Original Article

Protective Effects of Oxytocin and Progesterone on Paclitaxel-induced Neuropathy in Rats

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Abstract

Objective: Paclitaxel (Ptx), used to treat cancer, still causes neuropathic pain and peripheral neuropathy today. This study was conducted to evaluate the effects of progesterone (Pg) and oxytocin (Oxy) on peripheral neuropathy rat model induced by Ptx. **Materials and Methods:** A total of 38 male Sprague–Dawley rats were randomly divided into five groups, e.g., control (n = 6), Ptx (n = 8), Ptx + Oxy (n = 8), Ptx + Pg (n = 8), and Ptx + Oxy + Pg (n = 8). The rats were monitored daily for body weight change throughout the experiment. To evaluate peripheral neuropathy, electroneuromyography measurements (latency, amplitude, and motor nerve conduction velocity (MNCV)) were recorded from the sciatic nerve innervating the gastrocnemius muscle. Sciatic nerve tissue samples were collected for histopathological evaluation. **Results:** Ptx led to significant reductions in body weight from day 6 ($P < 0.05$). There was no difference between groups in the distal latency and amplitudes ($P > 0.05$). Proximal latency was prolonged in Ptx group rats than in other groups ($P < 0.05$). Importantly, it was found that MNCV was higher in the Ptx + Pg group than Ptx, Ptx + Oxy, and Ptx + Oxy + Pg groups ($P < 0.05$). Furthermore, Pg-administered rats had the lowest nerve degeneration compared to rats administered Oxy and Oxy + Pg ($P < 0.05$). **Conclusions:** The present findings suggest that Pg has a protective effect on peripheral neuropathy induced by Ptx in rat.

Keywords: *Motor nerve conduction velocity, neuropathy, oxytocin, paclitaxel, progesterone, rat*

Submitted: 08-Jun-2021
Revised : 10-Aug-2021
Accepted : 04-Sep-2021
Published : 29-Dec-2021

Introduction

Peripheral neuropathy, characterized by dysfunction or degeneration of nerve fibers, usually occurs in cancer patients administered paclitaxel (Ptx) in response to the treatment of solid tumors. Neuropathy may be dose and duration dependent after the treatment of Ptx which can cause physical inabilities and lower the quality of life.[1] The mechanism underlying peripheral neuropathy is associated with apoptosis due to stabilization and inhibition of G2/M phase of mitosis by Ptx that possibly degenerates peripheral nerves and deteriorates axonal transport ultimately resulting in peripheral neuropathy.[2,3] Basically, large nerve fibers are affected in Ptx-induced neuropathy characterized by the degeneration of sensory, motor, and autonomic neurons.[3] However, the exact mechanism of the development of Ptx-induced neuropathy has not yet been elucidated.

Access this article online

Quick Response Code:

Website: www.nsnjournal.org

DOI: 10.4103/nsn.nsn_113_21

Electrophysiological studies show that Ptx treatment in cancer patients impairs the sensory nerve conduction velocity.[4] Recently, higher doses and frequent administration of Ptx have resulted in increasing motor nerve neuropathy.[5] In addition, Ptx treated animals show the symptoms of hypo/hyperalgesia, mechanical allodynia, and lowered motor and nerve conduction velocities.[6-9] Axonal degeneration and demyelination along with the loss of large myelinated nerve fibers in the peripheral nervous system are seen depending on the dose and administration program in rodent

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How to cite this article: Ekici M, Balkaya M. Protective effects of oxytocin and progesterone on paclitaxel-induced neuropathy in rats. Neurol Sci Neurophysiol 2021;38:262-70.

neuropathy models induced by Ptx.[9-11] To date, no effective treatment of Ptx-induced neuropathy has been discovered.

Oxytocin (Oxy), a neuropeptide largely expressed in the paraventricular and supraoptic nucleus of the hypothalamus, plays a pivotal role in the regulation of birth and lactation. Oxy shows its biological activity through G protein bound receptors that are expressed throughout the body including the central ad peripheral nervous system.[12] Anti-inflammatory, anti-apoptotic, and antioxidant properties of Oxy underline its cytoprotective effects.[13,14] Condés-Lara *et al*. reported the antianalgesic effect of Oxy in neuropathic rats.[15] A recent study reported that chemotherapy-induced neurotoxicity can be reversed by Oxy.[16]

Progesterone (Pg) is a steroid hormone produced by the corpus luteum during the proestrus phase of estrous cycle in rodents and in the luteal phase of menstrual cycle in women. It is also produced in the central and peripheral nervous system. Pg is the most important steroid among the neuroactive steroids.[17] Recent findings have demonstrated the protective effects of neuroactive steroids including Pg on nerves suggesting that they may be used for the treatment of physical injuries, and neurological and hereditary demyelinating diseases.[18]

It has been previously shown that Pg and Oxy have a neuroprotective effect in peripheral neuropathy induced by several chemotherapeutics such as docetaxel, cisplatin, vincristine, oxaliplatin, but not by Ptx.[16,19-21] Thus, we hypothesized that Oxy and Pg could have protective effects on Ptx-induced peripheral neuropathy in rats.

Materials and Methods

Animals and experimental design

The study was conducted in the electroneuromyography (ENMG) Laboratory of the Faculty of Veterinary Medicine, with the approval of the Animal Experiments Local Ethics Committee of Aydın Adnan Menderes University (approval no: 64583101/2017/110). A total of 38 Sprague–Dawley male rats, 3–4-month old, with a mean bodyweight of 447 ± 4.85 g (min-max: 435–461 g) were used in the study. Rats were housed in type 4 macrolon cages at 22 ± 1°C room temperature, 50%–70% humidity, and 12:12 h light: dark cycle for 1-week adaptation period and subsequent experimental period. *Ad libitum* standard rat diet (Bil-Yem Nukleon®) and water were given during the experiment. Because females already have higher circulating Pg levels than males, experiments were conducted using male rats to avoid fluctuations in endogenous circulating Pg in females. All experiments were performed between 10:00 am and 2:00 pm. The rats were randomly divided into five groups: control (n = 6), Ptx (n = 8), Ptx + Oxy (n = 8), Ptx + Pg (n = 8), and Ptx + Oxy + Pg (n = 8). The control group received only saline intraperitoneally. Ptx (Ataxil® Deva Holding A. Ş. Istanbul, Turkey) was administered intraperitoneally at a dose of 3 mg/kg every other day throughout the experiment to induce peripheral neuropathy. Oxy (Vetaş 10 IU, Deva Holding, Tekirdag, Turkey) was given intraperitoneally at doses of 120 g/kg in the Ptx + Oxy group.[16,20,22] Pg (Sigma Aldrich, St. Louis, MO, US) was given intraperitoneally at doses of 12 mg/kg in the Ptx + Pg group.[23-25] We designed a combination group (Ptx + Oxy + Pg) in this study with the idea that when Oxy and Pg are administered together, their potential protective effects can become additive.[20,24] For this purpose, similar doses of Oxy and Pg were given intraperitoneally to the Ptx + Oxy + Pg group. This experimental protocol took 14 days [Figure 1]. Previously studies showed that Pg did not affect the normal nerve of rodents.[25-27] In addition, it is known that Oxy has a neuromodulatory effect on nerve cell only *in vitro* but not *in vivo*.[28-30] Therefore, we did not include additional positive control groups in this study.

Recording of electroneuromyographs

The compound muscle action potential (CMAP) is the summation of all underlying individual muscle fiber action potentials. The latency of CMAP is the time measured in milliseconds (ms) from baseline to the first CMAP deviation with the stimulus. The CMAP is a biphasic potential with an initial up deviation (negative) followed by a smaller down deviation (positivity). The amplitude of CMAP is recorded from baseline to negative peak which is demonstrated by an upward deflection and measured in millivolts (mV). To record the CMAP, the stimulating current (mA) is gradually raised from a baseline of 0 mA, generally by 5–10 mA, until no change in CMAP amplitude is seen when the stimulus is increased. It is only with this supramaximal stimulation, reproducible values for CMAP amplitude and duration of poststimulus CMAP latency can be accurately recorded. Motor nerve conduction velocity (MNCV) study is conducted by electrical stimulation of a nerve and recording the CMAP from surface electrodes overlying a muscle supplied by a stimulated nerve. The difference between the proximal latency and distal latency in ms shows the conduction time along the fastest nerve fibers between the anatomical regions, dispensing with the transition time from the distal site and across the neuromuscular junction, as well as muscle fiber depolarization time. The distance between the anatomical region in millimeters

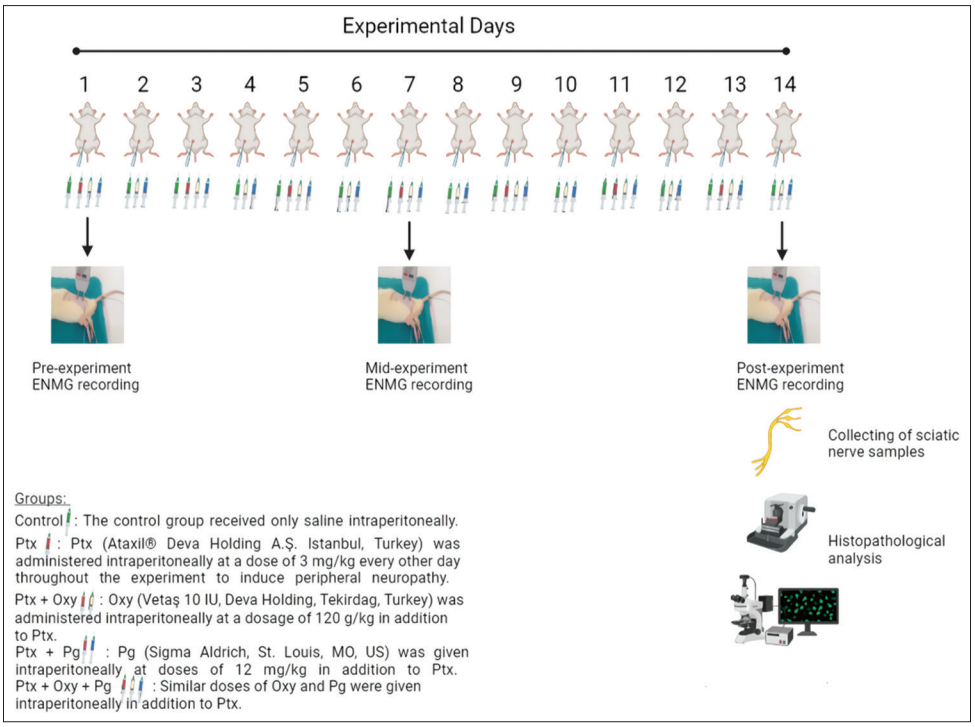

Figure 1: Experimental diagram of interventions

divided by the nerve conduction time is known as the conduction velocity (NCV [m/sec] = distance between stimulation sites [mm]/proximal latency-distal latency [ms]).[31] ENMG was conducted using a four-channel Nicolet Viking Quest (Natus Medical Incorporated, Pleasanton, CA, US) on days 1, 7, and 14 of the experiment. Rats were anesthetized by administering i.p. injection of a combination of 60 mg/kg ketamine (Alfamine®, Alfasan International B. V., The Netherlands) and 10 mg/kg xylazine (Alfazyne®, Alfasan International B. V., The Netherlands). The latency of CMAP and MNCV data recorded in ENMG from gastrocnemius muscle by stimulating the sciatic nerve was analyzed using VIASYS Nicolet Viking Quest® software program. Stimulation was performed using a bipolar surface stimulation electrode (Nicolet s403: Natus Medical Incorporated, Pleasanton, CA, USA). The active and reference electrodes were placed on the origin and insertion parts of the muscle. In addition, the grounding electrode was placed on the root of the tail. Supramaximal stimulations were performed proximally at the level of transverse processes of third and fourth lumbar vertebrae, and distally at the medial level of trochanter major. Records of each stimulation series were averaged to eliminate noise and to smooth the response curves. The time between the isoelectric line of the latency stimulus and the formation of the first negative deflection was measured in ms. Amplitude was measured as negative peak deflection assuming the baseline to the negative peak as the benchmark. The settings of the ENMG device were set as; amplifier filter 10 Hz to 10 kHz, sweep speed 1 ms, stimulation time 0.5 ms, and gain 10 mV. Electrical stimulations were performed manually at random intervals at right angles. The difference in distance between distal and proximal stimulation points was divided by the latency difference to calculate MNCV (m/sec). The distance between the two stimulation points was measured with a compass (±1 mm accuracy) [Figure 2a].

Histopathology

At the end of the experiment, rats were euthanized by an overdose of ketamine/xylazine combination. Sciatic nerve samples were collected in 10% buffered formalin solution and fixation was carried out for 48 h. Following fixation, tissues were placed in tracking cassettes, washed in running tap water for 6 up to 8 h, cassettes were placed in a tissue tracking machine (Leica TP1020) and embedded in paraffin. The samples were then sectioned (3–4 μm thickness) from the paraffin blocks using microtome (Leica RM 2125RT) perpendicular to the long axis of the nerve. Sections were stained with hematoxylin and eosin stain according to the procedure previously described by Carson and Hladik.[32] Images were recorded from 10 different sites of the prepared slides under the light microscope (OLYMPUS BX51) attached with a digital camera (OLYMPUS SC 180) using ×400 magnification of the objective lens. Recorded images were then analyzed using CellSens Life Science

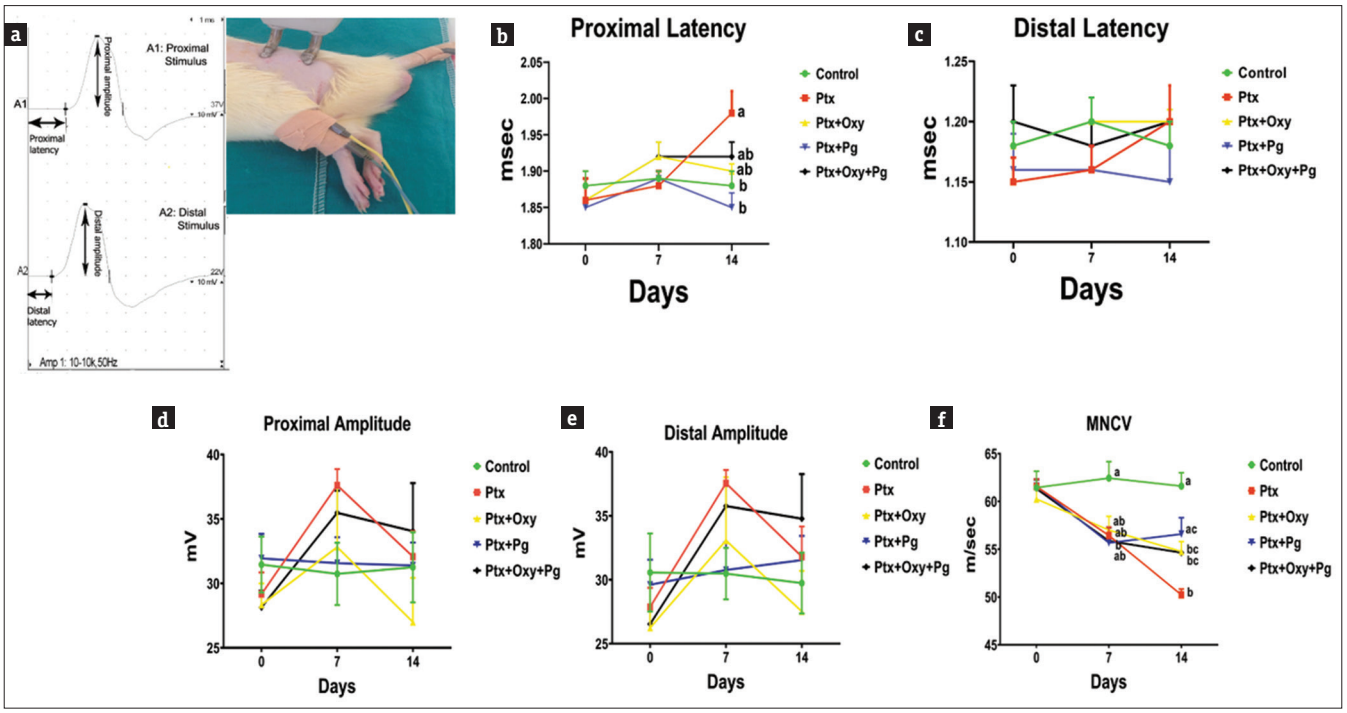

Figure 2: ENMG findings. ENMG recording example (a). Changes in proximal (b) and distal CMAP latency (c), proximal (d) and distal CMAP amplitude (e), and MNCV (f) on days 0, 7, and 14. Different letters on the same day are a significant difference. (b) On the 14th day of the experiment, proximal latency was higher in the Ptx group compared to control and Ptx + Pg groups ($P < 0.05$). (f) On the 7th day of the experiment, the mean MNCV value of the Ptx + Pg group was lower than that of the control group ($P < 0.05$). On the 14th day of the experiment, proximal latency was higher in the Ptx group compared to control and Ptx + Pg groups ($P < 0.05$).

Imaging Software® (version 1.18; OLYMPUS) and intact and degenerated axons were counted. At the end of quantification, degeneration (%) was calculated.[33]

Statistical analyses

Data were analyzed using a statistical software package SPSS (version 22.0, Armonk, NY, USA). Shapiro–Wilk's test was used for testing the normal distribution of the data, while homogeneity of variance was tested using Levene's test. Logarithmic or square root transformation was conducted for the data that have not normal distribution. Bodyweight and electromyographic data were analyzed using two-way ANOVA for repeated measures over time. When intervention (group) and/or interaction (time × intervention) are significant, multiple comparisons were done with *post hoc* GLM procedure using extra coding into the syntax menu of SPSS that allowed the *P* value to be corrected. Evaluation of histopathological data was conducted using Kruskal–Wallis test followed by separation of means using Bonferroni corrected Mann–Whitney U test as a *post hoc* test. In addition, the correlation analysis between MNCV and degeneration (%) was done using Spearman correlation coefficient test. Confidence interval was set at 95% ($P < 0.05$) and results were presented as mean ± standard error of mean.

Results

Bodyweight changes

At the end of experiment, body weight decreased ($P < 0.05$) by 9%, 15%, 13%, and 12% in Ptx, Ptx + Oxy, Ptx + Pg, and Ptx + Oxy + Pg groups, respectively, compared to the control group [Figure 3].

Electroneuromyography changes

Proximal latency values were longer in Ptx group compared to the control group ($P < 0.05$) whereas no difference was noted among control, Ptx + Oxy, Ptx + Pg, and Ptx + Oxy + Pg groups [Figure 2b]. Distal latency values [Figure 2c], proximal and distal amplitude [Figure 2d and e, respectively] were not different among the groups. Ptx led to reduction in MNCV throughout the experiment ($P < 0.05$) [Figure 2f]. In the middle of the experiment (day 7), mean MNCV value Ptx + Pg group was lower than that of the controls. On day 14, MNCV values between control and Ptx + Pg groups were not different. However, control group had greater MNCV than those of Ptx, Ptx + Oxy, and Ptx + Oxy + Pg groups ($P < 0.05$). In addition, rats in Ptx group had lower MNCV values than those in Ptx + Pg group ($P < 0.05$) while there was no difference between Ptx + Oxy and Ptx + Oxy + Pg groups [Figure 2f], suggesting that Pg administration normalized the

MNCV, whereas Oxy alone or in combination with Pg failed to normalize MNCV.

Histopathological changes

Histopathological examination of sciatic nerve revealed the occurrence of swelling, shrinkage, and vacuolization in axons due to degeneration. Thinning, collapse, or deterioration were examined as typical myelin changes. Degenerative damages such as demyelination and loss of axons were determined in Ptx group [Figure 4]. Degenerative changes and degeneration (%) were observed to a lesser extent in Ptx + Pg group compared to Ptx group ($P < 0.05$), however, degenerations they were not different in comparison with Ptx + Oxy and Ptx + Oxy + Pg groups [Figure 4]. On the other hand, a strong negative correlation was found between MNCV mean values and % degeneration at the end of experiment (r =-0.793; $P < 0.001$) [Table 1].

Discussion

In this study, the protective effects of Pg and Oxy hormones in the peripheral neuropathy model induced by Ptx were investigated. These hormones were not found to be significant in body weight changes. Contrary to expectations, Oxy hormone, and combination with Pg hormone did not affect the improvement in ENMG and histopathological data. However, Pg hormone improved latency and MNCV and histopathological changes. The results obtained in this study refer only to rapidly conducting myelinated axons of alpha motor neurons.

The results of these experiments, which analyzed Ptx-induced system toxicity, are consistent with results previously described in other studies.[34,35] Pg and Oxy did not alleviate Ptx-induced systemic toxicity nor did a combination of the two. This can be explained by a few factors. It has been shown in other research that Pg typically increases food intake and body weight.[19,36] However, our results showed that Pg did not cause such change. There was no difference in body weights between the Ptx and Px + Pg groups at the end of the experiment in our study. One reason for this effect could be that food intake decreased due to stress induced from repeated injections. Another reason could be due to significant anorexigenic effects of this chemotherapeutic agent, which has previously been described in laboratory animals and humans.[21,37,38] Finally, Oxy itself causes suppression of food intake, increased energy consumption, and lipolysis in rats and monkeys.[39,40] Therefore, Oxy, in combination with chemotherapeutic toxicity, might have increased the metabolic energy deficit by limiting the food intake.

Electrophysiological tests in studies on peripheral neuropathy animal models often focus on the

Table 1: Spearman correlation coefficients (rs) showing the correlation between motor nerve conduction velocity and degeneration (%) in nerve fibers

	MNCV	Degeneration (%)
MNCV	1	−0.793***
Degeneration (%)	−0.793***	1

MNCV: Motor nerve conduction velocity. A strong negative correlation was found between motor nerve conduction velocity mean values and % degeneration at the end of the experiment (r=-0.793; ***P<0.001)

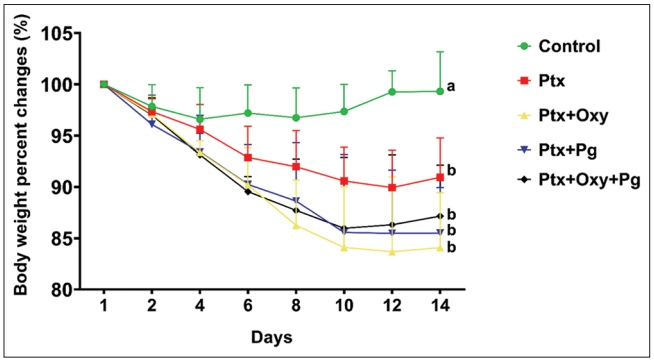

Figure 3: Changes in body weight (%). Different letters show the difference between the groups. Bodyweight percent changes were higher in all groups than in the control group ($P < 0.05$)

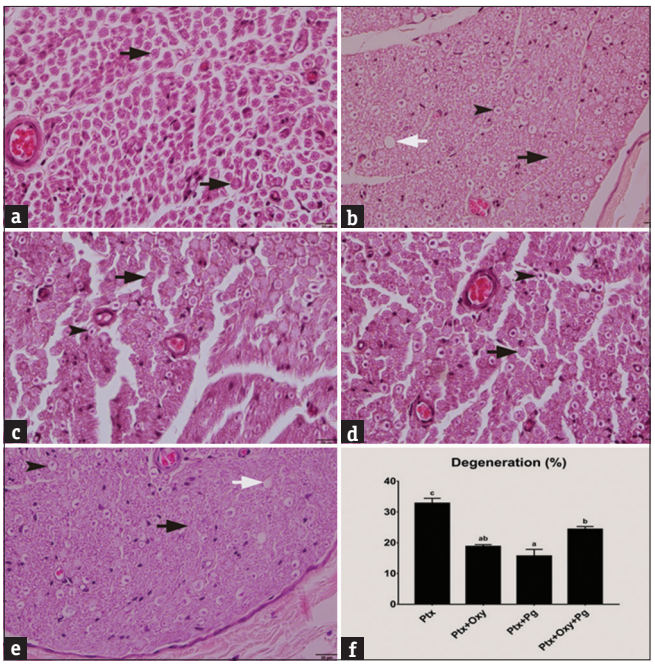

Figure 4: Histopathological changes in sciatic nerve fibers. (a) Control, (b) Ptx, (c) Ptx + Oxy, (d) Ptx + Pg, and (e) Ptx + Oxy + Pg. Black arrows indicate axonal degeneration and vacuolization; white arrow indicates myelin degeneration along with loss of axons; and black arrow heads indicate intact axons, (f) Nerve fiber degeneration (%). Bars bearing different letters on the same day are significantly different ($P < 0.05$). The percentage of degeneration was lower in Ptx + Oxy, Ptx + Pg, and Ptx + Oxy + Pg groups compared to Ptx group ($P < 0.05$)

evaluation of latency and/or nerve conduction velocity without measuring amplitude.[6,41,42] As expected, Ptx administration prolonged the proximal latency values and decreased MNCV [Figure 2a and f]. These results of our experiment indicate neuropathy consistent with other studies.[43,44] In this study, Ptx-induced neuropathy was also confirmed in histopathological examination [Figure 4]. Microtubule stability affects axonal transport of growth factors leading to abnormal nerve function and loss of axonal integrity. Therefore, Ptx causes apoptosis and collapse and fragmentation of the myelin sheath of some axons in sciatic nerve.[9] Nerve conduction velocity is essentially considered as a function of axonal diameter and degree of myelination which, in this study, the relationship between MNCV findings and histological analyses confirms this notion [Table 1]. The observed changes in peripheral nerve function as well as the increased susceptibility of longer axons to Ptx's effects are consistent with the idea that axonal pathology contributes to Ptx-induced neuropathy.

There was no change in amplitude despite increased axonal degeneration that might be due to early stage of Ptx's neurotoxic effects which indicates mild motor neuropathy accompanying the sensory deficits.[7] On the other hand, changes in continuous recording CMAP may be more difficult to understand than changes in nerve action potentials, although CMAP has a high amplitude and is therefore straightforward to monitor. This is due to the complicated time-dependent effects of sustained stimulation on facilitation and exhaustion at the neuromuscular junction and muscle.[45] The complexities of these phenomena are also interestingly seen in our study. CMAP recordings in each rat were not initiated until the CMAP amplitude reached a relatively constant value after the onset of continuous stimulation. This occurred over a period of several minutes and resulted in a CMAP with an amplitude slightly less than the maximum value. Thus, the amplitude of CMAP is not exactly a good predictor of axonal membrane properties.[46] At the end of the experiment, Pg showed complete protection in proximal latency whereas Oxy and Oxy + Pg caused partial protection. Interestingly, distal latency remained unaffected indicating that a segmental degeneration might have occurred in the sciatic nerve. Similarly, no difference in MNCV between control and Pg groups is a clear evidence of effective protection of Pg in Ptx-induced neurotoxicity. This protective effect was also observed by the histopathological examination [Figure 4]. Similar findings were reported by Roglio *et al*. who stated that docetaxel-induced reduction in nerve conduction velocity was prevented by Pg.[19] In addition to neuroprotective effects of Pg and Pg derivatives such as dihydroxyprogesterone, allopregnanolone, and tetrahydroxyprogesterone also have anti-inflammatory and antinociceptive effects[47] which might probably play important roles in terms of neuroprotective effects of Pg. The mechanisms that Pg shows its positive effects on peripheral nervous system may be due to the changes in certain variables such as mRNA levels of P0 and PM22 myelin proteins, activity of Na^+/K^+-ATPase, thermal threshold value, and intra-epidermal nerve fiber density.[48-50] Pg also shows its beneficial effects by improving the edema, axon diameter, myelin thickness, and abnormalities in sciatic nerve fibers along with myelin integrity.[51,52] Importantly, a recent article showed that hydroxyprogesterone caproate, which is a synthetic Pg derivative similar to the endogenous Pg, had both protective and therapeutic effects in chemotherapy-induced painful neuropathy in rats.[21]

Little is known about the protective effects of Oxy on peripheral nervous system. Oxy shows its curative and beneficial effects on peripheral nervous system through antioxidant and anti-inflammatory mechanisms.[16,53,54] In addition, Oxy administration causes and increase (~ 3-fold) in plasma concentration of a nerve growth factor, which is crucial for neuronal viability and differentiation.[55] Moreover, Oxy increases the plasma IGF-1 levels that enhance the survival of musculocutaneous flaps.[56] In the present study, however, Oxy administration did not affect MNCV, proximal latency, and other electrophysiological variables even though it led to a reduction in degenerative nerve cells. One explanation is that Oxy might have protective effects on cell survival as mentioned above, but the effect looks like limited to protection of the nerve cells. Another possible reason is that Oxy administration may show its possible protective effect in the long term. Erdogan *et al*. (2020) have found that the 4-week application of Oxy has a protective effect in vincristine-induced neuropathy in rats.[20] In another study, it was observed that Oxy administration for 12 weeks improved histological and electrophysiological changes in a sciatic nerve injury model in rats.[54]

In contrast to the expectations in our study, the combination of Pg and Oxy did not show any therapeutic effect in the PTX-induced neuropathy model. We think that there might be a relative competition between Pg and Oxy due to the fact that the neuroactive steroids such as Pg are thought to be neuromodulators which may act in cell surface either through ionic channels or through steroid receptors.[57] In addition, there might also be complex interactions between Pg, and Oxy through $GABA_A$ receptors which might have ultimately been led

to prevent the binding of Pg and/or Oxy to their receptors properly. Importantly, there are interconvertible affinities in terms of Pg and $GABA_A$ for the Oxy receptors.[12,58,59] On the other hand, Oxy has also been reported to regulate neurosteroids by shifting the mode of $GABA_A$ receptors (e.g., from a neurosteroid-sensitive to a nonreceptor-sensitive mode) which indicates there could be an inverse causal relationship between neurosteroid susceptibility of $GABA_A$ receptors and the proteins that $GABA_A$ receptors interact.[60] Interestingly, Oxy has negative modulatory effects on Pg and estrogen receptors in the uterus of immature female rats.[61] The underlying mechanism responsible for these complex interactions among $GABA_A$ receptors, Oxy, and Pg is unknown. Based on the available data and our current data on this mechanism, we conclude that, since phosphorylation is a positive regulator of steroid receptor function, Oxy may have activated the membrane receptor-mediated phosphoinositol signaling system which might cause a reduction in steroid receptor phosphorylation and reduce their binding capacity and neuroprotective effects.

Conclusions

In the study, the effects of Pg are intriguing and may provide new therapeutic strategies in Ptx-induced neuropathy. However, since therapeutic actions of Pg might be different in men, precise pharmacological approaches could be needed for male gender.

Acknowledgments

This study was part of a Ph.D. thesis project that was approved and financially supported by ÖYP Unit affiliated to Aydın Adnan Menderes University, Turkey (OYP Number: 14017).

Financial support and sponsorship

ÖYP Unit affiliated to Aydın Adnan Menderes University.

Conflicts of interest

There are no conflicts of interest.

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