Research Article

The Preventive Effect of Oxytocin to Cisplatin-Induced Neurotoxicity: An Experimental Rat Model

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Peripheral neurotoxicity is a frequent dose-limiting side effect of the chemotherapeutic agent cisplatin. This study was conducted to investigate the preventive effect of oxytocin (OT) on cisplatin-induced neurotoxicity in rats. Forty-four adult female rats were included in the study. Thirty-six rats were administered intraperitoneally (i.p.) single dose cisplatin 10 mg/kg and divided into 3 groups. The first group (n = 12) received saline i.p., whereas the second group (n = 12) and the third group (n = 12) were injected with 80 μg/kg and 160 μg/kg OT, respectively, for 10 days. The remaining 8 rats served as the control group. Electromyography (EMG) studies were recorded and blood samples were collected for the measurement of plasma lipid peroxidation (malondialdehyde; MDA), tumor necrosis factor (TNF)-α, and glutathione (GSH) levels. EMG findings revealed that compound muscle action potential amplitude was significantly decreased and distal latency was prolonged in the nontreated cisplatin-injected rats compared with the control group (P < 0.005). Also, nontreated cisplatin-injected rats showed significantly higher TNF-α and MDA levels and lower GSH level than control group. The administration of OT significantly ameliorated the EMG alterations, suppressed oxidative stress and inflammatory parameters, and increased antioxidative capacity. We suggest that oxytocin may have beneficial effects against cisplatin-induced neurotoxicity.

1. Introduction

Cisplatin (cis-diamminedichloroplatinum) is the first antineoplastic agent which has been used in cancer treatment. It is used for the treatment of various solid tumors such as lung, ovary, testis, bladder, head and neck, and cervical and endometrial cancers [1]. Autotoxicity, neurotoxicity, and nephrotoxicity are the dose-limiting side effects of cisplatin [2]. Cisplatin-induced peripheral neuropathy is a frequent adverse effect leading to a dose reduction or the early cessation of chemotherapy, thereby potentially impacting patient survival [3]. Peripheral neuropathy is characterized with decreased neural transmission rate, loss of vibration and position senses, tingling paresthesia, dysesthesia, loss of tendon reflexes, tremor, ataxia, and muscle weakness [4–6]. The side effects of the cisplatin on both human and animal nervous systems are demonstrated with electrophysiological and histopathological experiments [5, 7–9]. Oxidative stress, DNA damage, and inflammatory cytokines play major role in the mechanism of cisplatin-induced cytotoxicity [10]. On the other hand, pathophysiological mechanisms of cisplatin-induced neurotoxicity include oxidative damage, inflammation, mitochondrial dysfunction, DNA damage, and apoptotic cell death in the nervous system [11, 12].

Since cisplatin-induced neurotoxicity is the major dose-limiting adverse effect of cisplatin, there are numerous studies dealing with this issue [9]. The efficacy of antioxidative treatments on preventing neurotoxicity associated with platinum-based chemotherapeutic regimens has been demonstrated in several studies [9, 13, 14]. Antioxidants such as resveratrol, curcumin, vitamin E, thiamine pyrophosphate, and melatonin have been used to reduce this type of toxicity [9, 13–17].

Oxytocin (OT) is a neurohypophyseal nonapeptide synthesized at the paraventricular and supraoptic nuclei of the
hypothalamus. Although OT is essential for the milk let-
down reflex, studies in OT-deficient mice show that OT’s role
in parturition is obviously more complex [18]. OT exerts its
effects via G-protein-coupled receptors, which are expressed
abundantly in the central and peripheral nervous systems.
Moreover, OT plays a role in the endocrine and paracrine
activities such as various sexual and maternal behaviors,
social recognition, aggression, neuromodulation, cognition,
and tolerance development [19]. In addition, the impact of
OT on wound healing as an immunomodulatory and anti-
inflammatory agent, which regulates the anti-inflammatory
and proinflammatory cytokines, has also been shown [19–22].

As oxidative stress and inflammation play the major
role in the pathogenesis of cisplatin-induced neurotoxicity
and the antioxidant/anti-inflammatory effects of OT are well
known, we hypothesized that OT may be beneficial in
preventing the cisplatin-induced neurotoxicity. Therefore, we
aimed to evaluate the therapeutic potential of OT in cisplatin-
induced neurotoxicity by electromyography (EMG) record-
ings and measuring TNF-α levels, which is an important
inflammation marker for lipid peroxidation and antioxidative
capacity.

2. Materials and Methods

2.1. Animals. In this study 44 female Sprague-Dawley albino
mature rats, weighing 200–220 g, were used. Animals were
fed *ad libitum* and housed in pairs in steel cages, hav-
ing a temperature-controlled environment (22 ± 2°C) with
12 h light/dark cycles. The experimental procedures were
approved by the Animal Research Committee in Ege Univer-
sity. All animal studies are strictly conformed to the animal
experiment guidelines of the Committee for Human Care.

2.2. Experimental Procedure. Of the 44 rats included, 36 were
injected with a single dose of 10 mg/kg cisplatin i.p. to induce
neurotoxicity development [16]. The drug-administered rats
were divided into 3 groups. The first group (n = 12) received
1 mL/kg 0.9% NaCl (saline) i.p. for 10 days, whereas the
second group (n = 12) and the third group (n = 12) were
injected with 80 μg/kg and 160 μg/kg OT, respectively, for
the same duration of time. The remaining 8 rats served as the
control group and did not receive any treatment. Five rats
from the saline group and 3 rats from the OT-injected groups
died during the study.

2.3. Electrophysiological Recordings. Electromyographic
(EMG) studies were performed 10 days after the injection of
cisplatin. EMG recordings were obtained 3 times from the
right sciatic nerve, stimulated supramaximally (intensity 10 V,
duration 0.05 ms, frequency 1 Hz, in the range of 0.5–
5000 Hz, 40 kHz/s with a sampling rate) by a bipolar
subcutaneous needle stimulation electrode (BIOPAC Sys-
tems, Inc, Santa Barbara, CA, USA) from the sciatic notch.
Compound muscle action potentials (CMAP) were recorded
from 2-3 interosseous muscles by unipolar platinum
electrodes. Data were evaluated by Biopac Student Lab Pro
version 3.6.7 software (BIOPAC Systems, Inc) where distal
latency and amplitude of CMAP were used as the parameters.
During the EMG recordings, rectal temperatures of the rats
were monitored by a rectal probe (HP Viridia 24-C; Hewlett-
Packard Company, Palo Alto, CA, USA) and the body
temperature of each rat was kept at approximately 36-37°C by
a heating pad. Following the EMG recordings, animals were
euthanized and blood samples were collected with cardiac
puncture for biochemical measurements. These samples were
centrifuged at 3000 rpm for 10 minutes at room temperature
and stored at ~20°C until they are assayed.

2.4. Measurement of Lipid Peroxidation. Lipid peroxidation
was determined in the plasma samples by measuring the mal-
ondialdehyde (MDA) levels as thiobarbituric acid reactive
substances (TBARS). Briefly, trichloroacetic acid and TBARS
reagent were added to the plasma samples, then mixed, and
incubated at 100°C for 60 min. After cooling on ice, the
samples were centrifuged at 3000 rpm for 20 minutes and the
absorbance of the supernatant was read at 535 nm. MDA
levels were expressed as nM and tetraethoxypropane was
used for calibration [23].

2.5. Measurement of Plasma Glutathione Levels. Glutathione
(GSH) content in the plasma samples was measured spec-
trophotometrically according to Ellman’s method [24]. In this
method, thiols interact with 5,5’-dithiobis-(2-nitrobenzoic
acid) (DTNB) and form a colored anion with maximum peak
at 412 nm. GSH levels were calculated from the standard
 calibration curve and expressed as μM.

2.6. Measurement of Plasma Tumor Necrosis Factor Alpha-
(TNF-) α Level. Plasma TNF-α level was measured with
commercially available enzyme-linked immunosorbent assay
(ELISA) kit (Biosciences). The plasma samples were diluted
1:2 and TNF-α was determined in duplicate according to
the manufacturer’s guide. The detection range for the TNF-α
assay was <2 pg/mL.

2.7. Statistical Analysis. Statistical analysis was performed
with the Statistical Package for Social Sciences (SPSS) version
15.0 for Windows. Parametric variables were compared with
Student’s *t*-test and analysis of variance, whereas nonpara-
metric variables were compared with Mann-Whitney *U*
test. In addition, Shapiro-Wilk test was used for parametric-non-
parametric differentiation. Results are presented as “mean ±
standard error of mean (SEM)” A *P* < 0.05 was accepted as
statistically significant.

3. Results

3.1. Electromyographic Results. Table 1 shows the alterations
in EMG recordings in all groups. CMAP amplitude was sig-
ificantly lower and the latency was significantly prolonged
in the nontreated cisplatin-injected rats, compared to the
control group (*P* < 0.005). When the treatment groups
were compared, latency was shortened in both OT groups
compared to the nontreated cisplatin-injected rats; however,
the difference did not reach statistically significant level.
Moreover, CMAP amplitude increased in both OT groups, compared to the nontreated cisplatin-injected rats but this increase was statistically significant only in the rats that received 160 μg/kg of OT.

3.2. Plasma Malondialdehyde, Glutathione, and Tumor Necrosis Factor-α Levels. The effects of OT on plasma MDA, GSH, and TNF-α levels in all groups are shown in Table 2.

Figure 1 shows the effects of OT on plasma MDA levels in the cisplatin-injected rats. The injection of the cisplatin resulted in a significant increase in plasma MDA levels compared to the control group (128.6 ± 9.09 versus 62.5 ± 6.08 nM; \( P < 0.001 \)). OT treatment significantly decreased mean MDA levels in a dose-dependent manner (104.4 ± 8.11 nM for 80 μg/kg OT and 88.2 ± 5.54 nM for 160 μg/kg OT; \( P < 0.05 \) and \( P < 0.01 \), resp.).

Figure 2 demonstrates the effects of OT on plasma GSH levels in cisplatin-injected rats. Cisplatin administration significantly decreased plasma GSH levels, compared to the control group (7.78 ± 1.09 versus 19.4 ± 3.6 μM; \( P < 0.001 \)). OT treatment dose-dependently increased GSH levels (11.2 ± 1.9 μM for 80 μg/kg OT and 14.8 ± 1.6 μM for 160 μg/kg OT; \( P < 0.01 \)).

Figure 3 shows the effects of OT on plasma TNF-α levels in cisplatin-injected rats. Cisplatin administration significantly increased plasma TNF-α levels, compared to the control group (73.8 ± 7.7 versus 23.2 ± 2.6 pg/mL; \( P < 0.001 \)). OT treatment significantly decreased TNF-α levels and this decrease was more evident with the increased dose of OT (43.5 ± 7.9 pg/mL for 80 μg/kg OT and 31.6 ± 5.8 pg/mL for 160 μg/kg OT; \( P < 0.05 \) and \( P < 0.01 \), resp.).

4. Discussion

In this present study, we clearly demonstrated the protective effect of OT in cisplatin-induced neurotoxicity. To our knowledge, the prevention of neurotoxic effect of cisplatin with OT treatment has been demonstrated in this study for the first time. The neuroprotective effect seems to be associated with antioxidant (by the suppression of lipid peroxidation and increasing the antioxidative capacity) and anti-inflammatory (by decreasing the plasma TNF-α levels) activity of OT.
There are several mechanisms proposed for cisplatin-induced neurotoxicity. The drug accumulates especially in the dorsal root ganglia and causes nucleolar damage. Moreover, it affects Schwann cells, which have an important role in the nerve development and regeneration [25]. Another explanation for the mechanism of neuropathy is the binding of the cisplatin to DNA and inhibition of DNA synthesis [26]. Oxidative stress is another important mechanism. Cisplatin increases the production of free oxygen radicals and decreases the antioxidants, thus resulting in the deterioration of the oxidant/antioxidant balance and accumulation of reactive oxygen radicals in tissues [27]. Elevated free oxygen radicals interact with DNA and result in the production of 8-hydroxyguanine (8-OH Gua), which is responsible for DNA damage [27]. Some studies also demonstrated that DNA damage and caspase activation played an essential role in cisplatin-induced toxicity [28, 29]. Furthermore, proinflammatory cytokines such as TNF-α, interleukin- (IL-) 1, and IL-6 are induced with the nuclear factor- (NF-) kappa B activation and result in enhanced cisplatin toxicity [30, 31]. Apoptoses induced by hypoxia, inflammation, and accumulation of reactive oxygen free radicals in tissues are also basic mechanisms which play a role in cisplatin neurotoxicity.

The imbalance between oxidative and antioxidative mechanisms may play an important role in triggering axonal injury. Axonal transport is important for axonal integrity. Excessive reactive oxygen species (ROS) production causes distal axonal degeneration and interruption of axonal transportation. ROS can directly inhibit the axonal transportation in the early phase [32]. In addition to that, adenosine triphosphate (ATP) depletion and increased intra-axonal calcium levels caused by mitochondrial damage exacerbate the axonal damage. The decrease in the ATP levels inhibits the normal functions of the motor proteins [33].

Previous clinical and experimental studies demonstrated that antioxidant agents may prevent cisplatin-induced neurotoxicity [15, 19]. OT is a secretory peptide hormone and a biochemical antioxidant. It is demonstrated that OT decreases the free oxygen radicals in the brain membranes, prevents low density lipoprotein oxidation, and inhibits lipid peroxidation [34]. When it is used at physiologic levels, OT may also decrease the acute inflammatory response, cytokine release, and oxidative stress. OT prevents lipid peroxidation on the cell membrane by scavenging the free oxygen radicals. Moreover, OT decreases lipid peroxidation, neutrophil infiltration, and serum TNF-α level in septic animal model [22]. Another human study demonstrated that OT decreases the levels of proinflammatory mediators such as TNF-α, IL-4 and 6, macrophage inflammatory proteins 1a and 1b, monocyte chemoattractant protein-1, and vascular endothelial growth factor in lipopolysaccharide-induced inflammatory response and endotoxemia [35].

Our results revealed that the protective effect of OT in cisplatin-induced neuropathy may be due to its suppression on TNF-α production, lipid peroxidation, and elevation of antioxidant capacity. In this study, we used pharmacologic doses of OT (80 and 160 µg/kg) based on previous studies demonstrating their protective effects [36, 37]. We found that 160 µg/kg oxytocin dose was more effective in the prevention of cisplatin-induced neurotoxicity.

In conclusion, this is the first study which demonstrates that OT has a protective effect in cisplatin-induced neurotoxicity via increasing the endogenous antioxidants and decreasing the lipid peroxidation and inflammation. Based on these findings, OT may be considered as a potential agent that can be used for the prevention of cisplatin-induced neurotoxicity. However, new experimental and clinical studies are required for the clinical application of this treatment modality for preventing the neurotoxicity in cancer patients.

Conflict of Interests
The authors declare that there is no conflict of interests regarding the publication of this paper.

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