OMEPRAZOLE INHIBITS INFLAMMATORY RESPONSE BY BLOCKING THE TLR4/NF-KB SIGNALLING PATHWAY AND PLAYS A PROTECTIVE ROLE AGAINST CISPLATIN-INDUCED KIDNEY INJURY

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ABSTRACT

Objective: *To investigate the protective effect of omeprazole (OME) on kidney injury induced by cisplatin (CDDP) by inhibiting inflammatory response via blocking the toll-like receptor 4 (TLR4)/nuclear factor κB (NF-κB) signalling pathway.*

Methods: *Twenty-four SPF healthy male SD rats were randomly divided into four groups: a blank control group (control group), cisplatin administration group (CDDP group), cisplatin + omeprazole low-dose group (OME (A)) and cisplatin + omeprazole high-dose group (OME (B)). The control group was injected with an equal volume of normal saline for 5 consecutive days. The CDDP group was injected with an equal volume of normal saline for the first 4 days and then with CDDP (15mg/KGD) on the fifth day. The OME (A) group was injected with an equal volume of OME (1.8mg/KGD) on the first 5 days and then with CDDP (15mg/KGD) 2 hours after the injection on the fifth day. The rats in the OME (B) group were injected with an equal volume of OME (3.6mg/KGD) on the first 5 days and then with CDDP (15mg/KGD) 2 hours after the end of the 5th day. After the end of the OME intervention, the rats were sacrificed. The level of CRE was detected via sarcosine oxidase. BUN level was detected using the urease method. The expression levels of TNF-α, IL-1β and IL-6 were detected by ELISA. Western blot was used to detect the expression of TRaf-6, MyD88, TLR4 and NF-B protein in the cytoplasm of rat kidney tissue. The pathological changes and renal injury of rats were observed, and the western blot results were analysed.*

Results: *HE staining showed that when compared to the control group, the renal tissue and tubule epithelium in the CDDP group were severely damaged, the tubules were dilated and swollen, and inflammatory infiltration was obvious. The renal inflammatory response in the OME (A) group was relatively relieved. Moreover, the renal inflammatory response in the OME (B) group was significantly reduced. Compared to the control group, the expression levels of inflammatory factors in the kidney tissues of the CDDP group, OME (A) group and OME (B) group were significantly increased (P<0.05), while those of the OME (A) and OME (B) groups were significantly better than those the CDDP group (P<0.05). Compared to the control group, renal function in the CDDP group, OME (A) group and OME (B) group was significantly decreased (P<0.05), while that of the OME (A) and OME (B) groups was significantly better than that of the CDDP group (P<0.05). There was no significant difference in kidney weight among all groups (P>0.05). Compared to the control group, the kidney index values of the CDDP group, OME (A) group and OME (B) group were significantly higher (P<0.05), while those of the OME (A) and OME (B) groups were significantly better than those of the CDDP group (P<0.05). Compared to the control group, the levels of GSH and SOD in the CDDP group, OME (A) group and OME (B) group were significantly decreased (P<0.05), while the levels of MDA in the CDDP group and OME (A) group were significantly lower than those in OME (B) group (P<0.05). The CDDP group and OME (A) group were significantly higher than OME (B) group (P<0.05). Compared to the control group, the expression levels of TRAF-6, MyD88, TLR4 and nuclear NF-B protein in the kidney tissues of the CDDP group, OME (A) group and OME (B) group were significantly higher than those in the CDDP group (P<0.05).*

Conclusion: *OME can reduce the inflammatory response induced by CDDP in the kidney of rats, reduce the expression level of inflammatory factors, prevent the activation of the TLR4/NF-B signalling pathway and effectively alleviate the damage caused by CDDP to kidney tissue.*

Keywords: *Omeprazole, TLR4/NF-κB signalling pathway, inflammatory response, cisplatin, kidney injury.*

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Introduction

Cisplatin, also known as cis-dichlorodiamine platinum (CDDP), is a broad-spectrum anti-tumour chemotherapy drug that is widely used in the treatment of various solid tumours and osteosarcomas due to its good efficacy and remarkable anti-tumour effect[(1)]. It can be used in the treatment of head and neck cancer, non-small cell lung cancer, ovarian cancer and cervical cancer. The clinical efficacy of CDDP is proportional to its dose[(2)]. Within its effective dose range, CDDP can combine with DNA to form cross bonds, prevent DNA replication and affect the synthesis of RNA and protein, thereby promoting the apoptosis of tumour cells. However, CDDP has the characteristics of high renal aggregation,

high metabolism and high excretion, resulting in particularly obvious side effects. Xu Guanhua et al.[3] found that the common side effects of cisplatin include neurotoxicity, ototoxicity, nephrotoxicity, bone marrow toxicity, haemolytic anaemia and electrolyte disorder, among which renal damage caused by nephrotoxicity was the most common.

Since the clinical therapeutic effect of CDDP is dose-dependent, its use is restricted due to the possibility of acute kidney injury or acute renal failure when used in large doses. Therefore, determining how to reduce renal toxicity and protect renal function without affecting the efficacy of CDDP has become an urgent problem to be solved in clinical practice.

Proton pump inhibitors (PPIs) are commonly prescribed drugs for the treatment of acid-related diseases, such as peptic ulcers[4]. Omeprazole (OME) is a clinically common PPI that can effectively inhibit gastric acid secretion. It is mainly used for the treatment of reflux or erosive esophagitis, gastric ulcer, duodenal ulcer, zoe-Erii syndrome and other diseases. OME is mainly metabolised by the liver and has little effect on the kidneys. Xu Dan et al.[5] found that OME can reduce the generation of reactive oxygen species and protect epithelial cells and mucosa from oxidative stress damage. Moreover, Kok-ann et al.[6] found that PPIs have a variety of physiological mechanisms of anti-inflammatory and antioxidant action that can protect multiple organs such as the heart, lung, stomach, kidney and small intestine.

However, there is no clear statistical report on the protective effect of OME on cisplatin-induced renal injury. In this study, the protective effect of OME on patients with cisplatin-induced renal injury was investigated by establishing a rat model of cisplatin-induced renal injury and measuring various relevant indexes.

Methods

Experimental animals and experimental drugs

Experimental animals

The animal experiments used in this study met the requirements of animal ethics review. Twenty-four SPF healthy male SD rats (purchased from Nanjing Junke Biological Co., LTD.) were selected. The rats were 6-8 weeks old and weighed 200-220g. Twenty-four SD rats were used for feeding (room temperature was adjusted to 25°C and humidity was 30–70% under aseptic conditions), and all rats ate and drank normally. Light and dark cycles were maintained for 12h each.

Experimental drugs

Cisplatin injection (Jiangsu Hausen Pharmaceutical Co., LTD., National Drug Approval H20010743, drug specification: 20ml: 20mg/piece); Omeprazole sodium injection (Astrazeneca Pharmaceutical Co., LTD., National Drug Approval H2003094, Drug specification: 0mg dose).

Experimental reagents and instruments

Experimental reagents

Enzyme-linked immunosorbent assay, ELISA KitTLR4 (Abcam); Myeloid differentiation factor 88 (MyD88); TRAF-6 (Abcam); Nuclear factor kappa-B P65 (Nuclear factor kappa-B P65) NF-κB P65 (Abcam, UK); Histone-H3 (Abcam, UK); β-actinβ-actin antibody (Sigma-Aldrich, USA); Creatinine (CRE) test kit (Shanghai Enzyme-Linked Biotechnology Co., LTD.); Urea nitrogen, BUN test kit (Shanghai Enzyme-Linked Biotechnology Co., LTD.); Hematoxylin dye (Boster Company); Eosin (Boster Company); Dimethyl sulfoxide (DMSO; Sigma Company); Phosphate-buffered saline (PBS) (Sigma Company); BCA protein quantitative kit (Sigma Company); DAB colour kit (Boster Company).

Experimental instruments

5427R tabletop high-speed refrigerated centrifuge (Germany Eppendorf Company); Finesse ME+ automatic paraffin slicer (Sigma Company); KD-BM ii biological tissue implantation machine (Chengdu Yke Medical Instrument Co., LTD.); Hx320AElectronic Analytical Balance (Precisa); EnVision Multifunctional Plate Reader (Perkin Elmer Enterprise Management (Shanghai) Co., LTD.); LeicaDMi8 inverted microscope (Leica Microsystem (Shanghai) Trading Co., LTD.); FSH-2A high-speed tissue homogeniser (Jiangsu Zhengji Instrument Co., LTD.); HGZN-II-138 Electric thermostatic drying oven (Shanghai Xino Instrument Group Co., LTD.); HF-10 digital display electric thermostatic oven (Shanghai Juna Technology Co., LTD.); YJY-902HDecolorization shaker (Shanghai Xinnuo Instrument Group Co., LTD.); 164-5070 PowerPac™ Universal Electrophoresis Apparatus (BIO-RAD USA).

Drug configuration

Preparation of OME solution: Since omeprazole has poor stability, it needs to be used immediately. An appropriate amount of omeprazole powder was accurately weighed, fully dissolved with normal saline, and intraperitoneal injections were given.

Grouping and treatment of experimental animals

Twenty-four male SD rats were randomly divided into four groups: a blank control group (control group), cisplatin administration group (CDDP group), cisplatin + omeprazole low-dose group (OME (A) group) and cisplatin + omeprazole high-dose group (OME (B) group).

The control group was injected with an equal volume of normal saline for 5 consecutive days. The CDDP group was injected with an equal volume of normal saline on the first 4 days and then with CDDP (15mg/KGD) on the fifth day. The OME (A) group was injected with an equal volume of OME (1.8mg/KGD) on the first 5 days and then with CDDP (15mg/KGD) 2 hours after the injection on the fifth day. OME (B) group was injected with an equal volume of OME (3.6mg/KGD) on the first 5 days and then with CDDP (15mg/KGD) again 2 hours after the injection on the fifth day.

All rats were weighed and sacrificed on the second day after administration. After bloodletting, the plasma was left standing at room temperature for 30min and centrifuged at 2000r/min for 10min before the supernatant was taken and stored at -20°C for testing. The kidneys of rats were weighed, and part of the kidney tissue was rinsed with normal saline and fixed in 4% paraformaldehyde.

After 48-72 hours, the kidney tissue was embedded in paraffin and the kidney tissue was sectionalised. The other part was frozen with liquid nitrogen after weighing and then stored in a -80°C refrigerator.

Tissue sample processing

The rat kidney tissue was removed and immediately fixed in 10% formaldehyde.

After 24-72 hours, the kidney tissue was removed for tissue repair, then rinsed overnight under running water and a gradient elution with ethanol.

Then the repaired tissue was placed into soft paraffin for 2 hours to make paraffin-embedded tissue. The renal structure and pathological changes were observed using a light microscope.

HE dyeing

Baking

Paraffin sections of tissue samples were placed into an oven overnight.

Dewaxing

The sections were then placed into xylene for dewaxing for 20min. Thereafter, they were placed into an ethanol solution with different concentration gradients for elution for corresponding durations and then placed into distilled water for 5min.

Dyeing

Hematoxylin and eosin were added to stain the tissues. The excess floating colour was then washed away.

Dehydration sealing

After dehydration by anhydrous ethanol and xylene drop resin, the cover glass was sealed.

Observation

Pathological changes in renal tissue sections were observed and analysed using a light microscope.

Serological indexes and renal index

Serological indicators

CRE level was detected via the sarcosine oxidase method. BUN level was detected via the urease method. TNF-α, IL-1β and IL-6 expression levels were detected by the ELISA method. GSH level was detected using the dithio-nitrobenzene method. SOD level was detected via the ammonium molybdate method. The level of MDA was detected by the thiobarbituric acid method. The OD value of the corresponding wavelength was measured by a microplate analyser, and the content was calculated with the concentration.

Kidney index

The body weight and kidney weight of rats were weighed and recorded to calculate the kidney index (Kidney index = kidney weight (mg)/rat body weight (g) ×100).

Western blot detection

The kidney tissues of mice in different groups were collected and ground on ice to extract cytoplasmic and nuclear proteins. Then, the total protein content was detected using the BCA method

after the extraction of cellular protein. The total protein content of each group was then sampled for up-swimming. Following electrophoresis, the PVDF membrane was transformed and sealed with 5% defatted milk powder for 1 hour. Primary antibody TLR4 (1:500), MyD88 (1:500), TRAF-6 (1:500), NF-ϰB P65 (1:500), β-actin (1:1000) and histone-H3 (1:1000) were added and incubated at room temperature for 2 hours.

The secondary antibody was then added and incubated at 37°C for 1 hour. After washing three times with TBST, the ECL luminescent solution was added and the relative expression of each protein was analysed using a multi-functional imager.

Statistical methods

All data in this study were processed by SPSS 20.0 statistical software and measurement data were represented by ($\bar{x}\pm s$). One-way ANOVA was used for comparison between multiple groups and LSD-T was used for pial comparison. P<0.05 indicates a statistical difference between data.

Results

Comparison of the HE staining results for kidney tissues in each group

HE staining results showed that when compared with the control group, the renal tissue and tubule epithelium of the CDDP group were severely damaged, the tubules were dilated and swollen, and inflammatory infiltration was obvious. The renal inflammatory response in the OME (A) group was relatively relieved. Moreover, the renal inflammatory response in the OME (B) group was significantly reduced.

Comparison of TNF-α, IL-1β and IL-6 expression levels in the renal tissue of rats in each group

Compared to the control group, the expressions of TNF-α, IL-1β and IL-6 in the kidney tissues of the CDDP group, OME (A) group and OME (B) group were significantly increased (P<0.05), while those of the CDDP group were significantly higher than in the OME (A) and OME (B) groups. These differences were statistically significant (P<0.05) (see Table 1).

Effect of OME on the renal impairment of CDDP

Compared to the control group, the renal function of rats in the CDDP group, OME (A) group and OME (B) group were significantly decreased (P<0.05), while that of the CDDP group was significantly lower than that of the OME (A) and OME (B) groups. These differences were statistically significant (P<0.05) (see Table 2).

Group	N	TNF-α (pg/mL)	IL-1β (pg/mL)	IL-6 (pg/mL)
Control	6	20.36±9.48	47.69±7.87	38.46±10.21
CDDP	6	162.71±25.78*	150.12±18.89*	121.13±16.89*
OME (A)	6	137.76±20.47*#	125.34±14.47*#	96.43±13.72*#
OME (B)	6	80.96±14.31*#	96.46±10.29*#	70.13±9.48*#

Table 1: Comparison of TNF-α, IL-1β and IL-6 expression levels in the renal tissues of rats in each group.
*Note: *represents P<0.05 when compared to the control group, #represents P<0.05 when compared to the CDDP group.*

Group	N	CRE (μmol/L)	SUN (μmol/L)
Control	6	43.12±4.23	7.33±0.95
CDDP	6	94.45±8.87*	35.45±3.48*
OME (A)	6	80.16±7.43*#	27.36±2.59*#
OME (B)	6	62.74±6.03*#	20.06±1.34*#

Table 2: Effects of OME on CRE and SUN levels in rats with CDDP-induced renal injury.
*Note: *represents P<0.05 when compared to the control group, #represents P<0.05 when compared to the CDDP group.*

Changes in renal weight and renal index in each group

There was no significant difference in kidney weight among all groups (P>0.05). Compared to the control group, the kidney index values of the CDDP group, OME (A) group and OME (B) group were significantly increased (P<0.05), while those of the CDDP group were significantly higher than those of the OME (A) and OME (B) groups. These differences were statistically significant (P<0.05) (see Table 3).

Group	Dose	Kidney weight	Kidney index
Control	——	1.84±0.08	6.13±0.21
CDDP	——	1.91±0.05	7.34±0.56*
OME (A)	1.8	1.87±0.11	6.69±0.42*#
OME (B)	3.6	1.86±0.14	6.47±0.54*#

Table 3: Changes in renal weight and renal index in each group.
*Note: *represents P<0.05 when compared to the control group, #represents P<0.05 when compared to the CDDP group.*

Comparison of GSH, SOD and MDA levels in rats with CDDP-induced renal damage treated with OME

When compared to the control group, the levels of GSH and SOD in the CDDP group, OME (A) group and OME (B) group were significantly

decreased (P<0.05). The levels of MDA in the CDDP group and OME (A) group were significantly lower than those in OME (B) group (P<0.05). The CDDP group and OME (A) group were significantly higher than OME (B) group (P<0.05) (see Table 4).

Group	N	GSH (U/mL)	SOD (U/mL)	MDA (mol/L)
Control	6	32.05±2.16	9.15±0.76	1.45±0.37
CDDP	6	20.96±3.44*	5.06±0.41*	4.54±0.77*
OME (A)	6	22.13±3.73*	6.22±0.77*	3.77±0.56*
OME (B)	6	29.84±4.13*#	8.96±0.86*#	3.14±0.29*#

Table 4: Comparison of GSH, SOD and MDA levels in each group.
*Note: *represents P<0.05 when compared to the control group, #represents P<0.05 when compared to the CDDP group.*

OME affects the expression of TRAF-6, MyD88 and TLR4 in the cytoplasm of renal tissue in rats with CDDP-induced renal injury and the expression of NF-B protein in the nucleus

When compared to the control group, the expression of TRAF-6, MyD88, TLR4 and nuclear NF-B protein in the kidney tissue of the CDDP group, OME (A) group and OME (B) group were significantly increased, while the OME (A) and OME (B) groups were significantly better than CDDP group. These differences were statistically significant (P<0.05)

Discussion

CDDP, a cell cycle non-specific drug, is a platinum complex composed of divalent platinum, two Cl atoms and two ammonia molecules[7]. As a widely used chemotherapy drug in clinical practice, CDDP has a significant inhibitory effect on cellular DNA replication but also has particularly prominent gastrointestinal reactions[8], nephrotoxicity and bone marrow suppression[9], and other adverse reactions. After CDDP enters into the systemic circulation, it mainly accumulates in the kidneys. In the early stage of drug treatment, it causes renal tubular epithelial cells to experience ischaemia, hypoxia and cell apoptosis or necrosis-especially the straight segment in proximal convoluted tubule cells.

This leads to renal tubular cell structure and function disorder[10], renal tubular vasoconstriction and decreases in renal blood flow and glomerular filtration rate. CRE and SUN are key indicators of renal function, and their levels can be used to determine the degree of renal function injury.

The main cause of kidney injury caused by CDDP is oxidative stress injury. Zheng et al.[11] found that CDDP directly damages mitochondrial DNA. After entering the body, CDDP can produce a large number of reactive oxygen free radicals and hydroxyl free radicals, which react with unsaturated fatty acids on the biofilm, resulting in changes in mitochondrial membrane permeability and the generation of a variety of toxic degradation substances. MDA is the main product of lipid peroxidation, and the content of MDA can indirectly reflect the severity of kidney damage[12]. SOD and GSH are important free radical scavengers in the body[13] and are negatively correlated with the CRE and SUN content in serum. However, when CDDP is applied to the body, the activities of SOD and GSH, as well as the free radical clearance rate, can be reduced. Giacomo et al.[14] found that the toll-like receptor (TLR) is a type of natural immune receptor that is widely distributed and mainly expressed on the surface of macrophages, dendritic cells, monocytes, lymphocytes, polymorphonuclear cells and natural killer cells. Different pathogen-related molecular patterns can be recognised and combined to initiate a series of signal transductions. The structure of TLR4 is divided into the intracellular domain, transmembrane domain and extracellular domain. In the extracellular domain, the leucine sequence can bind to CD14 to mediate the recognition of pathogen-related molecular patterns[15].

The intracellular domain highly conserved sequence is also called the TIR region. The activation of kernel-related genes promotes the expression of TNF-α, IL-1β, IL-6 and other inflammatory cytokines[16]. Notably, NF-κB is an important inflammatory regulator. NF-κB in the cytoplasm of the body is a complex composed of p50-P65 inhibitory dimer and inhibitory protein IκBα[17], generally in a non-activated state. When cells are stimulated by oxidative stress or drugs, IκBα degrades and is activated by TLR4.

OME is a commonly used clinical PPI that is mainly metabolised through the liver. OME can selectively act on gastric mucosal parietal cells, regulate parietal enzymes and inhibit gastric acid secretion[18] to reduce the oxidative stress damage of epithelial cells and inhibit various inflammatory reactions mediated by TLR4/NF-κB[19]. This study confirmed that OME has anti-inflammatory, antioxidant and drug accumulation reduction effects at the animal and cell levels. Moreover, it confirmed that OME also alleviates CDDP-induced kidney injury and effectively plays the role of 'detoxification and synergism'. In the renal injury

model used in this study, the expression of TLR4/NF-Bp65 was significantly increased in the CDDP group, which could be inhibited by different doses of OME. Moreover, the inhibitory effect became more obvious with an increase in the OME dose. Liu Chongbin et al.[20] found that CDDP-induced renal injury was related to the excessive release of inflammatory factors. In this study, the production of TNF-α, IL-1β, IL-6 and other pro-inflammatory factors in the renal tissues of mice treated with OME was reduced, and renal function indexes were significantly increased in a dose-dependent manner, which was consistent with literature results. These results suggest that OME can regulate the TLR4/NF-ϰB signalling pathway to reduce CDDP-induced inflammatory responses.

In conclusion, OME can reduce the inflammatory response induced by CDDP in the kidneys of rats, reduce the expression level of inflammatory factors, prevent the activation of the TLR4/NF-ϰB signalling pathway and effectively alleviate damage to kidney tissue caused by CDDP.

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