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EFFECTS OF CAPSAICIN ON RAT SCIATIC NERVE IN VINCRISTINE-INDUCED NEUROPATHIC PAIN MODEL

Thanaa A. El-Masry *[1], Magda E. El Sayaad [1], Ibrahim A. Gaaboub [2] and Wafaa M. Fouda [1]

Department of Pharmacology & Toxicology, Faculty of Pharmacy, Tanta University [1], Egypt
Department of Plant Protection, Faculty of Agriculture, Banha University [2], Egypt

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Correspondence to Author:

Thanaa A. El-Masry

Department of Pharmacology & Toxicology, Faculty of Pharmacy, Tanta University, Egypt

E-mail: fofo_pharm2007@yahoo.com

ABSTRACT

Capsaicin, the pungent ingredient of red pepper, is used topically to treat different types of neuropathic pain, in rat model of vincristine induced neuropathic pain we tried to investigate the effect of capsaicin on sciatic nerve through electrophysiological and histopathological studies. We found that treatment of animals with vincristine results in significant decrease in sciatic nerve conduction velocity and degeneration of the nerve fibers, where combined treatment of vincristine and capsaicin showed highly significant decrease in sciatic nerve conduction velocity and degeneration of the nerve fibers compared with that treated with vincristine only. In new trial, we tried to investigate the effect of direct capsaicin titration on sciatic nerve fibers that results in nearly abolishment of nerve conduction velocity. All of these findings may illustrate the mechanism of capsaicin effect through afferent nerves degeneration.

INTRODUCTION: The pungent ingredient of red pepper, Capsaicin, is used topically in treatment of post-hepatic neuralgia, diabetic neuropathy and osteoarthritis [1]. Capsaicin therapeutic effects are based on modification of sensory nerve endings. Capsaicin renders animals and man insensitive to further noxious stimuli after initial irritation [2]. Examination of the function of sensory neurons specifically peripheral C-fibers can be mediated by capsaicin .it was found that capsaicin high doses cause desensitization to chemical stimuli, loss of neurogenic inflammation, and depletion of neuropeptides.

Analgesic (and anti-inflammatory) effects of capsaicin can be accounted for by a rapid degeneration/ destruction of sensory ganglion cell axons and/or peripheral and central axon terminals, these effects were suggested due to the rapid onset and the long duration of the antinociceptive effect of vanilloids [3, 4, 5, 6, 7].

Indeed, independent laboratories experimental data support the notion that capsaicin antinociceptive effects, administered through different routes, are associated with degenerative changes within the different domains of the nociceptive primary sensory neuron and the consequent loss of peripheral or central nociceptor specific macromolecules and receptors [4, 8]. One of the most common chemo-therapeutic drugs used to treat various types of malignancies is vincristine [9, 10]. Its major dose-limiting side effect is neurotoxicity that requires discontinuation of treatment and thus greatly affects the survival of cancer patients [11, 12, 13].

In this study, we investigate the degenerative effects of capsaicin on sciatic nerve by systemic repeated doses of capsaicin in vincristine induced neuropathy model through electrophysiological study and histo-pathological examination of sciatic nerve.

MATERIAL AND METHODS:

1. **Animals:** Fifteen female Egyptian rats (140-160 g).Rats were housed in groups of five under a 12-h light/dark cycle. Food and water were available. Experiments were carried out in accordance with NIH regulations for animal care and with the approval of the Institutional Animal Care and Use Committee of the University of California, San Francisco. All efforts were made to minimize the number of animals used and their suffering.

2. **Drugs:** Vincristine-treated group: Vincristine (Vincristine Pierre Fabre1 1 mg/ml, Boulogne, France) was diluted in normal saline (NaCl 0.9%, Braun, Melsungen, Germany) just before administration to give a final concentration between 50 and 100 mg/ml, depending on the animal weight and ensuring that volumes of less than 1 ml would be injected I.P. Capsaicin-treated group: Capsaicin dissolved in (10% methanol + 10% tween 80 and 80% D.W) Solvent. Control groups: Injected volumes of saline (NaCl 0.9%) were calculated according to the weight of the rat.

3. **Experimental Procedures:** Animals were classified into 3 groups Vincristine- treated group: Vincristine was administered I.P. every 2 days until five injections had been given 150 mg/kg (cumulative dose: 750 mg/kg). To avoid acute effects the injections were given after the behavioral tests were performed. Capsaicin – treated group: Rats were I.P. injected with Vincristine dose (150µg/kg) once every 2 days till 5 injections with Capsaicin I.P. (500µg/kg) once every 2 days 30 minutes before each Vincristine injection till 7 injections. Control group: animals will be injected with volumes of normal saline according to body weight.

4. **Electrophysiological study:** Rats were initially anesthetized by ether inhalation as induction anesthesia for approximately 5 minutes and then mounted in plasticine, ventral side up, with four legs immobilized by hooks in plasticine. Extracellular activity of the nerve was recorded with suction electrode from the sciatic nerve. Recording from the sciatic nerve was done using the extracellular recording technique [14] (Andrew 1972). The suction electrode containing the saline (0.9% NaCl) was placed over the sciatic nerve. The signals of the nerve were amplified by an AC amplifier, filtered, then displayed on an Tektronic 502 Oscilloscope and recorded on a magnetic tape.

5. **Statistical analysis:** The data are expressed as means SE, significance of differences between groups was assessed with Student's t-test (comparison of two groups). Significance was adopted at $p<0.05$ for interpretation of results of tests of significance.

6. **Histology:** Samples of sciatic nerve were processed and paraffin embedded sections cut at 3-5 mm thickness on glass and charged slides for routine hematoxylin and eosin staining method for light microscopy examination.

RESULTS: As shown in **figure 1 and 2**, treatment of rats with Vincristine (150µg/kg) showed a significant decrease in sciatic nerve conduction velocity as compared to that of the control (saline) group. Treatment of rats with (Vincristine (150µg/kg) + Capsaicin (500µg/kg)) showed a significant decrease in nerve conduction velocity as compared to that of the Vincristine (150µg/kg) treated group. Direct Capsaicin titration on sciatic nerve in(Vincristine (150µg/kg) + Capsaicin (500µg/kg)) treated animals showed significant decrease in nerve conduction velocity compared to (Vincristine (150µg/kg) + Capsaicin (500µg/kg)). Washing the nerve with normal saline after capsaicin titration resulted in a significant increase in the nerve conduction velocity.

As shown in **figure 3** histopathological examination of sciatic nerve section of animals treated with Vincristine (150µg/kg) showed degenerated sciatic nerve fibers and perineuronal mononuclear cell infiltrations. Combined treatment of rats with (Vincristine (150µg/Kg) and Capsaicin (500µg/kg) showed sciatic nerve fibers section with degenerated myelin (vacuolar degeneration).

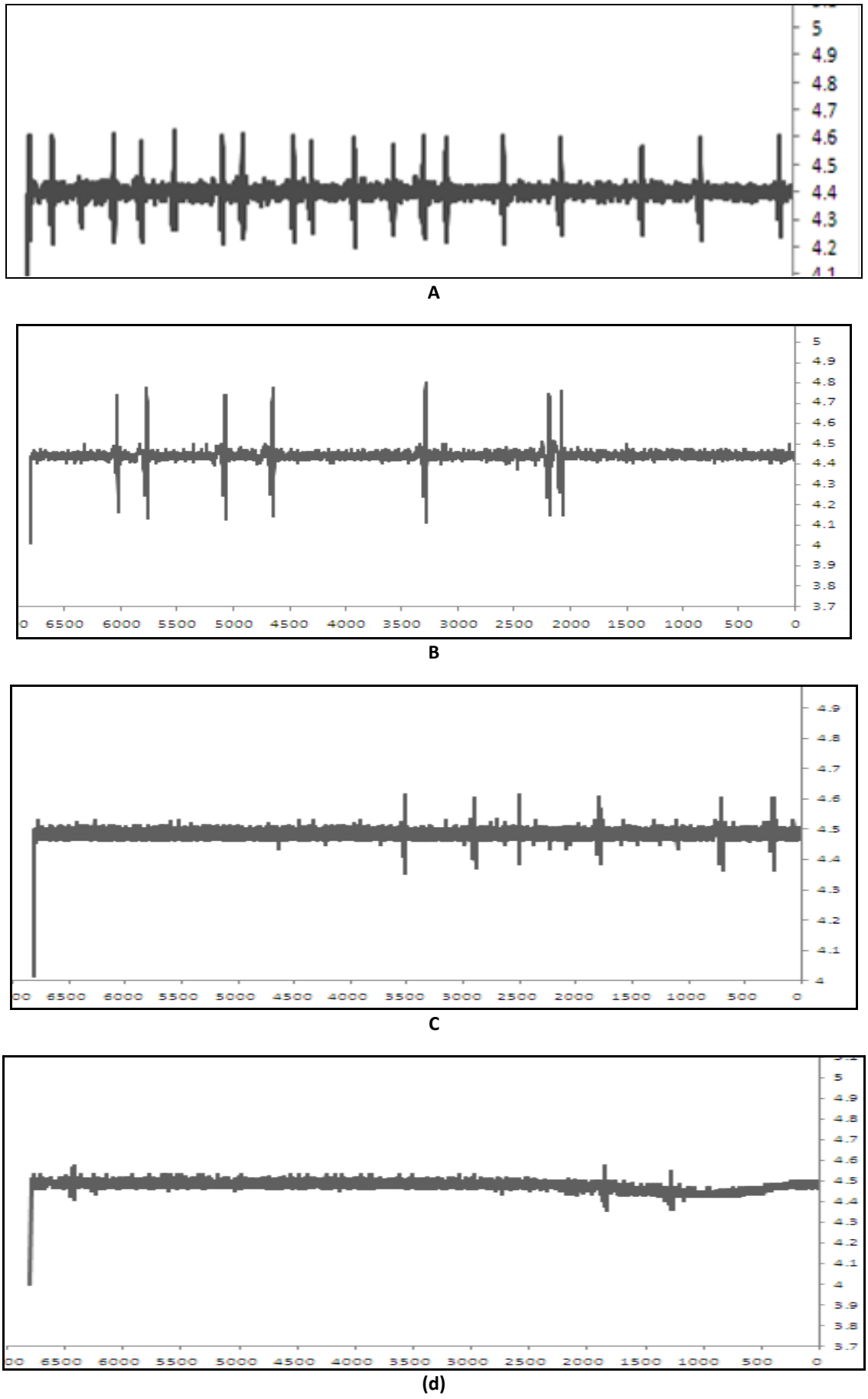


FIGURE 1: SPIKE DISCHARGES IN SCIATIC NERVE OF RAT IN RESPONSE TO :NORMAL SALINE (A), VINCRISTINE (B), CAPSAICIN (C), CAPSAICIN WITH DIRECT CAPSAICIN TITRATION ON THE NERVE (D)

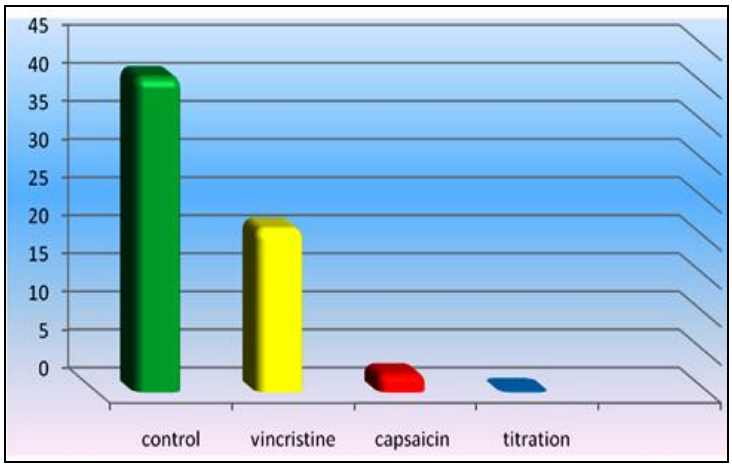
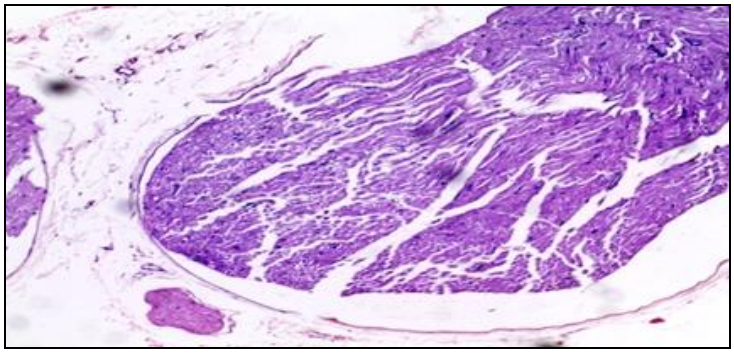
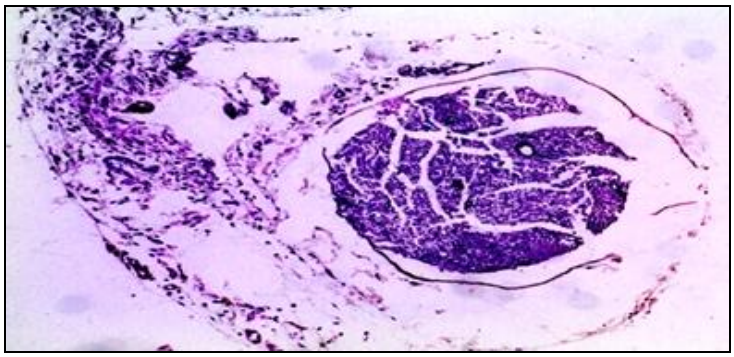


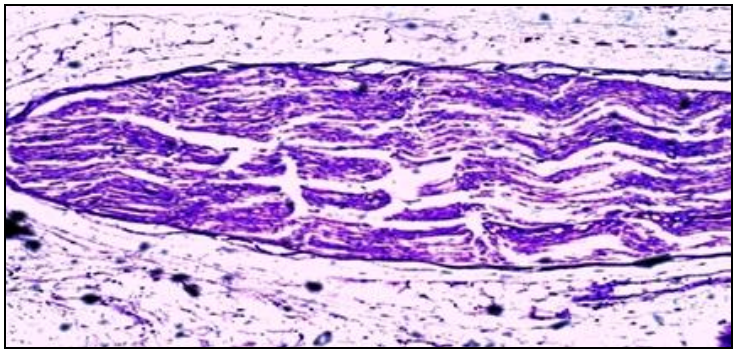
FIGURE 2: EFFECT OF DIFFERENT DRUG TREATMENTS ON SPIKE FREQUENCIES



A



B



C

FIGURE 3: PHOTOMICROGRAPH OF HISTOPATHOLOGICAL EXAMINATION OF DIFFERENT DRUG TREATMENTS: NORMAL SALINE (A), VINCRISTINE (B) OR CAPSAICIN (C)

DISCUSSION: In new animal model of neuropathic pain, vincristine, antineoplastic agent, used to induce sciatic nerve injury. Capsaicin the main agonist of transient receptor potential vanilloid 1(trpv1) used as repeated systemic doses as analgesic for vincristine induced neuropathic pain.

In this study, we tried to investigate the effect of capsaicin on rat sciatic nerve through electrophysiological study and histopathological examination of the nerve. The results showed that vincristine treatment alone resulted in a significant decrease in sciatic nerve conduction velocity as compared to that of the control (saline) group representing (51.71 % of control saline value). While combined treatment of animals with vincristine and capsaicin resulted in highly significant decrease in sciatic nerve conduction velocity compared with vincristine treated only representing (10.55% of vincristine treated only value, 5.46% of control saline value). Direct capsaicin titration on sciatic nerve nearly abolished the nerve conduction velocity representing (0.00011% of control saline value).

These results was confirmed by histopathological examination of sciatic nerve that showed different degrees of nerve damage where vincristine treatment showed degenerated sciatic nerve fibers and perineuronal mononuclear cell infiltrations and combined treatment of animals with vincristine and capsaicin resulted in sciatic nerve fibers section with degenerated myelin (vacuolar degeneration).

Our results were agree with [14] who found that treatment of vincristine (150µg/kg) resulted in significant decrease in sciatic nerve conduction velocity ($P < 0:05$, 23%) and sciatic nerve fibers with various degrees of axonal degeneration microscopically.

All of these finding showed the degenerative effect of capsaicin on sciatic nerve fibers in agree with [3, 4, 6, 7] who reported that the rapid onset and the long duration of the antinociceptive effect of vanilloids have led to the suggestion that the analgesic (and anti-inflammatory) effects of capsaicin may be accounted for by a rapid degeneration/ destruction of sensory ganglion cell axons and/or peripheral and central axon terminals.

CONCLUSION: In conclusion, vincristine treatment results in sciatic nerve injury with induction of neuropathic pain. Capsaicin was used as an analgesic for vincristine induced neuropathic pain as it cause nearly total destruction of afferent nerves.

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