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Selenium partially prevents cisplatin-induced neurotoxicity: A preliminary study

Haydar Ali Erken [a,*], Emine Rabia Koç [b], Haşmet Yazıcı [c], Arzu Yay [d], Gözde Özge Önder [d], Saim Furkan Sarıcı [e]

[a] Balikesir University, Faculty of Medicine, Department of Physiology, Balikesir, Turkey
[b] Balikesir University, Faculty of Medicine, Department of Neurology, Balikesir, Turkey
[c] Balikesir University, Faculty of Medicine, Department of Ear Nose Throat, Balikesir, Turkey
[d] Erciyes University, Faculty of Medicine, Department of Histology and Embryology, Kayseri, Turkey
[e] Hacettepe University, Faculty of Medicine, Department of Oncology, Ankara, Turkey

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ABSTRACT

Cisplatin is an anticancer drug and it has neurotoxic effects. On the other hand, the neuroprotective effect of selenium was observed in previous studies. However, the effect of selenium on cisplatin-induced neurotoxicity has not been studied yet. Therefore, we aimed to investigate whether selenium prevent cisplatin-induced neurotoxicity. Twenty-one male Wistar albino rats were divided into three groups: control (C), cisplatin (CS), cisplatin and selenium (CSE, $n = 7$ in each group). Cisplatin (12 mg/kg/day, i.p.) was administered for 3 days to CS and CSE groups. Also, CSE group received via oral gavage 3 mg/kg/day (twice-a-day as 1.5 mg/kg) selenium 5 days before of cisplatin injection and continued for 11 consecutive days. The same volumes of saline were intraperitoneally and orally administered to C group at same time. At the end of experimental protocol, electrophysiological and histopathological examinations were performed. The nerve conduction velocity, amplitude of compound action potential and number of axon of CS group were significantly lower than the C group. However, the same parameters of CSE group were significantly higher than the CS group. Although, cisplatin has a peripheral neurotoxic effect in rats, this effect was partially prevented by selenium treatment. Thus, it appears that co-administration of selenium and cisplatin may be a useful approach to decrease severity of peripheral neurotoxicity.

1. Introduction

Cisplatin, an alkylating agent, is the first agent of platinum-based anticancer drugs, which was approved for the treatment of testicular and ovarian cancer in 1978, firstly (Amptoulach and Tsavaris, 2011). Although cisplatin is very effective in cancer therapy, it is extremely toxic and it has severe side effects such as neurotoxicity, nephrotoxicity, ototoxicity and vomiting (Li et al., 2006; Paksoy et al., 2011; Screnci and McKeage, 1999; Sweeney et al., 2001; Ta et al., 2006). Due to the neurotoxicity potential of the cisplatin, peripheral neuropathy was frequently seen in patients and causes dose limiting problems in treatment process (Brouwers et al., 2009; Siegal and Haim, 1990). Clinically, peripheral neuropathy is characterized by decreased nerve conduction velocity (NCV), loss of vibration and position sense, tingling paraesthesia, dysesthesia, loss of tendon reflexes, tremor, ataxia, and weakness (Kelland, 2007; Orhan et al., 2004; Ozols and Young, 1985; Pace et al., 2010; Roelofs et al., 1984; Ward et al., 1971). The adverse effects of cisplatin on nervous system were demonstrated in animals and humans with electrophysiological and histopathological examination of the peripheral nerve in literature (Carozzi et al., 2009; Krarup-Hansen et al., 2007; Orhan et al., 2004; Turan et al., 2014). Similarly, neurotoxicity was observed in human treated with cisplatin in an autopsy study (Krarup-Hansen et al., 1999). Several pathophysiological mechanisms are proposed to explain the cisplatin-induced neurotoxicity such as oxidative damage, inflammation, mitochondrial dysfunction, DNA damage and apoptotic cell death in the nervous system (Englander, 2013; Gill and Windebank, 1998).

Selenium is a trace element that plays a major role in cellular redox state regulation and essential to the function of glutathione peroxidase, since it is a structural component of the active site of

* Corresponding author. Tel.: +90 2666121454; fax: +90 2666121459.
E-mail addresses: haerken@yahoo.com, erken@balikesir.edu.tr (H.A. Erken).

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selenoenzyme which has critical role in protecting cellular components from oxidative damage (Cao et al., 2012; Türker et al., 2011; Weeks et al., 2012). Also, selenium exhibits physiological activities including antioxidant effect, regulation of thyroid hormone metabolism, maintenance of the integrity of keratins, and stimulation of antibody synthesis (Hawkes et al., 2013; Miller et al., 2001). In addition, in many previous studies reported that selenium has a neuroprotective effect (Ahmad et al., 2011; Ben Amara et al., 2009; Godoi et al., 2013; Li et al., 2013; Uğuz and Nazıroğlu, 2012).

Many studies have examined the efficacy of antioxidant therapies administered together with platinum agents in human and animal model (Mendonça et al., 2013; Pace et al., 2003; Turan et al., 2014). Also, several agents, such as resveratrol, curcumin, vitamin E, thiamine pyrophosphate, and melathonin were used to prevent cisplatin toxicity in neural tissues (Mendonça et al., 2013; Pace et al., 2003; Rezvanfar et al., 2013; Tuncer et al., 2010; Turan et al., 2014; Valentovic et al., 2014). Although it was observed that selenium prevents cisplatin-induced toxicity in many tissue (Naziroglu et al., 2004; Ognjanović et al., 2012; Rezvanfar et al., 2013), as far as we know, there are no study showing the effect of selenium against cisplatin-induced neurotoxicity on peripheral nerves.

Therefore, in this study, we investigated that whether selenium has a neuroprotective effect on cisplatin-induced neurotoxicity.

2. Materials and methods

2.1. Animals and study design

All of the experiments were approved by the Local Ethical Committee of Animal Care (Approval number: 2013-13-94; approval date: July 3, 2013) and the experiments were performed according to the guidelines (NIH, UCSF) on animal use. Twenty-one adult male Wistar albino rats weighing 280–300 g were used. All of the rats were maintained in a 12-h light/dark cycle environment (lights on 7:00–19:00 h) at a temperature of 22 ± 1 °C and 50% humidity. Rats had access to food and water ad libitum.

The rats were randomly assigned to the following three groups ($n = 7$ in each group): control (C), cisplatin (CS), cisplatin and selenium (CSE). Cisplatin (Sigma–Aldrich Co, Germany) was administered to rats in CS and CSE groups at a dose of 12 mg/kg body weight/day, intraperitoneally for 3 consecutive days (Ajith et al., 2009; Erdem et al., 2012). Also, 3 mg/kg body weight/day selenium (sodium selenite, Sigma–Aldrich Co., Germany) was given by oral gavage to rats in CSE group twice-a-day as 1.5 mg/kg (Bilginoglu et al., 2009; Gupta et al., 2013) for 11 consecutive days starting at 5 days before cisplatin. On the other hand, C group received only saline intraperitoneally and orally at same volume and at same time. At the end of experimental protocol, right and left sciatic nerve was removed for electrophysiological and histopathological examination, respectively.

2.2. Electrophysiological recordings

The recording of compound action potentials (CAPs) was performed according to the previous studies (Moreira et al., 2001; Leal-Cardoso et al., 2004; Erken et al., 2013). Briefly, each rat was anesthetized with ketamine/xylazine (90 and 10 mg/kg respectively i.p.) and their hind limb were shaved and disinfected with batticon (Batticon, Adeka Co., Turkey). After the sciatic nerves were exposed, right sciatic nerves of all rats were removed and put into Ringer's solution. Later, nerve fibers were placed into the nerve chamber and the proximal end of sciatic nerve was electrically stimulated by a PowerLab stimulator (ADInstruments Co., Australia) for thirty times in 1-s intervals (10 V, 0.15 ms). Evoked CAPs were recorded by PowerLab 26T data acquisition system and Chart 7 program (ADInstruments Co., Australia). All experiments were carried out at room temperature (controlled within 24 ± 1 °C). The amplitudes of CAPs were measured from the baseline to the peak and the latencies were measured from the stimulus artifact to the beginning of the first deflection from baseline. NCV values were calculated according to the following formula: NCV (m/s) = distance between stimulating and recording point − 15 mm (m)/latency (s). The average value of NCV and amplitude of CAP taken from each rat was the defined NCV and amplitude of CAP value of that rat.

2.3. Histopathological evaluation

Di Scipio et al.'s method was used for Masson's trichrome staining (Di Scipio et al., 2008). Briefly, freshly removed nerve samples were fixed in 10% formaldehyde (Fluka) in phosphate buffered saline. These samples were embedded in paraffin wax after dehydration with graded ethanol series (50, 70, 80, 95, and 100%). The specimens were sectioned at 5 μm on a microtome (Leica Microsystems) and then put into a drying oven overnight. The slides were deparaffinized with xylene and rehydrated with decreasing ethanol series. Afterwards, slides were stained using a Masson's trichrome kit.

To morphological evaluation and count the number of axons in a cross-section of sciatic nerve, 5 images were captured using a photomicroscope (Olympus BX-51, Olympus Co., Tokyo, Japan) and an AxioVision software from random fields of each sample in the same high magnification (×100 magnification). The number of axons in the sciatic nerve were counted using NIH Image J software program (Bethesda, MD) in accuracy to quantitative histomorphometry according to a previously described method (Yang and Bashaw, 2006).

2.4. Statistical analysis

One way ANOVA and post hoc Tukey test were used for comparison of experimental groups. All results were expressed as mean ± SD and $p < 0.05$ was considered as statistically significant.

3. Results

3.1. Electrophysiological results

The NCV values were found as 34.65 ± 1.54, 26.52 ± 2.43, 29.89 ± 1.23 m/s, in the C, CS and CSE groups, respectively. Also, the amplitude values of CAPs were found as 4.87 ± 0.38, 1.61 ± 0.51, 2.68 ± 0.33 mV, in the C, CS and CSE groups, respectively. The NCV and amplitude values of CAP of CS and CSE groups were significantly lower than the control group. Also, the NCV and amplitude values of CAP of CSE groups were significantly higher than the CS group (Fig. 1A and B).

3.2. Histological findings

Nerve tissue is composed of a vast number of axons held together by connective tissue in the C group. Contrary to C group, some pathologies were observed such as axonal degeneration, losing of inter axonal connective tissue and edema among axons in the CS group. Similar to CS group, same findings were observed in the CSE group but these findings at a more moderate level compared to CS group (Fig. 2A–C).

Also, the number of axon of CS group was significantly lower than the C group. However, the number of axon of CSE group was significantly higher than the CS group (Fig. 1C).