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Original Investigation

The Effects of Agomelatine on The Biochemical and Pathological Features of Cisplatin-Induced Peripheral Neuropathy: The First Experimental Study in Rats

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ABSTRACT

AIM: To evaluate the effects of agomelatine on the biochemical and pathological features of cisplatin-induced peripheral neuropathy.

MATERIAL and METHODS: This study included a total of 30 male Wistar albino rats that weighed 285–300 grams and were divided into three groups: healthy controls (HC, n=10); cisplatin group (CIS, n=10) and agomelatine plus cisplatin group (AC, n=10). The CIS group received only cisplatin (EbeweLiba, Turkey) at a dose of 2.5 mg/kg, whereas the AC group received both agomelatine (25 mg/kg, Les Laboratoires Servier, France) and cisplatin (2.5 mg/kg). The animals were sacrificed by thiopental anaesthesia (50 mg/kg, IE Ulagay, Turkey) and sciatic nerves were dissected. The sciatic nerve tissue was analysed for the levels of malondialdehyde (MDA), myeloperoxidase (MPO), total glutathione (tGSH) and superoxide dismutase (SOD) and was examined histopathologically.

RESULTS: The mean levels of MDA, MPO, tGSH and SOD were 34.90 ± 13.83, 41.30 ± 18.03, 15.40 ± 6.06 and 48.60 ± 18.19, respectively. MDA and MPO were significantly lower in the AC group than in the CIS group ($p<0.001$ for both). However, the anti-oxidative parameters tGSH and SOD were significantly higher in the AC group than in the CIS group ($p<0.001$ for both). Pathological examinations revealed swollen myelinated nerve fibres and evident myelin sheath degeneration in the CIS group; in the AC group, the myelin sheath degeneration was less and the blood vessels were normal.

CONCLUSION: Agomelatine decreased the oxidative status in an experimental rat model of cisplatin-induced peripheral neuropathy Myelin sheath degeneration was less in the AC group than in the CIS group. To our knowledge, this was the first study that showed the positive effects of agomelatine on cisplatin-induced neuropathy in rats.

KEYWORDS: Agomelatine, Cisplatin, Neurotoxicity, Peripheral Neuropathies, Rat

INTRODUCTION

Anti-neoplastic chemotherapeutic regimens may cause a wide range of neurological complications through the direct toxicity of the drug on neurons, electrolyte disturbances or cerebrovascular disorders (19,22,42,46). Cisplatin, which is a platinum-based compound, is one of the most commonly known chemotherapeutic medications that may cause neurotoxicity. In fact, cisplatin at a cumulative dose of ≥300 mg/m^2 had been reported to cause symmetric and predominantly sensory peripheral neuropathy (3,4,25). In some patients, the peripheral neuropathy may continue or progress for a long period, even after discontinuation of cisplatin (45,51). Therefore, prevention of this complication is important.

Several studies revealed that sodium thiosulfate and amifostine were beneficial in reducing cisplatin-induced ototoxicity (11,12,24,27,32). Vitamin E; carnitine; anti-convulsants, such as carbamazepine or oxcarbazepine; glutathione; all-trans retinoic acid and nimodipine, were the agents previously studied for the prevention of neuropathy

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associated with platinum-based chemotherapy (4-6,8,9,14-16,18,34,36,37,40,43,47,50). Although the anti-depressant drugs amitriptyline and venlafaxine had been investigated for the prevention of neuropathy associated with platinum-based agents (23,31,54), there had been no adequate evidence for the prophylactic use of anti-depressant drugs in the prevention of chemotherapy-induced peripheral neuropathy. Recent studies concluded that amitriptyline or venlafaxine should not be offered to prevent this complication (2,28).

Agomelatine is an atypical anti-depressant that acts on melatonin receptors (i.e. MT1 and MT2) and had been indicated for the treatment of major depressive disorder (30). It has a relatively favourable side effect profile, but its therapeutic benefit is similar with that of the other anti-depressants. Unlike the other anti-depressants, agomelatine does not lead to weight gain, sexual dysfunction or withdrawal. To our knowledge, the use of agomelatine for the prevention of cisplatin-associated neuropathy has not been investigated. In this study, we aimed to determine the effects of agomelatine on the biochemical and pathological features of cisplatin-induced peripheral neuropathy.

MATERIAL and METHODS

A total of 30 male albino Wistar rats that weighed 285–300 grams were included in our study. All experimental animals were obtained from the local Medical Experimental Research and Application Centre and were kept and fed under normal room temperature (i.e. 22 °C). This study was approved by the local Animal Experimentation Ethics Committee (ATADEM 2018, Decision No: 196).

The experimental animals were divided into three groups: healthy controls (HC, n=10); cisplatin group (CIS, n=10); and agomelatine plus cisplatin group (AC, n=10). The CIS group received only cisplatin (EbeweLiba, Turkey) at a dose of 2.5 mg/kg, whereas the AC group received both agomelatine (25 mg/kg, Les Laboratoires Servier, France) and cisplatin (2.5 mg/kg). Cisplatin was administered to induce peripheral neuropathy and agomelatine was administered to investigate its ability to prevent the biochemical and pathological features of peripheral neuropathy. First, distilled water was given by oral route to the CIS and HC groups and agomelatine was administered by oral gavage to the AC group. One hour later, intraperitoneal cisplatin was administered to the AC and CIS groups. This protocol was continued each day for 14 days, with the same doses. Based on available literature, the potentially protective drugs were administered to the experimental animals one hour before cisplatin administration. Thereafter, the animals were sacrificed by thiopental anaesthesia (50 mg/kg, IE Ulagay, Turkey), and the bilateral sciatic nerves were dissected. The levels of malondialdehyde (MDA), myeloperoxidase (MPO), total glutathione (tGSH) and superoxide dismutase (SOD) were measured in the dissected nerve tissue and histopathological analysis of the dissected sciatic nerve was performed. The nerve, axonal structure, myelin sheath and Schwann cell nucleus were analysed using hematoxylin–eosin staining. The biochemical and pathological features of the tissue were compared among the three groups.

Biochemical Analyses

Malondialdehyde

MDA measurements were based on the method used by Ohkawa et al. and involved spectrophotometric measurement of the absorbance of the pink-coloured complex that was formed by thiobarbituric acid and MDA. The serum/ tissue homogenate sample (0.1 mL) was added to a solution that contained 0.2 mL of 80 g/L sodium dodecyl sulfate, 1.5 mL of 200 g/L acetic acid, 1.5 mL of 8 g/L 2-thiobarbiturate and 0.3 mL of distilled water. The mixture was incubated at 95 °C for one hour. Upon cooling, 5 mL of n-butanol: pyridine (15:1) was added. The mixture was vortexed for one minute and centrifuged for 30 minutes at 4000 rpm. The absorbance of the supernatant was measured at 532 nm. The standard curve was obtained using 1,1,3,3-tetramethoxypropane (35).

Myeloperoxidase

To measure MPO, a pH-6 potassium phosphate buffer containing 0.5% hexadecyltrimethyl ammonium bromide was prepared. Then, the solution was centrifuged at +4 °C and 10,000 rpm for 15 minutes. The supernatant portion was used for analysis. To determine the activity of the MPO enzyme, an MPO-based H_2O_2 oxidation reaction using the substrate of a 4-amino antipyrin/ phenol solution was performed (10).

Total glutathione

Measurements were performed according to the method defined by Sedlak J and Lindsay RH. 5,5′-dithiobis (2-nitrobenzoic acid) disulfite (DTNB) was chromogenic in the medium and was reduced easily by sulfhydryl groups; the yellow colour produced during the reduction was measured by spectrophotometry at 412 nm. For the measurement, a cocktail solution of 5.85 mL of 100-mM sodium phosphate buffer, 2.8 Ml of 1-mM DTNB, 3.75 mL of 1-mM NADPH and 80 µL of 625-U/L glutathione reductase was prepared. Before the measurement, 0.1 mL of meta-phosphoric acid was added to 0.1 mL of the serum/ tissue homogenate; this mixture was centrifuged for two minutes at 2,000 rpm for deproteinisation. The 0.15-mL cocktail solution was added to 50 µL of the supernatant. The standard curve was obtained using GSSG (44).

Superoxide dismutase

Measurements were performed following the method by Sun et al. (48). SOD is formed when xanthine is converted into uric acid by xanthine oxidase. Upon addition of nitro blue tetrazolium (NBT) to this reaction, SOD reacts with NBT and produces a purple-coloured formazan dye. For this study, the sample was weighed and homogenised in 2 mL of 20-mmol/L phosphate buffer that contained 10 mmol/L EDTA at a pH of 7.8 and was centrifuged at 6,000 rpm for 10 minutes. Then, the brilliant supernatant was used as an assay sample. The measurement mixture that contained 2,450 µL of the measurement mixture (0.3 mmol/L xanthine, 0.6 mmol/L EDTA, 150 µmoL/L NBT, 0.4 mol/L Na_2CO_3 and 1 g/L bovine serum albumin); 500 µL of the supernatant and 50 µL of xanthine oxidase (167 U/L) was vortexed. Then, the mixture was incubated for 10 minutes. At the end of the reaction, a

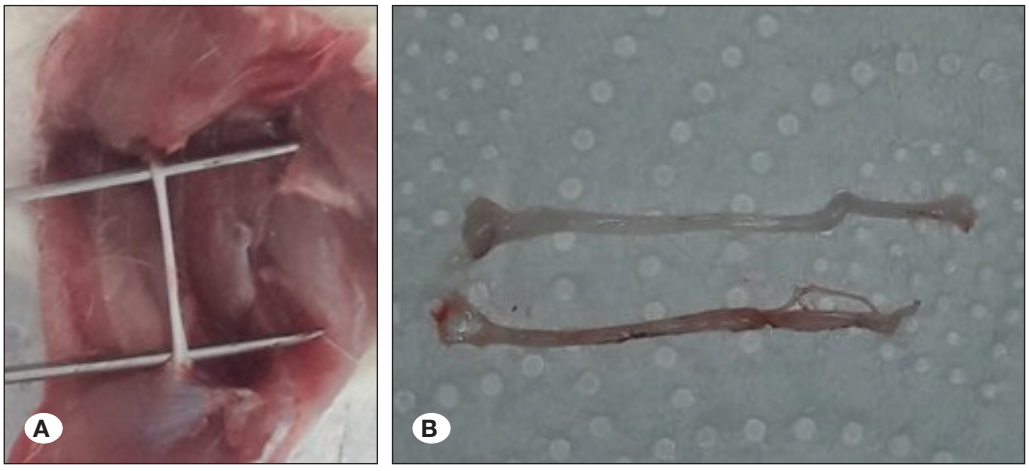

Figure 1: A) Dissection of the sciatic nerve. **B)** Dissected sciatic nerves.

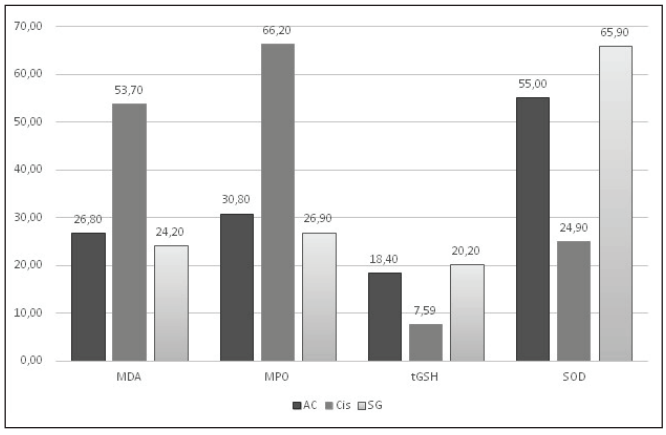

Figure 2: Comparison of the oxidative and anti-oxidative parameters among the groups.

purple-coloured formazan was formed, and its absorbance was measured at 560 nm. A relatively high amount of enzyme caused the least reaction between the $O2^-$ radical and NBT.

Histopathological Analysis

Figures 1A, B show the dissected sciatic nerve and pathological analysis. First, all tissue samples were identified in a 10% formaldehyde solution for light microscopy assessment. Following the identification process, the tissue samples were washed under tap water in cassettes for 24 hours. The samples were then treated with conventional grades of alcohol (70%, 80%, 90% and 100%) to remove water from the tissues. Thereafter, the tissues were passed through xylol and embedded in paraffin. The paraffin-embedded tissue was cut into 4–5-µm sections and stained with hematoxylin–eosin. Photomicrographs were taken, following the Olympus DP2-SAL firmware programme (Olympus® Inc., Tokyo, Japan) assessment. Histopathological assessment was carried out by a pathologist who was blinded about the study grouping.

Statistical Analysis

SPSS 25.0 (IBM Corporation, Armonk, New York, United States) was used for statistical analysis. The conformity of the data to a normal distribution was evaluated using the Shapiro–Wilk test. Homogeneity of variance was evaluated with the Levene test. One-way analysis of variance (Robuts Statistic: Brown-Forsythe) was used to compare the quantitative variables of MDA, MPO, tGSH and SOD among the groups. For multiple comparison analysis of MDA, MPO and SOD, which had homogeneous variance, the Fisher's Least Significant Difference test was used. Games–Howell multiple comparison test was used for tGSH, which did not have homogeneous variance. The quantitative variables were expressed in tables as mean (standard deviation, SD)/ minimum–maximum and median (minimum–maximum). Categorical variables were shown as frequency (%). The variables were evaluated with a 95% confidence level, and $p<0.05$ was accepted as significant.

■ RESULTS

As shown in Table I, the mean levels of MDA, MPO, tGSH and SOD were 34.90 ± 13.83, 41.30 ± 18.03, 15.40 ± 6.06 and 48.60 ± 18.19, respectively. The levels of all oxidative and anti-oxidative parameters were significantly different among the three groups ($p<0.001$ for all). The MDA and MPO levels were significantly lower in the AC group than in the CIS group ($p<0.001$ for both). On the other hand, the levels of the anti-oxidative parameters tGSH and SOD were significantly higher in the AC group than in the CIS group ($p<0.001$ for both). Compared with the HC group, the AC group had significantly higher MPO ($p=0.028$) and significantly lower SOD ($p<0.001$). Compared with the HC group, the CIS group had significantly higher levels of the oxidative enzymes MDA and MPO ($p<0.001$ for both) and significantly lower levels of the anti-oxidative parameters tGSH and SOD ($p<0.001$ for both) (Table II and Figure 2).

Histopathological Findings

In the HC group, the sciatic nerve structure was normal, the axons were surrounded by centrally located myelin sheaths and the Schwann cell nucleus was normal in shape. In the CIS group (Figures 3, 4), the myelinated nerve fibres were swollen, myelin sheath degeneration was evident and the myelin sheath surrounding the axons was not in a central position. Moreover,

Table I: The Levels of Oxidative and Antioxidative Parameters of the Animals

No	Groups	MDA	MPO	tGSH	SOD
1	HC	25	24	15	63
2	HC	28	20	17	64
3	HC	23	28	20	71
4	HC	26	30	21	70
5	HC	22	27	18	58
6	HC	21	30	25	61
7	HC	24	31	17	77
8	HC	29	26	26	66
9	HC	20	28	23	60
10	HC	24	25	20	69
11	CIS	59	70	7,3	19
12	CIS	55	65	6,4	17
13	CIS	43	72	6,8	20
14	CIS	56	68	7	25
15	CIS	53	60	6,5	21
16	CIS	49	59	8,7	27
17	CIS	50	74	8	31
18	CIS	60	67	7,9	30
19	CIS	58	61	8,1	27
20	CIS	54	66	9,2	32
21	AC	27	30	15	59
22	AC	26	29	16	47
23	AC	25	35	17	58
24	AC	28	33	20	61
25	AC	27	32	17	47
26	AC	23	31	20	55
27	AC	28	32	17	66
28	AC	32	29	22	52
29	AC	22	30	20	55
30	AC	30	27	20	50
Mean		34.90	41.30	15.40	48.60
Standard deviation		13.83	18.03	6.06	18.19
Median		28	31	17	55
Minimum		20	20	6.4	17
Maximum		60	74	26	77

AC: *Cisplatin + Agomelatin group,* ***MDA:*** *Malondialdehyde,* ***MPO:*** *Myeloperoxidase,* ***tGSH:*** *Total glutathione,* ***SOD:*** *Superoxide dismutase,* ***CIS:*** *Cisplatin group,* ***HC:*** *Control group.*

the Schwann cells were hypertrophied and hyperplastic, there were no local myelin sheath degeneration and loss and the blood vessels were normal. In the AC group (Figure 5), the myelinated nerve fibres were partially swollen but generally normal and the axons were located centrally. Majority of the Schwann cells were normal in shape, there was less degeneration of myelin sheaths and the blood vessels were normal.

■ DISCUSSION

In our study, all of the oxidative and anti-oxidative parameters significantly differed among the three groups. We found out that MDA and MPO were significantly lower in the AC group than in the CIS group. However, we should note that the levels

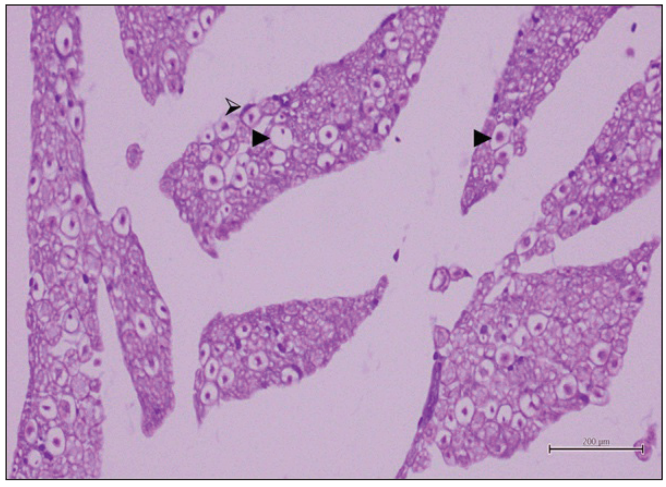

Figure 3: Hematoxylin–eosin staining of sciatic nerve tissue in the cisplatin group (CIS). There are swollen and degenerated myelinated axons (►) and hypertrophic and hyperplasic Schwann cell nucleus (➢) (×400).

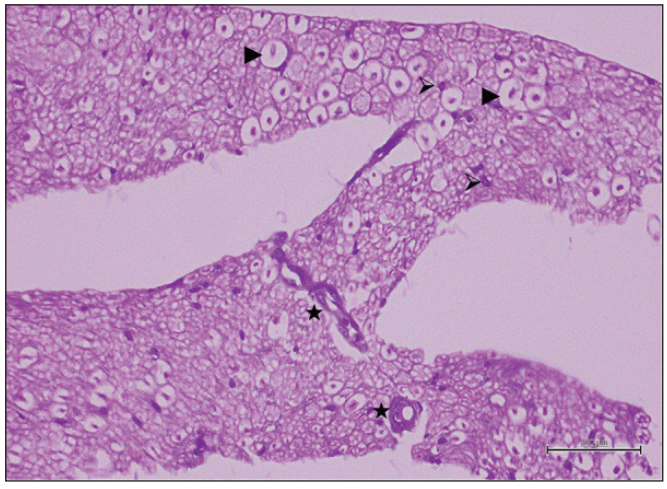

Figure 4: Hematoxylin–eosin staining of sciatic nerve tissue in the cisplatin group (CIS). There are degenerated myelinated axons (►), hypertrophic and hyperplasic Schwann cell nucleus (➢) and blood vessels (★) (×400).

Table II: Comparison of Oxidative and Antioxidative Parameters Between Groups

Groups		MDA	MPO	tGSH	SOD
		Mean ± SD. / Min.- Max.	**Mean ± SD. / Min.- Max.**	**Mean ± SD. / Min.- Max.**	**Mean ± SD. / Min.- Max.**
AC	=I	26.80 ± 3.01 / 22-32	30.80 ± 2.30 / 27- 35	18.40 ± 2.27 / 15- 22	55.00 ± 6.18 / 47- 66
CIS	=II	53.70 ± 5.21 / 43-60	66.20 ± 5.07 / 59- 74	7.59 ± 0.94 / 6.4- 9.2	24.90 ± 5.36 / 17- 32
HC	=III	24.20 ± 2.90 / 20-29	26.90 ± 3.31 / 20- 31	20.20 ± 3.61 / 15- 26	65.90 ± 5.86 / 58- 77
p		**<0.001**	**<0.001**	**<0.001**	**<0.001**
Pairwise comparison	I vs II	**<0.001 lsd**	**<0.001 lsd**	**<0.001 gh**	**<0.001 lsd**
	I vs III	0.143 [lsd]	**0.028 lsd**	0.399 [gh]	**<0.001 lsd**
	II vs III	**<0.001 lsd**	**<0.001 lsd**	**<0.001 gh**	**<0.001 lsd**

One Way ANOVA (Robuts Statistic: Brown-Forsythe), ***Post Hoc Test:*** *lsd Fisher's Least Significant Difference (LSD) - ghGames Howell,* ***SD:*** *Standard deviation,* ***Min:*** *Minimum,* ***Max:*** *Maximum,* ***AC:*** *Cisplatin + Agomelatin group,* ***MDA:*** *Malondialdehyde,* ***MPO:*** *Myeloperoxidase,* ***tGSH:*** *total glutathione,* ***SOD:*** *Superoxide dismutase,* ***CIS:*** *Cisplatin group,* ***HC:*** *Control group.*

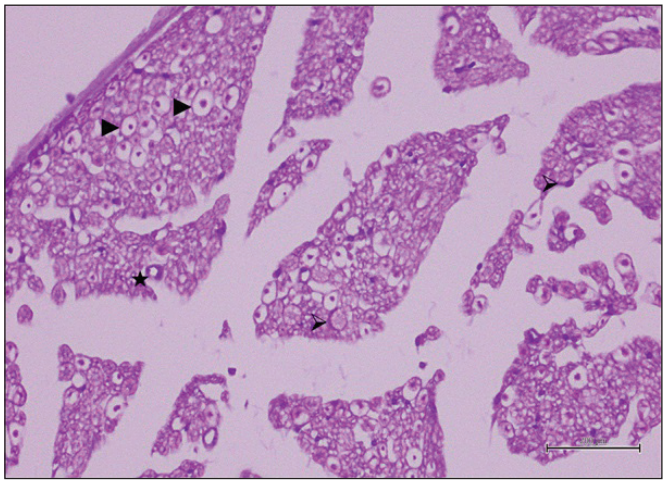

Figure 5: Hematoxylin–eosin staining of sciatic nerve tissue in the cisplatin + agomelatin group (AC). There are myelinated axons (►), normal Schwann cell nucleus (➢) and normal blood vessels (★) (×400).

of anti-oxidative parameters tGSH and SOD were significantly higher in the AC group than CIS group. MPO was significantly higher, SOD was significantly lower in the AC group than in the HC group. Oxidative enzymes were higher and anti-oxidative parameters were lower in CIS group than in the HC group. Our results implied that agomelatine decreased the oxidative status in cisplatin-treated rats. Schwann cell hypertrophy and hyperplasia, swelling of myelinated nerve fibres and local myelin sheath degeneration and loss were detected in CIS group. Myelinated nerve fibres were partially swollen but generally normal, axons were located centrally, the myelin sheath degeneration was less in AC group.

De Mello et al (20) investigated the effects of agomelatine on the oxidative stress parameters in the brain of male Wistar rats and showed that the brain tissue levels of lipid peroxidation and protein carbonylation did not change with agomelatine administration. They also found out that the SOD and catalase activities increased in the posterior cortex and striatum after agomelatine administration. These effects may be attributed to the anti-depressant effect of agomelatine. However, we should note that these researchers did not examine any chemical, drug-induced or metabolic neuropathy. In our study, we showed that the anti-oxidative parameters increased and the degree of myelin sheath degeneration was less after agomelatine administration with cisplatin. These positive effects on neuropathy were probably based on the anti-oxidative effects of agomelatine. Although this anti-oxidative effect of agomelatine had been investigated in many studies, improvement of cisplatin-neuropathy with agomelatine had been less known and investigated. Demirdas et al (21) investigated the oxidative status in male albino rats, in which depression was experimentally induced by chronic mild stress, such as overnight illumination or exposure to an empty water bottle immediately after acute water deprivation. They showed that the levels of tGSH and glutathione increased in the brain, liver and kidney tissues after agomelatine treatment. However, their findings did not show any differences in the vitamin A, vitamin E and carotene levels among the rat groups. Although agomelatine administration increased the inflammatory cytokines, its effect of increasing the tGSH may have led to the protective effects on the brain, kidney and liver. Unlike our present study, that previous study did not measure the biochemical parameters of drug-induced neuropathy and did not histopathologically examine the liver, kidney, brain or other neurons. However, we did not investigate the other tissues, such as the liver or kidney. In human subjects, several intriguing mechanisms that lead to depression may be encountered. Therefore, the applicability of our results to routine clinical practice may need to be proven further.

The anti-oxidative effect of agomelatine had been evaluated and demonstrated in other types of disorders that arise from oxidative stress (1,21,29,52). For example, in one study,

agomelatine treatment of streptozocin-induced diabetic rats was found to be effective in addressing the oxidative status of testicular tissue by decreasing spermatogenic degeneration and interstitial oedema and decreasing the levels of TNFα and nitric oxide synthase (53). In addition, agomelatine was found to decrease neuropathic hyperalgesia evoked by intrathecal BDNF or sciatic nerve ligation in rats (33). One study reported that the protective effects of agomelatine against neuropathic pain in streptozocin-induced diabetic rats was mediated by increased synaptic catecholamine levels (7). In another study on rats with neuropathic pain evoked by oxaliplatin, streptozocin or sciatic nerve ligation, agomelatine was found to have a clear anti-hypersensitivity effect, which was measured by an analgesiometer (17). Moreover, that study showed that the anti-hypersensitivity effects of agomelatine were mediated by melatonergic, 5-HT2c and alpha-2 adrenergic receptors and that gabapentin had an additive effect with agomelatine. That study was especially important, because oxaliplatin and cisplatin are both in the same class of platinum-based chemotherapy agents. Oxaliplatin causes chelation of calcium by oxalate and causes the disinhibited peripheral nerves to become hyper-excitable (26,39). In the later stages, chronic nerve dysfunction and sensory loss become the predominant features (38). Compared with cisplatin, oxaliplatin forms less platinum–DNA adducts and is less neurotoxic, but it seemed to have a similar mechanism for causing neuropathy (49). Based on this, agomelatine may have anti-hypersensitivity effects in cisplatin-treated rats; however, to our knowledge, this effect had not been investigated. In our study, the positive effects of agomelatine in cisplatin-treated rats were shown in both biochemical and histopathological analyses. However, future studies are needed to clearly delineate the anti-oxidative and protective effects of agomelatine against cisplatin-induced neuropathy.

Can et al. investigated the effects of agomelatine in streptozocin-induced diabetic rats and found out that agomelatine enhanced the learning and memory performance and reversed neuronal loss in the hippocampal region (13). However, agomelatine was shown to have no effect on motor activity. Although that study did not analyse the histopathological features of the peripheral neurons and did not measure the anti-oxidative enzymes in the tissues, their findings may be likely attributed to the anti-oxidative effects of agomelatine. In another study, agomelatine increased the anti-oxidative enzymes in the rat ovarian tissue after ischaemia–reperfusion injury (52). Based on these previous studies, agomelatine had protective effects on both the central and peripheral nervous system, as well as on other tissues. To our knowledge, there had been no study that simultaneously investigated both central and peripheral nervous systems in cisplatin-treated rats or in any other neuropathy model.

Limitations and Strengths

One of the limitations in this study was that we examined only the dissected sciatic nerves; the brain and other tissues, such as the liver or kidney, were not dissected and analysed. Both sciatic nerves and brain tissue would be evaluated in further studies. In this study, the serum levels of the oxidative and anti-oxidative enzymes were not measured and correlated with the corresponding tissue levels. Besides peripheral neuropathy, encephalopathy, nephrotoxicity and ototoxicity are the other possible effects of cisplatin. Agomelatine had been shown to decrease oxidative stress in the kidney, liver, brain, testes and ovaries. Therefore, biochemical and histopathological examinations of all these tissues would be needed to detect all possible positive effects of agomelatine in cisplatin-treated rats. Nevertheless, to our best knowledge, this was the first study to reveal the positive effects of agomelatine in cisplatin-treated neuropathic rats by both biochemical and histopathological analyses.

CONCLUSION

Agomelatine decreased the oxidative status in an experimental rat model of cisplatin-induced peripheral neuropathy. Moreover, agomelatine administration before cisplatin treatment in rats led to relatively less myelin sheath degeneration. Future studies that examine multiple tissues will delineate the scope of the preventive effects of agomelatine against cisplatin-induced neuropathy.

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