Changes in Glutathione Peroxidase System and Pyridine Nucleotide Phosphate Levels in Kidneys of Cephaloridine-Administered Rats

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Abstract—To elucidate the nephrotoxic mechanisms of cephaloridine (CER), changes in renal contents of glutathione (GSH), glutathione disulfide (GSSG), reduced and oxidized nicotinamide adenine dinucleotide phosphates (NADPH and NADP) and changes in renal activities of glutathione peroxidase, glutathione reductase and glucose-6-phosphate dehydrogenase were examined for 15 days in rats that received single intravenous injections of CER in doses of 0 (control), 100 and 1,000 mg/kg body weight. Significantly different changes from the control group were observed in the 1,000 mg/kg group. The 1,000 mg/kg group showed elevations in renal NADP and NADPH contents and decrements in renal GSH content in the period of the 1st to 3rd hour after the CFR-administration. Thus, the fall in renal GSH content was considered to be a cause for renal injury due to the oxygen radicals observed in the early period. After the 6th hour, the 1,000 mg/kg group showed decreases of renal glutathione peroxidase and glutathione reductase activities and increases of renal glucose-6-phosphate dehydrogenase activity as well as GSH content. Although accumulation of GSH in the kidney was clearly observed in the late period, the more highly aggravated renal injury was speculated to be due to the decreased level in the utilization of GSH according to the fall of renal glutathione peroxidase activity.

As to the nephrotoxicity induced by cephaloridine (CER), several biochemical mechanisms have been proposed (1–7). Although the precise toxic mechanisms of CER remain to be investigated, lipid peroxidation ascribable to oxygen radicals produced in the kidney has been proposed to be one of the major mechanisms of nephrotoxicity (5, 6, 8, 9). On the basis of the hypothesis that the oxygen radicals might participate in the etiology of CER-induced nephrotoxicity, we previously reported the changes in activities of xanthine oxidase, superoxide dismutase and catalase, which produce or become scavengers of oxygen radicals, in the kidneys of CER-administered rats (10). The previous paper (10) indicated a promotion in renal lipid peroxidation 3 hours after the intravenous injection of CER at a dose of 1,000 mg/kg body weight. In contrast, no changes in renal activities of the above three enzymes were observed for the first 6 hours. This fact suggested that the elevation of the renal lipid peroxidation was ascribable not to a disturbance(s) in the above system of producing- and scavenging the oxygen radicals, but ascribable to a disturbance(s) in other renal systems for the protection from oxidative stress. Among the other renal systems, the “glutathione-peroxidase system” with glutathione, an endogenous antioxidant, is considered to be one of great importance (8, 11–14).

Based on this point of view, we investigated changes in contents of glutathione (GSH), glutathione disulfide (GSSG), reduced- and oxidized nicotinamide adenine dinucleotide phosphates (NADPH and NADP) and changes in the activities of glutathione peroxidase, glutathione reductase,
and glucose-6-phosphate dehydrogenase in the kidneys of CER-administered rats.

Materials and Methods

Chemicals and animals: Cephaloridine (Keflodin) was purchased from Shionogi & Co., Ltd. (Osaka, Japan); glutathione (GSH), glutathione disulfide (GSSG), and reduced and oxidized nicotinamide adenine dinucleotide phosphates (NADPH and NADP) from Sigma Chem. Co. (St. Louis, MO, U.S.A.); and enzymes from Boehringer Mannheim GmbH (Mannheim, F.R.G.). All other reagents were purchased from commercial sources. Male Wistar rats weighing 210–230 g were obtained from Sankyo Labo Service Co. (Tokyo, Japan).

General procedure: The rats were housed in ordinary cages under the following conditions: a temperature of 22±3°C, a relative humidity of 50±10%, light (12 hours light, 8:00 to 20:00; 12 hours dark, 20:00 to 8:00), and an air-exchange of 14 times per hour. The rats were allowed free access to water and fed a standard diet of pellets (MF; Oriental Yeast Co., Chiba, Japan). In order to avoid any diurnal changes, drug-administration and other operations were done between 10:00 a.m. to 11:00 a.m. CER was administered to the rats at the designated 0 day or hour. The rats received single injections of CER in a saline solution (4 ml/kg body weight) through the tail vein, with doses of 100 or 1,000 mg/kg body weight. The control rats received an equivalent volume of saline. At the 0, 1st, 2nd, 3rd, 6th, 12th and 24th hour and on the 2nd, 3rd, 4th, 5th, 6th, 7th, 10th and 15th day after the CER-administration, the operation for obtaining the renal tissue samples was performed.

Protocol 1. Preparation for determinations of renal activities of enzymes: After the abdominal cavity was opened through a ventral incision under ether-anesthesia, the left kidney was perfused by saline through the abdominal aorta. The kidney was removed, weighed, and homogenized by a glass/Teflon homogenizer with 8 ml of 0.25 M sucrose. To the homogenate of one kidney, 0.25 M sucrose was added to make a total volume of 10 ml. This homogenate was used for making determinations of renal activities of the enzymes described below.

Protocol 2. Preparation for determinations of renal contents of GSH, GSSG, NADP and NADPH: Under ether anesthesia, the other rats received a ventral incision in order to open the abdominal cavity. The left kidney was removed and rapidly fixed by the “quick-freeze” method (15) using liquid nitrogen and then powdered in liquid nitrogen. The tissue powder was used for determinations of renal contents of the substances described below.

Analytical procedures: For the determination of renal activities of glutathione peroxidase, glutathione reductase and glucose-6-phosphate dehydrogenase, the homogenate was treated by Triton X-100 (1% v/v in final concentration). Since there are two kinds of glutathione peroxidases, such as selenium-dependent and selenium-independent enzymes (16, 17), the enzyme activity was determined with hydrogen peroxide by the method of Paglia and Valentine (18), and it was also determined with cumene hydroperoxide by the method of Lawrence and Burk (19). Glutathione reductase activity was determined by the method of Goldberg and Spooner (20). Glucose-6-phosphate dehydrogenase activity was determined by the method of Löhr and Waller (21). Renal contents of GSH and GSSG were determined by the method of Griffith (22). Renal contents of NADP and NADPH were determined by the high-performance liquid chromatographic method of Kalhorn et al. (23). As to the representation of the contents and activities of the above determinations, all were expressed in values per one kidney, since the protein content and the tissue wet weight in the kidney were fluctuating factors in this kind of toxicological examination (24).

Statistics: Results are given as the mean±S.E.M. To define statistically significant differences among the groups, the data were subjected to one-way analysis of variance and subsequently to the Bonferroni's method (25); P values of less than 0.05 were considered to be significant.

Results

In the experiments of Protocol 1, changes in the activities of glutathione peroxidase, glutathione reductase and glucose-6-phos-
Changes of renal activity of glutathione peroxidase following single intravenous injections of cephaloridine in rats. Glutathione peroxidase activity was determined by use of either hydrogen peroxide (upper figure) or cumene hydroperoxide (lower figure) as its substrates. Rats received single intravenous injections of cephaloridine in doses of 0 (Control), 100 (CER, 100 mg/kg) and 1,000 mg/kg body weight (CER, 1,000 mg/kg). Points and bars represent the mean±S.E.M. Number of rats was 6 for each time-point. Asterisks denote significant differences in comparison to the control group at each time-point: *P<0.05, **P<0.01. Abbreviations: CER, cephaloridine; Inj. of CER, injection of cephaloridine.

Figure 2 shows the changes of renal activities of glutathione reductase. The 100 mg/kg group showed no significant changes in activity.

The renal activities of glutathione peroxidase were determined separately with either hydrogen peroxide (Fig. 1, upper figure) or cumene hydroperoxide (Fig. 1, lower figure) as its substrates. The activities determined with hydrogen peroxide (Fig. 1, upper figure) in the 100 mg/kg group did not change throughout the whole process, showing no significant differences in comparison to the control group. In contrast, the activities in the 1,000 mg/kg group fell from the 1st day with significant differences as compared with those in the control group, and they reached the lowest level, 46% of the control level, on the 3rd day. Later, the activities began to revert toward the control level, but the activities were still lower than the control even on the 15th day.

The activities determined with cumene hydroperoxide (Fig. 1, lower figure) in the control and the CER-administered groups showed similar tendencies to those that were determined with hydrogen peroxide throughout the whole process, excluding the 6th hour time-point in the 1,000 mg/kg group: at the 6th hour time-point, the activities in the 1,000 mg/kg group showed a significantly lower value as compared with those in the control group.

Figure 2 shows the changes of renal activities of glutathione reductase. The 100 mg/kg group showed no significant changes in activity.
comparison to the control group throughout the whole process. The activities in the 1,000 mg/kg group fell at the 2nd and 3rd hours, reverted to the control level, and then fell again from the 24th hour, reaching its lowest level, 68% of the control level, on the 3rd day. The activities then began to revert and reached the control level on the 15th day.

Figure 3 shows the changes of renal activities in glucose-6-phosphate dehydrogenase. No significant changes were observed between the control and the 100 mg/kg groups throughout the whole process. The activities in the 1,000 mg/kg group rose from the 12th hour, and they reached its highest level, about 2.5 times that of the control level, on the 4th day. Later the activities began to revert toward the control level, but the activities were still higher than the control even on the 15th day.

Next, in the experiments of Protocol 2, changes of renal contents of GSSG, NADPH...
and NADP were investigated in the control and the CER-administered groups.

Figure 4 shows the changes of renal contents of GSH and GSSG. In terms of the renal contents of GSH (Fig. 4, upper figure), the 100 mg/kg group, as compared with the control, showed a rise solely at the 2nd hour, and there were no significant changes at the other points of the whole time course. The GSH contents in the 1,000 mg/kg group fell at the 2nd and the 6th hours, reverted to the control level at the 3rd hour, began to rise from the 12th hour, and reached its maximal level on the 2nd day. Then, the contents began to revert toward the control level, while the GSH content remained at a higher level until the 15th day in comparison to the control group.

As to the renal contents of GSSG (Fig. 4, lower figure), the 100 mg/kg group showed a rise at the 6th hour. In comparison to the control group, no significantly different changes were observed at the other time-points in the 1,000 mg/kg group and during the whole time course in the 100 mg/kg group.

Figure 5 shows the changes of renal contents in NADPH and NADP. The contents of renal NADPH (Fig. 5, upper figure) in the 1,000 mg/kg group rose from the 1st to the 6th hour: the peak was found at the 2nd hour. In comparison to the control group, no significant changes were observed at the other time-points in the 1,000 mg/kg group and throughout the time course in the 100 mg/kg group.

The contents of renal NADP (Fig. 5, lower figure) in the 1,000 mg/kg group was high at the 2nd and 6th hours: the highest value was found at the 6th hour. In comparison to the control group, no significantly different changes were observed at the other time-points in the 1,000 mg/kg group and during the whole time course in the 100 mg/kg group.

Discussion

It has been established that there are two kinds of glutathione peroxidases (one is selenium-dependent and the other is selenium-independent) and that the two enzymes are found in the cytosol and mitochondria of cells (16, 17). Also, it has been confirmed that the selenium-dependent enzyme catalyzes the conversion of organic hydroperoxide and hydrogen peroxide into organic alcohols and water, while the selenium-independent enzyme only catalyzes the conversion of organic hydroperoxide (26, 27). Hydrogen peroxide and organic hydroperoxide are a causal substance and an intermediate product, respectively, of lipid peroxidation in cellular membranes (17–19, 26, 27). Therefore, investigation of alteration in ability to scavenge
the hydrogen peroxide and organic hydroperoxide in the kidney is considered to give some important information for elucidating the nephrotoxic mechanism of CER. Based on this view, the two substrates, hydrogen peroxide and cumene hydroperoxide, were used for determination of the enzyme. In the comparison of renal enzymatic activities determined by the above two substrates, the ability to scavenge cumene hydroperoxide in the 1,000 mg/kg group showed a sporadic and modest fall at the 6th hour after the CER administration. Investigations on whether this fall is toxicologically significant or not remain to be carried out. At the other timepoints, the abilities to scavenge the two substrates showed similar alterations, suggesting that the abilities to scavenge the hydrogen peroxide and organic hydroperoxide were both similarly affected by the CER.

Regarding the etiology of the nephrotoxicity induced by CER, oxygen radical production has been proposed to be one of the major mechanisms in relation to lipid peroxidation (5, 7-9). In a biological system, primary defense against cytotoxic oxygen radicals is provided by antioxidants such as GSH, ascorbic acid, alpha-tocopherol, etc. and by enzymes such as superoxide dismutase, catalase, glutathione peroxidase, etc., which scavenge the intermediates of oxygen reduction (28-31). With regards to these protective factors against the attack due to the oxygen radicals, we previously investigated the changes of malondialdehyde formation and activities of xanthine oxidase, superoxide dismutase and catalase in the kidneys of rats that were intravenously injected with CER at a dose of 1,000 mg/kg body weight (10). The results indicated that the renal malondialdehyde formation was accelerated in two stages, from the 3rd hour to the 2nd day following the CER administration and from the 2nd to the 7th day, and that an elevation in renal activities of xanthine oxidase and decrements in renal activities of superoxide dismutase and catalase, were recognized after the 12th hour. Thus, these findings suggested that the elevation of renal lipid peroxidation observed during the 3rd to the 12th hour was not directly due to the changes in the renal activities of xanthine oxidase, superoxide dismutase and catalase, but rather due to alterations of other factors such as endogenous antioxidants and the other enzymatic systems. In this respect, the "glutathione peroxidase system" has been recognized as another system for protection against the oxygen radicals, and its function involving the glutathione reduction-oxidation cycle and hexose monophosphate shunt has been proposed as the following (8, 11-14, 32): the conversions of cytotoxic lipid hydroperoxides to innocuous lipid alcohols and of hydrogen peroxide to water by glutathione peroxidase are linked to the activities of glutathione reductase and glucose-6-phosphate dehydrogenase, which supply reducing equivalents in the form reduced glutathione and NADPH, respectively.

On the basis of this view, the present study was carried out to elucidate interrelations of enzymes and substances in this glutathione peroxidase system in the kidneys of rats that were treated by CER. Since our present results showed that the 1,000 mg/kg group showed significantly different changes, but the 100 mg/kg did not, in comparison to the control group, the discussions below are mainly concerned with the results obtained from the 1,000 mg/kg group.

In the initial 3 hours following CER-administration, the 1,000 mg/kg group showed elevations in NADP and NADPH contents, decrements in GSH content and glutathione reductase activity, and no changes in GSSG content, glucose-6-phosphate dehydrogenase and glutathione peroxidase activities in the kidney. This fact indicated that the renal hexose monophosphate shunt activity remained normal and that the renal level of NADPH that was spent for the redox cycle of GSSG to GSH was sufficiently supplied. Accordingly, the renal decreased level of GSH was presumed to be ascribable to the decreased conversion of GSSG to GSH that was brought about by the decreased activity of glutathione reductase, and it was also ascribable to the increased consumption of GSH in non-enzymatic removal of the oxygen radicals. If the conversion occurred, then the rise of renal GSSG level could be expected (5). However, a rise in the renal GSSG was hardly observed in the 1,000 mg/kg group,
but was seen in the 100 mg/kg group. As possible causes for the non-increased level of renal GSSG in the 1,000 mg/kg group, it was speculated that when the renal cells were lethally damaged, the converted GSSG was used to form mixed disulfides with proteins and enzymes (33) and/or was degraded into amino acids by contact with peptidases (34) that were liberated from the cellular components during their disintegration.

Schraufstatter et al. (14) reported in their in vitro study that the biochemical events important in the lethal injury of cells induced by oxidants were caused in the initial 30 min of exposure of the cells to the oxidant. This fact implied that when the cells were not protected against the oxidants in the early period, the cells could not be rescued from the lethal damage. Thus, the renal elevation of lipid peroxidation that was observed in the early period in our previous report (10) was considered to be attributed to the renal depletion of GSH in that period. Our data are consistent with previous reports (5, 6, 8) on renal GSH depletion. In terms of the renal glutathione reductase, few reports have indicated its depression in the early period. Nevertheless, the fall in renal glutathione reductase during this period might be a definite factor in the lethal damage which occurs in the renal cells.

In regard to the items at the late period (later than the 6th hour) in this study, the 1,000 mg/kg group showed falls in renal glutathione peroxidase and glutathione reductase activities and rises in renal glucose-6-phosphate dehydrogenase activity and GSH content. In comparison to the early period, as reported previously (10), there was a large amount of renal lipid peroxidation in this late period. The present study indicated that GSH was largely accumulated in the kidney. Therefore, promotion in the renal lipid peroxidation might be explained, in part, by the decreased level in utilization of GSH according to the fall in renal glutathione peroxidase activity. In addition, the decrements in superoxide dismutase and catalase activities and the increment in xanthine oxidase activity in the kidney, as reported previously (10), could also be causes for the elevated level of renal lipid peroxidation in this late period.

Concerning the alterations observed in the 100 mg/kg group, the renal levels of GSH and GSSG were elevated at the 2nd hour and at the 6th hour, respectively. The other items determined were all within the normal levels throughout the whole process. It has been reported that CER in the dose of 100 mg/kg body weight hardly had any nephrotoxic effect on the rats (1, 5, 6, 8, 35–37). Nevertheless, our present finding and a previous report (38) suggest that the single intravenous injection of CER, at the dose of 100 mg/kg, slightly promotes lipid peroxidation in the kidneys and that the rise of GSH level hides the injury due to the oxygen radicals in the kidney.

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