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Research Report

# Comparison of paclitaxel and cisplatin effects on the slowly adapting type I mechanoreceptor

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ABSTRACT

Cisplatin and paclitaxel are two of the most widely used chemotherapy drugs for the treatment of several forms of cancer. Both agents produce significant levels of peripheral neuropathy that can result in changes of treatment regimen. Although there have been recent efforts to understand the effects of these agents on nociceptor populations, little study has been made on their effects on large afferent populations. Here we report acute and chronic effects of paclitaxel and cisplatin administration on the type I mechanoreceptor using a skin-nerve preparation in rat and a standardized mechanical stimulus to compare mechanoreceptor response before and after treatment. In a control preparation, suppression of type I mechanoreceptor response during 2-min, arterial infusion of paclitaxel or cisplatin was significant for paclitaxel (28%, 1 μM; 33%, 10 μM; $p<0.025$), but not cisplatin (9%, 500 μM; 19%, 5 mM; $p>0.05$). Response returned to baseline within a 2-min washout period. Following pretreatment with paclitaxel or cisplatin, baseline response was significantly reduced from control animals. In addition, unlike the control preparation, a subsequent infusion of paclitaxel induced prolonged response suppression. Nerve fascicles innervating the preparation showed significant reduction in conduction velocity relative to control (cisplatin pretreatment: Aβ, 22%, $p<0.01$; C-fiber, 33%, $p<0.01$. paclitaxel pretreatment: Aβ, 17%, $p<0.05$; C-fiber, 23%, $p<0.05$). It was concluded that chronic paclitaxel or cisplatin treatment not only significantly alters the type I mechanotransduction process, but also increases susceptibility of the type I ending to further paclitaxel exposure.



## 1. Introduction

Peripheral neuropathy is characterized as a structural or functional derangement of peripheral sensory, motor, or autonomic neurons that causes symptoms such as numbness, tingling, weakness and pain. In addition to bone marrow suppression and renal toxicity, the majority of damage induced by chemotherapeutic agents such as cisplatin and paclitaxel is to peripheral sensory neurons (Quasthoff and Hartung, 2002). Paclitaxel and cisplatin express similar clinical indices of large-fiber damage, including impaired mechanical perception (e.g., increased tactile threshold), electrophysiological measures (e.g., prolonged

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*Abbreviations:* C, centigrade; CGRP, calcitonin gene-related peptide; cm, centimeter; DRG, dorsal root ganglion; i.m., intramuscular injection; m, meter; min, minute; g, gram; kg, kilogram; ml, milliliter; mM, millimolar; NGF, nerve growth factor; PBS, phosphate-buffered saline; rpm, revolutions per minute; SA, slowly adapting; s, second; SEM, standard error of mean; SIF, synthetic interstitial fluid; SP, substance P; vs., versus; μl, microliter; μm, micrometer; μM, micromolar

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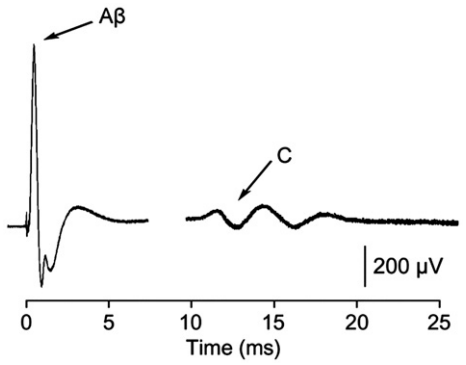


**Fig. 1 – Example of a compound action potential evoked by electrical stimulation recorded from a control animal. Abscissa indicates time from the beginning of the stimulus artifact (time 0). Voltage calibration is for both A- and C-wave components. Aβ and C-wave responses were generated by 0.1 ms and by 1 ms pulse widths, respectively. Nerve length = 9.5 mm. Also see Table 1.**

conduction latency), and sensory experience (e.g., numbness and paraesthesia) (Cata et al., 2006).

Touch domes are widely spread receptor elements in many mammals (e.g., rat, mouse, cat, and rabbit) innervated by large-diameter (Aβ) sensory neurons. They are clearly visible following hairy skin depilation and are uniquely identified by their specialized epithelial constituents, highly-vascularized dermal connective tissue, and sensory nerve terminal structure. Touch domes contain large, radially oriented keratinocytes with abundant cytoplasm situated on a well-defined basal lamina. Merkel cells are positioned at this interface and are innervated by a specific mechanosensory afferent neuron (slowly adapting (SA) type I mechanoreceptor (English, 1977)). Mechanical coupling of radial keratinocytes and Merkel cell/type I endings produces a characteristic response pattern that includes a velocity sensitivity during indentation which decays during sustained indentation and is absent during probe retraction. These response characteristics are present in several types of slowly adapting mechanoreceptors (Burgess and Perl, 1973).

Immunocytochemistry has revealed a variety of neuronal constituents in both Merkel cells and type I endings, such as neuron specific enolase, synaptophysin, and chromogranin as well as amino acids, neurotransmitters, and neuropeptides. The type I receptor has also been shown to be chemosensitive (Lucarz and Brand, 2007); for example, type I response is altered by serotonin (He et al., 1999), and serotonin antagonists (He et al., 2003) and has immunocytochemically identified serotonin (English et al., 1992b) in the type I complex, as well as small substance P (SP)- and calcitonin gene-related peptide (CGRP)-containing nerve terminals within the touch dome (Zhang et al., 2002). Furthermore, type I mechanoreceptor modulation by the endogenous pain-producing compound bradykinin (Beck and Handwerker, 1974), suggests a general influence by substances involved in peripheral nociceptive mechanisms. Vincristine, a chemotherapy agent with clinical neurotoxicity, has been reported to alter "dome function" in rat (Leon and McComas, 1984).

During the past several decades, paclitaxel and cisplatin have been two of the most widely used and effective compounds for treatment of several malignancies, including ovarian, breast, and small-cell and non-small-cell lung cancers (de Jongh et al., 2002; du Bois et al., 1999; Mollman et al., 1988; Rowinsky and Donehower, 1995). The study's primary goal was to investigate whether these neurotoxic agents (Cata et al., 2006) produce functional alterations in the terminal complex of a large-diameter, cutaneous sensory neuron. To this end, we performed *in vitro* experiments to determine whether paclitaxel or cisplatin exposure might alter receptor function. The SA type I mechanoreceptor was chosen because of its known chemosensitivity to endogenous and exogenous substances.

## 2. Results

### 2.1. *Conduction velocity of Aβ- and C-type nerve fibers*

Fig. 1 shows compound action potentials evoked by electrical stimulation adjusted to recruit maximal Aβ- or C-fiber waves from an *in vitro* cutaneous nerve fascicle (see Experimental procedures). For Aβ axons (see Table 1), control, paclitaxel and cisplatin conduction velocity samples differed significantly ($p<0.005$). Whereas paclitaxel and cisplatin samples differed significantly relative to control animals, they did not differ significantly from each other ($p=0.28$).

For C-fiber axons (see Table 1), control, paclitaxel and cisplatin conduction velocity samples differed significantly ($p<0.005$). Whereas paclitaxel and cisplatin conduction velocity samples differed significantly relative to control animals, they did not differ significantly from each other ($p=0.19$).

### 2.2. *Acute effects of paclitaxel and cisplatin on type I response in control rats*

Fig. 2 shows the response of a single type I mechanoreceptor to a standardized mechanical stimulus (see Experimental procedures) in a control, *in vitro* preparation before, during, and after paclitaxel infusion. Total impulse count during the standardized mechanical stimulus during the baseline, paclitaxel infusion, and washout runs differed significantly (1 μM, 10 μM, $p<0.01$). As shown in Table 2, paclitaxel significantly suppressed type I response relative to baseline during 2-min infusion. For 1-μM paclitaxel, response during infusion and washout differed significantly (1 μM, $p<0.025$) and was significant at 10 μM infusion ($p<0.025$). Baseline and washout levels of mechanoresponse did

**Table 1 – Influence of paclitaxel and cisplatin chronic pretreatment on peripheral nerve conduction velocity**

| Treatment | Aβ fiber | | C-fiber | |
|---|---|---|---|---|
| | $v$ (m/sec) | $n$ | $v$ (m/sec) | $n$ |
| Control | 33.6±1.6 | 9 | 0.70±0.05 | 9 |
| Paclitaxel | 28.0±0.46** | 6 | 0.54±0.02* | 6 |
| Cisplatin | 26.2±1.3*** | 6 | 0.47±0.05* | 6 |

Data presented as mean±SEM. $v$, conduction velocity. $n$, sample size. Comparison to sham: *$p<0.025$, **$p<0.01$, ***$p<0.005$.