Effects of Systemic Administration of Cisplatin and Hydrogen Sulfide on Cerebrum and Cerebellum Tissue in Rats

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AIM

We have previously shown that cisplatin (CIS) causes nephrotoxicity [1], hepatotoxicity [2] and autotoxicity [3] by oxidative damage and inflammatory pathway at doses of 5 mg/kg and 16 mg/kg in rats, respectively. In this study, we aimed to investigate the effects of systemic administration of CIS (7.5 mg/kg) and a combination of CIS with hydrogen sulfide (H2S, 10 µmol/kg), an endogenous gasotransmitter that exerts antioxidant and anti-inflammatory properties [4], on cerebrum and cerebellum in rats.

METHODS

Thirty-two rats were randomly divided into four groups as follows; Control, CIS (7.5 mg/kg intraperitoneal (ip) single-dose CIS), H2S+CIS (10 µmol/kg ip NaHS for 7 days and 7.5 mg/kg single dose ip CIS on 4th day) and CIS+H2S (4 days after 7.5 mg/kg single dose ip CIS administration 10 µmol/kg ip NaHS for 7 days). Histopathological and biochemical analyses of cerebrum and cerebellum were carried out.

RESULTS

In the sections stained with H-E staining method, cerebral tissue belonging to control group showed a normal appearance. In the cerebral cortex of control group was mostly observed regular and intact neurons and the number of intact neurons was calculated as 52.17±8.47 (Fig. 1A). There was a slight decrease in the number of intact neurons in the CIS group (48.37±8.62) however, this reduction was not statistically significant when compared to the control group (Fig. 1B). In the H2S+CIS group, number of intact neurons (47.83±9.16) was similar to CIS group (Figure 1C). On the other hand, there was a slight increase in the number of intact neurons in CIS+H2S group (52.57±8.93) but this increase was not statistically significant compared to CIS group (Fig. 1D).

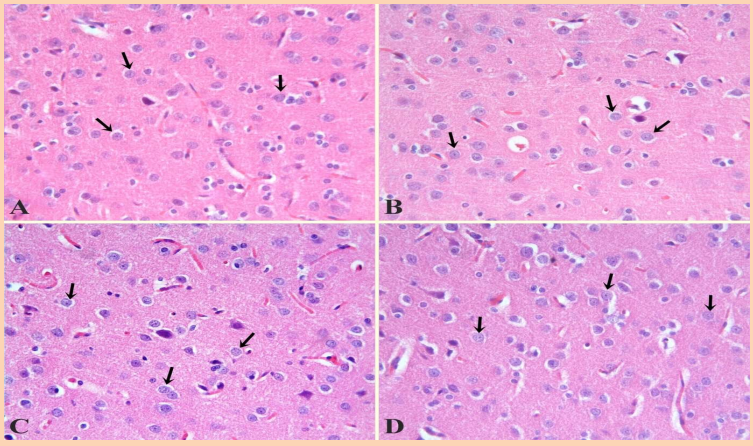

Figure 1. Arrows indicate to the intact neuron in the cerebral cortex of control (A), CIS (B), H2S+CIS(C) and CIS+H2S (D) groups. H-E; x40.

Table 1. The number of intact neurons of the groups.

Groups	Number of intact neuron
Control	52.17±8.47
CIS	48.37±8.62
H2S+CIS	47.83±9.16
CIS+H2S	52.57±8.93

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Table 2. MDA and GSH levels, and SOD, CAT and GSH-Px activities in the cerebrum tissue.

Parameters	Control group	CIS group	H2S+CIS group	CIS+H2S group	p*
MDA (nmol/g)	116.96 (88.4-129.2)	123.76 (89.08-166.6)	153a,b (116.96-178.16)	144.16a (125.8-184.28)	0.0051
GSH (nmol/g)	533.17 (500.61-557.59)	508.75 (488.4-529.1)	508.75 (492.47-569.8)	527.07 (504.68-651.2)	0.1767
SOD (U/g)	139.02 (42.96-685.28)	307.77 (56.69-351.71)	68.1 (12.61-2240.4)	183.88 (83.52-345.65)	0.4485
CAT (K/g)	7.19 (3.39-26.05)	15.77 (3.59-39.42)	13.71 (3.73-48.95)	NA	0.5261
GSH-Px (U/g)	288.97 (56.5-784.43)	1140.87a (332.15-1565.53)	1026.22 (69.29-1196.81)	NA	0.0379

MDA, malondialdehyde; GSH, reduced glutathione; SOD, superoxide dismutase; CAT, catalase; GSH-Px, glutathione peroxidase. CIS, cisplatin; H2S, hydrogen sulphur. NA, Not Applicable.

a: significantly different from Control group (p<0.05; Conover test); b: significantly different from CIS group (p<0.05; Conover test); The data are expressed as median (min-max); *: Kruskal Wallis test

Table 3. MDA, GSH and SOD levels in the cerebellum tissue.

Parameters	Control group	CIS group	H2S+CIS group	CIS+H2S group	p*
MDA (nmol/g)	115.26 (91.12-177.48)	140.08 (114.24-173.4)	136.68 (97.92-193.12)	140.76 (97.92-163.2)	0.2718
GSH (nmol/g)	500.61 (447.7-765.16)	520.96 (500.61-537.24)	549.45 (415.14-622.71)	512.82 (390.72-716.32)	0.2454
SOD (U/g)	590.77 (91.24-1985.81)	361.51 (62.93-565.49)	97.14 a,b (56.81-256.34)	148.78a (97.26-234.87)	0.0058

MDA, malondialdehyde; GSH, reduced glutathione; SOD, superoxide dismutase. CIS, cisplatin; H_2S, hydrogen sulphur.

a: significantly different from Control group (p<0.05; Conover test); b: significantly different from CIS group (p<0.05; Conover test); The data are expressed as median (min-max); *: Kruskal Wallis test

DISCUSSION

In the current study it was observed that single dose of CIS leads to mild histopathological alterations in the brain. There was a slight decrease in the number of intact neurons in the CIS group when compared to the control group, and a slight increase in CIS+H2S group when compared to the CIS group. In a study, CIS has been reported to cause the cell infiltration in cerebral cortex, shrinkage of the cytoplasm and extensively dark pyknotic nuclei in neurons of the cerebral cortex. Also, CIS has been noted to significantly increase percentage of caspase-3-positive cells in cerebral cortex. CIS has been observed to lead to deeply stained, shrunken, and variously shaped purkinje cells with pyknotic nuclei in cerebellar cortex. Also, the sciatic nerve degenerations (axonal degeneration and demyelination) due to CIS have been shown [5]. In another study, CIS (12 mg/kg/day, i.p. for 3 days) has been noted to cause axonal degeneration, losing of inter axonal connective tissue and axonal edema even decrease in number of axons in sciatic nerve [6].

In this study, it was observed that while CIS did not increase lipid peroxidation (MDA) significantly, H2S (10 µmol/kg ip NaHS for 7 days) significantly elevated lipid peroxidation when given both as pre-treatment or post-treatment in the cerebrum. Also, while CIS decreased antioxidant defense (SOD) slightly but not significantly, H2S significantly reduced antioxidant defense when given both as pre-treatment or post-treatment in cerebellum. While most of the relevant studies in the literature reported that H2S reduces oxidative stress [7-9], there are a few studies that obtained parallel results with our study. In a study, H2S has been reported to increase lipid peroxidation in the liver, gill, kidney, and brain of fishes [10].

CONCLUSION

Systemic administration of CIS at a dose of 7.5 mg/kg did not cause significant cerebrum damage in the rats. Morever, H2S administration induced a further increase in lipid peroxidation in the cerebrum and exacerbated a deficiency of antioxidant defense caused by CIS in the cerebellum. Further investigations with detailed study design are needed to test the our results.

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