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Preventive effect of L-carnosine on ischemia/reperfusion-induced acute renal failure in rats

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Abstract

We investigated the effect of L-carnosine (β-alanyl-L-histidine) on ischemic acute renal failure in rats. Ischemic acute renal failure was induced by occlusion of the left renal artery and vein for 45 min followed by reperfusion, 2 weeks after contralateral nephrectomy. Renal function in untreated acute renal failure rats markedly decreased at 1 day after reperfusion. Pre-ischemic treatment with L-carnosine dose-dependently (1, 10 μg/kg, i.v.) attenuated the ischemia/reperfusion-induced renal dysfunction. Histopathological examination of the kidney of untreated acute renal failure rats revealed severe renal damage, which was significantly suppressed by pre-treatment with L-carnosine, at each dose given. In untreated acute renal failure rats, norepinephrine concentrations in renal venous plasma remarkably increased within 2 min after reperfusion and thereafter rapidly decreased. Pre-ischemic treatment with L-carnosine at a dose of 10 μg/kg significantly depressed the elevated norepinephrine level. On the other hand, although the higher dose of L-carnosine given 5 min after reperfusion tended to ameliorate the renal dysfunction after reperfusion, the improvement was moderate compared with those seen in pre-ischemic treatment. These results indicate that L-carnosine prevents the development of ischemia/reperfusion-induced renal injury, and the effect is accompanied by suppression of the enhanced norepinephrine release in the kidney immediately after reperfusion. Thus, the preventing effect of L-carnosine on ischemic acute renal failure is probably through the suppression of enhanced renal sympathetic nerve activity induced by ischemia/reperfusion.

Keywords: Carnosine; Renal sympathetic nerve activity; Norepinephrine; Acute renal failure; Ischemia/reperfusion

1. Introduction

A commercial chicken extract known as Brand's Essence of Chicken (BEC), which is promoted in some Asian regions, has a potential to recover from mental stress and enhance the mental efficiency of students (Nagai et al., 1996). BEC is an extract of chicken muscle processed with water under high temperature conditions. It contains mainly protein, amino acids and peptides such as L-carnosine. We have noted that the supplement of BEC suppresses the development of hypertension and a concomitant renal damage in deoxycorticosterone acetate-salt-induced hypertensive and stroke-prone spontaneously hypertensive rats (Matsumura et al., 2001, 2002).

L-Carnosine, a dipeptide composed of β-alanine and L-histidine, is found in high concentrations in BEC and is abundant in skeletal muscle of humans and many species of animals. This peptide is known to possess antioxidative and free radical scavenging functions (Dahl et al., 1988; Aruoma et al., 1989; Hartman et al., 1990; Stvolinsky and Dobrota, 2000; Kang et al., 2002). Resent studies indicated that L-carnosine decreased cell death after hypoxia/reoxygenation in phenochromocytoma PC12 cells (Tabakman et al., 2002) and reduced the levels of hypoxia-inducible factor-1 α in H9c2 cardiomyoblasts during hypoxia (Bharadwaj et al., 2002). In addition, we have found that an intravenous injection of L-carnosine suppressed renal sympathetic nerve activity in urethane-anesthetized rats (Niijima et al., 2002). These findings raise the possibility that administration of L-carnosine to experimental animals may ameliorate diseases caused by ischemia/reperfusion or enhanced sympathetic nerve activity.

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The aim of the present study is to evaluate the potential of L-carnosine to protect renal dysfunction and histological damage in ischemic acute renal failure. Furthermore, we examined the effect of L-carnosine on norepinephrine levels in renal venous plasma as an index of norepinephrine release from renal noradrenergic nerve endings, since renal sympathetic nerves and circulating catecholamines are considered to be involved in the development of acute renal failure (Baines, 1983; Iaina and Eliahou, 1983).

2. Materials and methods

2.1. Animals and experimental design

Male Sprague–Dawley rats (10 weeks of age, Japan SLC, Shizuoka, Japan) were used. Animals were housed in a light-controlled room with a 12-h light/dark cycle and were allowed ad libitum access to food and water. Experimental protocols and animal care methods in the experiments were approved by the Experimental Animal Committee at Osaka University of Pharmaceutical Sciences. Two weeks before the study (at 8 weeks of age), the right kidney was removed through a small flank incision under pentobarbital anesthesia (50 mg/kg, i.p.). After a 2-week recovery period, these rats were separated into five groups: (1) sham-operated control, (2) untreated acute renal failure, (3) pre-ischemic treatment with L-carnosine (1 μg/kg, i.v.) in acute renal failure, (4) pre-ischemic treatment with L-carnosine (10 μg/kg, i.v.) in acute renal failure, (5) post-ischemic treatment with L-carnosine (10 μg/kg, i.v.) in acute renal failure. To induce ischemic acute renal failure, rats were anesthetized with pentobarbital (50 mg/kg, i.p.), and the left kidney was exposed through a small flank incision. The left renal artery and vein were occluded with a nontraumatic clamp for 45 min. At the end of the ischemic period, the clamp was released to allow reperfusion. L-Carnosine or vehicle (0.9% saline) was injected (pre-ischemic treatment, 5 min before ischemia; post-ischemic treatment, 5 min after reperfusion) in a volume of 1 ml/kg into the external jugular vein. In sham-operated control rats, the kidney was treated identically, except for the clamping.

Animals exposed to 45-min ischemia were housed in metabolic cages 24 h after the ischemia. At the end of urine collection for 5 h, blood samples were drawn from the thoracic aorta, and then the left kidneys were excised under pentobarbital anesthesia (50 mg/kg, i.p.). The plasma was separated by centrifugation. These samples were used for measurement of renal function parameters.

In separate experiments, we examined the effect of L-carnosine (10 μg/kg i.v.) on changes in norepinephrine levels in renal venous plasma after the 45-min ischemia and reperfusion. Under pentobarbital (50 mg/kg, i.p.) anesthesia, an abdominal midline incision of uninephrectomized rats was made and the left kidney was exposed. A 26-gauge needle was inserted into the left renal vein for venous blood sampling. Each blood sample was taken during 2 min at the start of reperfusion, and at 15 min or 1 day after reperfusion. Plasma was immediately separated by centrifugation. These samples were stored at −20 °C until the assay for norepinephrine concentration.

2.2. Histological studies

The kidneys were preserved in phosphate-buffered 10% formalin, after which the kidneys were chopped into small

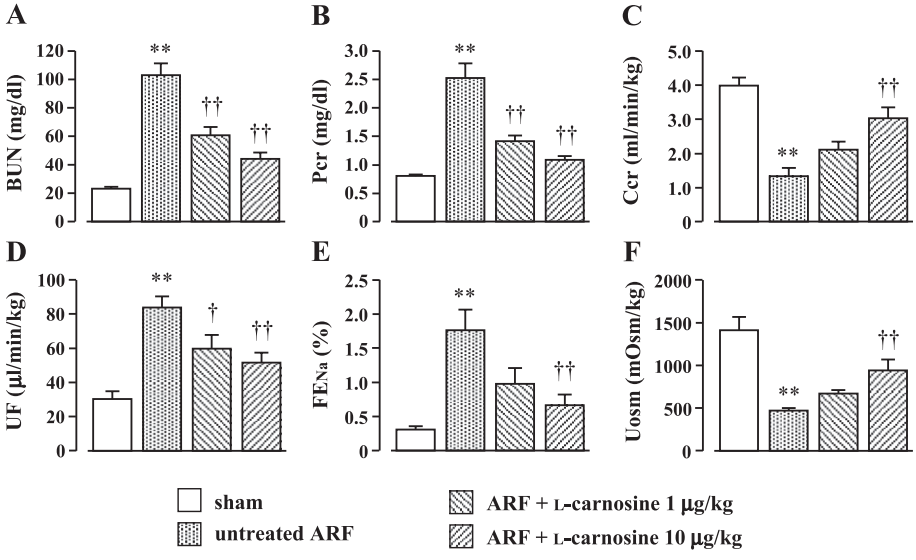

Fig. 1. Effect of L-carnosine on blood urea nitrogen (BUN, A), plasma creatinine concentration (Pcr, B), creatinine clearance (Ccr, C), urine flow (UF, D), fractional excretion of sodium (FE_{Na}, E) and urinary osmolality (Uosm, F) at 1 day after reperfusion. L-Carnosine was given intravenously 5 min before ischemia. Each column and bar represents the mean ± S.E.M. ($n = 6$). **$P < 0.01$, compared with sham-operated rats. †$P < 0.05$, ††$P < 0.01$, compared with untreated ARF rats. ARF: acute renal failure.

Table 1
Histopathological changes in the kidneys of untreated or L-carnosine-treated acute renal failure rats and sham-operated rats

Experimental group	Proteinaceous casts in tubuli	Medullary congestion	Tubular necrosis
Untreated ARF ($n=6$)	3.67 ± 0.21	3.17 ± 0.31	3.83 ± 0.12
ARF + L-carnosine 1 μg/kg ($n=6$)	2.17 ± 0.31[a]	2.33 ± 0.21	2.50 ± 0.34[b]
ARF + L-carnosine 10 μg/kg ($n=6$)	1.00 ± 0.37[a]	1.17 ± 0.31[a]	1.17 ± 0.40[a]

Values represent the mean ± S.E.M. of histopathological grade. Grade: no change (0), mild (1), moderate (2), severe (3), very severe (4). ARF: acute renal failure.

[a] $P<0.01$, compared with untreated ARF rats.

[b] $P<0.05$, compared with untreated ARF rats.

pieces, embedded in paraffin wax, and cut at 5 μm and stained with hematoxylin and eosin. Histopathological changes were graded as no change (0), mild (1), moderate (2), severe (3), and very severe (4) based on the microscopical observations of each section. The evaluations were made by an observer who was blind to the treatment origin of the tissue.

2.3. Analytical procedures

Blood urea nitrogen and creatinine levels in plasma or urine were determined using the blood urea nitrogen-test-Wako and creatinine-test-Wako (Wako, Osaka, Japan), respectively. Creatinine clearance (Ccr, ml/min/kg) was calculated from the formula $Ccr = Ucr \times UF/Pcr$, where Ucr and Pcr are creatinine concentration in urine and plasma, respectively, and UF is urine flow. Urinary osmolality was measured by freezing point depression (Fiske Associates, Ux-bridge, MA, USA). Urine and plasma sodium concentrations were determined using a flame photometer (205D; Hitachi, Ibaraki, Japan). Fractional excretion of sodium (FE_{Na}, %) was calculated from the formula $FE_{Na} = U_{Na}V/(P_{Na} \times Ccr) \times 100$, where $U_{Na}V$ is urinary excretion of

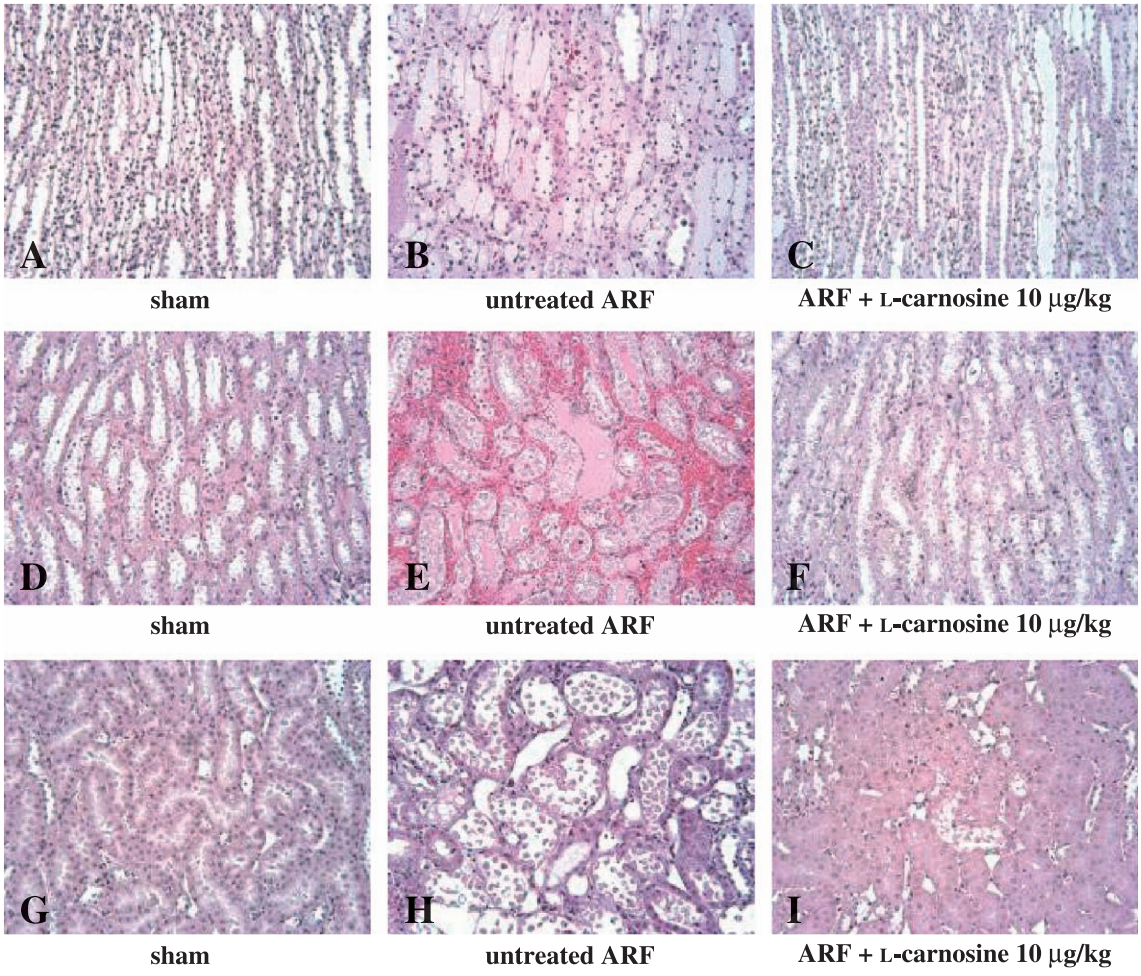

Fig. 2. Light microscopy of inner zone (A–C), outer zone inner stripe (D–F) and outer zone outer stripe (G–I) of medulla of the kidney of ARF rats untreated and treated with L-carnosine (10 μg/kg) at 1 day after reperfusion, and sham-operated rats. Severe proteinaceous casts in tubuli (B), congestion and hemorrhage (E) and tubular necrosis (H) are observed in untreated ARF rats. ARF: acute renal failure. Magnification ×200.

sodium and P_{Na} is the plasma sodium concentration. Norepinephrine concentration in renal venous plasma was measured by high-performance liquid chromatography with an amperometric detector (EC-100; Eicom, Kyoto, Japan), as previously reported (Hayashi et al., 1991).

2.4. Drugs

L-Carnosine was obtained from Wako. It was dissolved in saline (0.9%). Other chemicals were obtained from Nacalai Tesque (Kyoto, Japan) and Wako.

2.5. Statistical analysis

Values were expressed as mean ± S.E.M. The data were analyzed for significant differences between the sham-operated and untreated acute renal failure groups using Student's unpaired *t*-test. Statistical analysis for renal functional studies was performed using one-way analysis of variance followed by a Dunnett-type multiple comparison test. Histological data were analyzed using Kruskal–Wallis nonparametric test combined with a Steel-type multiple comparison test. For all comparisons, differences were considered significant at $P < 0.05$.

3. Results

3.1. Renal function at 1 day after the ischemia/reperfusion and effect of pre-ischemic treatment with L-carnosine

As shown in Fig. 1, renal function of rats subjected to 45-min ischemia showed a marked deterioration when measured at 1 day after reperfusion. As compared with sham-operated rats, untreated acute renal failure rats showed significant increases in blood urea nitrogen, plasma creatinine concentration, urine flow and fractional excretion of sodium, and significant decreases in creatinine clearance and urinary osmolality. Administration of L-carnosine (1 μg/kg, 10 μg/kg, i.v.), at 5 min before ischemia, dose-dependently attenuated the ischemia/reperfusion-induced renal dysfunction.

3.2. Histological renal damage at 1 day after the ischemia/reperfusion and effect of pre-ischemic treatment with L-carnosine

Histopathological examination revealed severe lesions in the kidney of untreated acute renal failure rats (1 day after reperfusion). These changes were characterized by proteinaceous casts in tubuli in the inner zone of medulla, medullary congestion and hemorrhage in the outer zone inner stripe of medulla, and tubular necrosis in the outer zone outer stripe of medulla. L-Carnosine dose-dependently attenuated the development of all these lesions (Table 1). Typical photographs are shown in Fig. 2.

3.3. Renal venous plasma norepinephrine concentration after the ischemia/reperfusion and effect of pre-ischemic treatment with L-carnosine

As shown Fig. 3, renal venous plasma norepinephrine concentrations in untreated acute renal failure rats were remarkably increased just after reperfusion (within 2 min), and thereafter, the increased level rapidly declined 15 min after reperfusion but the norepinephrine concentration maintained at higher levels even 1 day after reperfusion, compared with that seen in sham-operated control animals. The increase in renal venous plasma norepinephrine concentration immediately after reperfusion was markedly suppressed by pre-ischemic treatment with L-carnosine (10 μg/kg), which also significantly decreased the norepinephrine levels at 15 min and 1 day after reperfusion.

3.4. Renal function at 1 day after the ischemia/reperfusion and effect of post-ischemic treatment with L-carnosine

We next examined whether L-carnosine would improve renal dysfunction induced by ischemia/reperfusion even when this drug was administered to acute renal failure rats after the start of reperfusion. As shown in Table 2, post-ischemic treatment with L-carnosine (10 μg/kg), at 5 min after reperfusion, tended to attenuate the ischemia/reperfusion-induced renal dysfunction, but such effects were moderate compared with those seen in pre-ischemic treatment

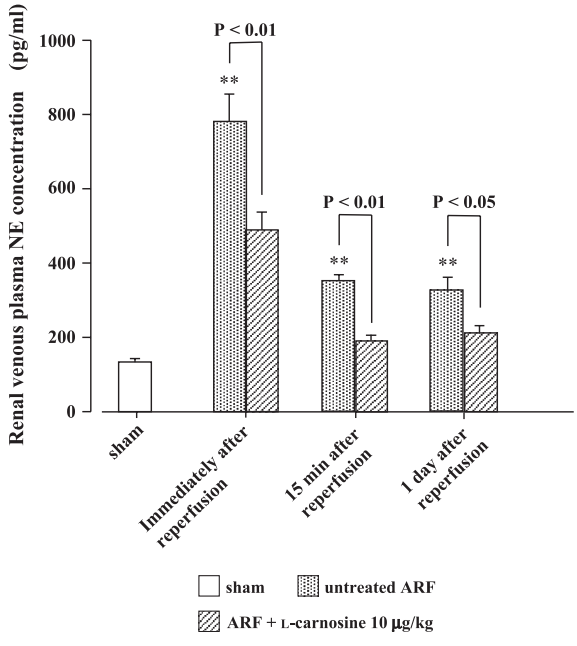

Fig. 3. Effect of L-carnosine on renal venous plasma NE concentrations of ischemic ARF rats untreated or treated with L-carnosine. L-Carnosine (10 μg/kg) was given intravenously 5 min before ischemia. Blood samples were taken during 2 min at the start of reperfusion, and 15 min and 1 day after reperfusion. Each column and bar represents the mean ± S.E.M. ($n = 6$). $^{**}P < 0.01$, compared with sham-operated rats. ARF: acute renal failure.

Table 2
Effect of L-carnosine administered after reperfusion on blood urea nitrogen (BUN), plasma creatinine concentration (Pcr), creatinine clearance (Ccr), urine flow (UF), fractional excretion of sodium (FE_{Na}) and urinary osmolality (Uosm) at 1 day after reperfusion

Experimental group	BUN (mg/dl)	Pcr (mg/dl)	Ccr (ml/min/kg)	UF (μl/min/kg)	FE_{Na} (%)	Uosm (mosM/kg)
Sham ($n=6$)	23.3 ± 1.40	0.80 ± 0.03	3.98 ± 0.24	30.4 ± 4.50	0.31 ± 0.05	1412 ± 155
Untreated ARF ($n=6$)	102.9 ± 8.22[a]	2.52 ± 0.26[a]	1.33 ± 0.24[a]	83.9 ± 6.43[a]	1.76 ± 0.30[a]	472 ± 24[a]
ARF + L-carnosine 10 μg/kg ($n=6$)	79.7 ± 8.55	1.72 ± 0.17[b]	1.90 ± 0.22	80.2 ± 5.93	0.93 ± 0.18	528 ± 49

Each value represents the mean ± S.E.M. L-Carnosine was given 5 min after reperfusion.
[a] $P<0.01$, compared with sham-operated rats.
[b] $P<0.05$, compared with untreated ARF rats.

and observed changes were not statistically significant, except for plasma creatinine concentration.

4. Discussion

In the current study, we obtained evidence that prior administration of L-carnosine markedly overcame the ischemia/reperfusion-induced renal dysfunction in rats. Histological examination of the postischemic kidney of untreated acute renal failure rats revealed tissue injuries, such as proteinaceous casts in tubuli, medullary congestion and tubular necrosis, and these lesions were significantly suppressed by pre-ischemic treatment with L-carnosine. These results indicate that L-carnosine has preventing effects on the ischemia/reperfusion-induced renal dysfunction and degeneration.

Renal sympathetic nerves and circulating catecholamines are considered to be involved in the development of acute renal failure since pharmacological blockade of sympathetic nerve exerts an efficient protective effect on this failure (Baines, 1983; Iaina and Eliahou, 1983). The severity of renal injury in experimental models such as hemorrhage- or renal artery clamping-induced renal ischemia is reduced by α-adrenoceptor antagonist phenoxybenzamine (Henrich et al., 1981), α_2-adrenoceptor agonist clonidine (Solez et al., 1980) or β-adrenoceptor antagonist propranolol (Solez et al., 1977a,b; Chevalier and Finn, 1980). We also have observed that a ganglion blocking agent or renal denervation suppresses renal dysfunction and degeneration induced by ischemia/reperfusion (Fujii et al., unpublished observation). In the present study, when norepinephrine concentrations in renal venous plasma after reperfusion were measured as an index of norepinephrine release from renal noradrenergic nerve endings, the levels were markedly elevated immediately after reperfusion (within 2 min) and thereafter, the increased level rapidly declined 15 min after reperfusion but the norepinephrine concentration maintained at higher levels even 1 day after reperfusion. Taken together, it seems likely that the renal sympathetic nerve system enhanced by ischemia/reperfusion has a crucial role in the pathogenesis of ischemic acute renal failure and that substances which depress renal sympathetic nerve activity exhibit protective effects on renal injury induced by ischemia/reperfusion.

Recent studies revealed that L-carnosine could suppress renal, adrenal and hepatic sympathetic nerve activities and facilitated the pancreatic vagal nerve activity in urethane-anesthetized rats (Yamano et al., 2001; Niijima et al., 2002). In the present study, we therefore asked if L-carnosine can suppress the increase in renal venous plasma norepinephrine concentrations after the ischemia/reperfusion. Results clearly indicated that the pre-ischemic treatment with L-carnosine at a dose of 10 μg/kg significantly suppressed the increased norepinephrine levels after reperfusion. This effect of L-carnosine seems to result from its suppressive action on the renal sympathetic nerve activity enhanced by ischemia/reperfusion. In the present study, we observed that the pre-ischemic treatment with L-carnosine (10 μg/kg) efficiently improved the deterioration of renal function induced by ischemia/reperfusion, whereas its efficacy was considerably attenuated when the same dose of L-carnosine was administered 5 min after reperfusion. Thus, norepinephrine released as early as 2 min after reperfusion seems to contribute to the post-ischemic renal injury. This view is supported by the fact that the infusion of norepinephrine into a renal artery in dogs and rats can produce the depression in renal function and renal hemodynamic abnormality (Cronin et al., 1978; Conger et al., 1991).

L-Carnosine possesses antioxidative and free radical scavenging functions (Dahl et al., 1988; Aruoma et al., 1989; Hartman et al., 1990; Kang et al., 2002). Stvolinsky et al. (2000) have indicated that L-carnosine at a dose of 150 mg/kg reduces the mortality of rats after global brain ischemia induced by occlusion of the carotid arteries and that this action of L-carnosine is due to its antioxidative effect. Interestingly, a recent study demonstrated that L-carnosine at a dose of 5 nmol/rat (the dose corresponds to about 4 μg/kg) produced an inhibitory action on neural activities of sympathetic efferent nerves (Yamano et al., 2001). In the present study, we found that even at doses of 1–10 μg/kg, L-carnosine could efficiently prevent the ischemia/reperfusion-induced acute renal failure, accompanying the suppression of the elevated norepinephrine levels in renal venous plasma. Taken together, there is a possibility that L-carnosine has an inhibitory action on the sympathetic nervous system at lower doses, independent of its antioxidative characteristic. However, oxidative stress is definitely involved in the development of ischemic acute renal failure, since radical scavengers and antioxidants improve the ischemia/reperfusion-induced renal injury (Paller et al., 1984; Chatterjee et al., 2000; Takaoka et al., 2002).

Thus, a possibility that L-carnosine improves the ischemia/reperfusion-induced renal injury via its antioxidative activity cannot be ruled out.

While antioxidants appear to prevent ischemia/reperfusion injury, few studies have shown benefit after the induction of ischemia and the therapeutic window for intervention remains obscure. Thus, we examined whether L-carnosine could reverse the ischemia/reperfusion-induced renal dysfunction when given after reperfusion. The results showed that the efficacy of post-ischemic treatment with L-carnosine at the dose of 10 μg/kg was moderate compared with that seen in pre-ischemic treatment. With respect to the matter, further studies are required to evaluate whether post-ischemic treatment with higher doses of L-carnosine, at which would exhibit antioxidative effect, can improve renal injury induced by ischemia/reperfusion. On the other hand, the fact that the effective renoprotection was observed when L-carnosine was administered prior to ischemia, suggests that L-carnosine can be used in situations where renal ischemia can be predicted, e.g. prior to abdominal surgery or renal transplantation.

The naturally occurring dipeptide L-carnosine (β-alanyl-L-histidine) is known to be hydrolyzed by an enzyme, carnosinase in rat tissues (Tamaki et al., 1985) and human serum (Willi et al., 1997). Therefore, L-histidine cleaved by carnosinase from L-carnosine or its decarboxylated metabolite L-histamine may be involved in L-carnosine's action. Most recently, Yamano et al. (2001) found that the suppressive effect of L-carnosine on hyperglycemia induced by intracranial injection of 2-deoxy-D-glucose is eliminated by histamine H_3 receptor antagonist thioperamide. They also observed a similar suppressive effect of L-histamine on the 2-deoxy-D-glucose-induced hyperglycemia. In addition, we have obtained evidence that histamine H_3 receptor plays a role as an inhibitory modulator of renal noradrenergic neurotransmission in anesthetized dogs (Yamasaki et al., 2001). Taken together, one can speculate that the effect of L-carnosine is mediated by the histamine/H_3 receptor system. However, there is no available evidence regarding the conversion of administered L-carnosine into histamine. Further experiments are required to clarify whether histamine and H_3 receptor are contributive to L-carnosine-induced ameliorative effect on the acute renal failure.

The present study clearly indicates that pre-ischemic treatment with L-carnosine attenuates the development of the ischemia/reperfusion-induced acute renal failure and suppresses elevated norepinephrine release in the kidney after the ischemia/reperfusion. It is reasonable to consider that the protective effect of L-carnosine against the renal injury induced by ischemia/reperfusion is closely related to the inhibition of renal sympathetic nerve activity by this peptide.

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