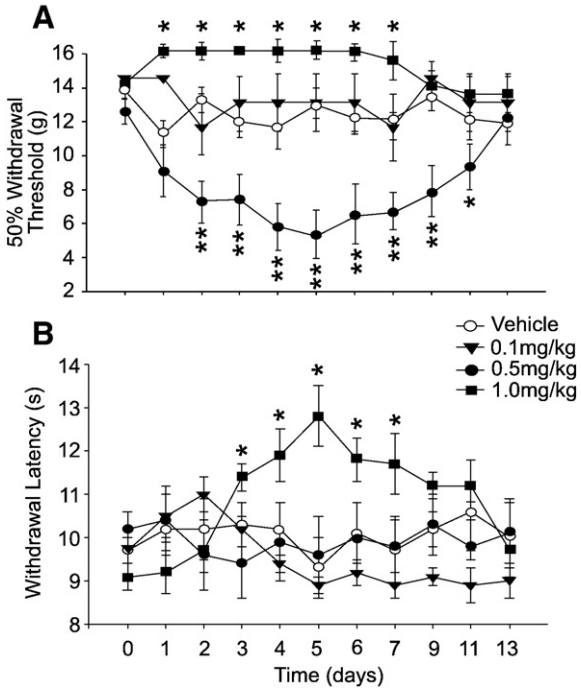

Fig. 1 – (A) The upper panel shows the 50% withdrawal threshold to mechanical stimulation of the hindpaws in saline (open circles), and cisplatin-treated animals (filled symbols). Rats receiving 0.1 mg/kg cisplatin (filled triangles) showed no changes in responses to mechanical stimulation. Rats receiving 0.5 mg/kg cisplatin treatment (filled circles) showed a significant decrease in the 50% withdrawal threshold that was evident at day 2 and that continued to day 11. Finally, rats receiving treatment with 1.0 mg/kg cisplatin (filled squares) showed an increase in 50% withdrawal threshold from days 1 to 7. (B) The lower panel shows the mean paw withdrawal latency to thermal stimulation over time with chemotherapy. The only differences that were found occurred in the rats receiving 1.0 mg kg cisplatin treatment where a significant prolongation of withdrawal latency occurred from days 3 to 7. Stars indicate differences between labeled data points and saline controls. One asterisk, $p<0.05$; two asterisks, $p<0.01$.