Renoprotective Effects of L-Carnosine on Ischemia/Reperfusion-Induced Renal Injury in Rats

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Received June 28, 2006; accepted August 15, 2006

ABSTRACT

We examined the renoprotective effects of L-carnosine (β-alanyl-L-histidine) on ischemia/reperfusion (I/R)-induced acute renal failure (ARF) in rats. Ischemic ARF was induced by occlusion of the left renal artery and vein for 45 min followed by reperfusion, 2 weeks after contralateral nephrectomy. In vehicle (0.9% saline)-treated rats, renal sympathetic nerve activity (RSNA) was significantly augmented during the renal ischemia, and renal function was markedly decreased at 24 h after reperfusion. Intracerebroventricular injection of L-carnosine (1.5 and 5 pmol/rat) to ischemic ARF rats dose-dependently suppressed the augmented RSNA during ischemia and the renal injury at 24 h after reperfusion. N-α-Acetyl-L-carnosine [N-acetyl-β-alanyl-L-histidine; 5 pmol/rat intracerebroventricular (i.c.v.)], which is resistant to enzymatic hydrolysis by carnosinase, did not affect the renal injury, and L-histidine (5 pmol/rat i.c.v.), a metabolite cleaved from L-carnosine by carnosinase, ameliorated the I/R-induced renal injury. Furthermore, a selective histamine H3 receptor antagonist, thioperamide (30 nmol/rat i.c.v.) eliminated the preventing effects by L-carnosine (15 nmol/rat intravenously) on ischemic ARF. In contrast, a selective H3 receptor agonist, R-α-methylhistamine (5 pmol/rat i.c.v.), prevented the I/R-induced renal injury as well as L-carnosine (5 pmol/rat) did. These results indicate that L-carnosine prevents the development of I/R-induced renal injury, and the effect is accompanied by suppressing the enhanced RSNA during ischemia. In addition, the present findings suggest that the renoprotective effect of L-carnosine on ischemic ARF is induced by its conversion to L-histidine and L-histamine and is mediated through the activation of histamine H3 receptors in the central nervous system.

L-Carnosine (β-alanyl-L-histidine) is abundant in skeletal muscles of most vertebrates. This peptide is also detected in brain and cardiac muscle, but it is not detected in several other organs, such as kidney, liver, and lung (Jackson and Lenney, 1996). L-Carnosine is known to possess free radical scavenging functions (Dahl et al., 1988; Hartman et al., 1990) and to exert neuroprotective and cardioprotective effects in phoehromocytoma PC12 cells and cardiomyoblasts exposed to hypoxia/reoxygenation, respectively (Bharadwaj et al., 2002; Tabakman et al., 2002). Moreover, it has been demonstrated that L-carnosine reduces mortality in rats after global brain ischemia (Stvolinsky et al., 2000) and overcomes ischemia/reperfusion (I/R)-induced acute renal failure (ARF) in rats (Fujii et al., 2003b).

The molecular mechanisms underlying I/R-induced ARF are not fully understood, but it has been reported that several causal factors (e.g., ATP depletion, reactive oxygen species, phospholipase activation, neutrophil infiltration, and vasoactive peptides) are contributive to the pathogenesis of this renal damage (Edelstein et al., 1997). Enhancement of renal sympathetic nerve activity (RSNA) and its consequent effect on norepinephrine (NE) overflow from nerve endings have also been considered as factors that cause the I/R-induced ARF (Baines, 1983; Iaina and Eliahou, 1983). We have found that RSNA is significantly augmented during renal ischemia and that ischemic ARF is ameliorated by renal denervation or ganglionic blockade and that the effect is accompanied by

ABBREVIATIONS: I/R, ischemia/reperfusion; ARF, acute renal failure; RSNA, renal sympathetic nerve activity; NE, norepinephrine; BUN, blood urea nitrogen; Pcr, plasma creatinine concentration; Ccr, creatinine clearance; UF, urine flow; FE Na, fractional excretion of sodium; Uosm, urinary osmolarity; R-HA, R-α-methylhistamine.
suppression of elevated renal venous NE levels immediately after reperfusion (Fujii et al., 2003a). Similar suppressive effects on renal venous NE levels have already observed in ischemic ARF rats given l-carnosine (Fujii et al., 2003b); however, it remains unknown whether this peptide can suppress enhanced RSNA during the renal ischemia. Yamano et al. (2001) reported that both central and peripheral administration of l-carnosine inhibited neural activities of sympathetic nerves innervating the adrenal gland and liver in anesthetized rats. Thereafter, they found that i.v. or i.c.v. injection of l-carnosine evoked suppression of RSNA in anesthetized rats. We have consequently obtained evidence that the enhanced RSNA during the renal ischemia is suppressed by l-carnosine i.c.v. treatment as well as i.v. treatment. These findings led us to further examine whether i.c.v. treatment with l-carnosine would attenuate the I/R-induced renal injury.

l-Carnosine is known to be hydrolyzed by a carnosinase-degrading enzyme, carnosinase, which is present in several tissues and serum of humans or animals (Lenney et al., 1985; Kunze et al., 1986; Jackson et al., 1991; Nagai et al., 2003). These findings raise a possibility that enzymatic hydrolysis of exogenous l-carnosine by carnosinase may be involved in l-carnosine actions on ischemic ARF. Therefore, we investigated the effect of N-acetyl-l-carnosine (N-acetyl-β-alanyl-l-histidine, acetyl-l-carnosine) resistant to enzymatic hydrolysis by carnosinase (Kunze et al., 1986; Babizhayev et al., 1996; Pegova et al., 2000) or l-histidine cleaved from l-carnosine by carnosinase on renal injuries induced by I/R, and the findings were compared with those observed by the l-carnosine treatment. Furthermore, we examined whether renoprotective effects of l-carnosine on ischemic ARF would be affected by a histamine H3 receptor antagonist, thioperamide, since Yamano et al. (2001) reported that the suppressive effect of l-carnosine on hyperglycemia induced by i.c.v. injection of 2-deoxy-d-glucose was attenuated by the H3 antagonist.

Materials and Methods

Animals and Experimental Design. Male Sprague-Dawley rats (280–320 g; 10 weeks of age; Japan SLC, Shizuoka, Japan) were used. The 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 (Osaka, Japan). 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, uninephrectomized rats were anesthetized with pentobarbital (50 mg/kg i.p.). Surgical preparation of the animals and basic experimental techniques were identical to those described previously (Shokoji et al., 2003). RSNA was recorded from the left renal nerve branch before and during ischemia. The nerve was isolated near the aortic-renal arterial junction through a left flank incision and placed on a Teflon-coated stainless steel bipolar electrode. The renal nerve and electrode were covered with silicone rubber. The renal nerve discharge was amplified using a differential amplifier (AVB-10; Nihon Kohden, Osaka, Japan) with a band-pass filter (low frequency, 50 Hz; high frequency, 1 kHz). The amplified and filtered signal was visualized on a dual-beam oscilloscope (VC-10; Nihon Koden) and monitored by an audio speaker. The output from the amplifier was integrated by an integrator (Nihon-Denki Sanei 1322; Nihon-Denki Sanei, Osaka, Japan) with 1-s resetting. The output from the integrator was displayed on a polygraph system recorder (Nihon-Denki Sanei SM14). For the quantification of RSNA, the height of integrated nerve discharge was measured for 30 s in each experiment. The changes in nerve activity were expressed as percentages of control resting spontaneous nerve activity. During the experiment, a polyethylene catheter inserted into the abdominal aorta through right femoral artery was connected with a Statham pressure transducer (transducer 2351D) and systemic blood pressure was continuously monitored in a multichannel polygraph (Nihon-Denki Sanei 360).

Drugs. l-Carnosine and l-histidine were obtained from Wako Pure Chemicals. Thioperamide and R-α-methylhistamine (R-HA) were...
purchased from Sigma-Aldrich (St. Louis, MO). Acetyl-l-carnosine was obtained from Suntory Co., Ltd. (Osaka, Japan). These drugs were dissolved in 0.9% saline. Other chemicals were obtained from Nacalai Tesque (Kyoto, Japan) and Wako Pure Chemicals.

Statistical Analysis. Values were expressed as means ± S.E.M. Relevant data were processed by InStat (GraphPad Software Inc., San Diego, CA). For statistical analysis, we used the unpaired Student’s t test for two-group comparison and one-way analysis of variance followed by Dunnett’s tests for multiple comparisons. Histological data were analyzed using the Kruskal-Wallis nonparametric test combined with the Steel-type multiple comparison test. For all comparisons, differences were considered significant at \( P < 0.05 \).

**Results**

**Effects of l-Carnosine on RSNA and Blood Pressure during Ischemic Period.** Typical RSNA responses to the 45-min ischemia with or without i.v. l-carnosine injection are shown in Fig. 1A. There was a marked increase in integrated RSNA (164 ± 33%), immediately after the start of ischemia, compared with the basal level. Thereafter, the increased level declined to 57 ± 11%, but significant increases lasted throughout the 45-min ischemic period. Intravenous injection of l-carnosine (1.5 and 15 nmol/rat) at 5 min before ischemia dose-dependently suppressed the enhanced RSNA during the ischemic period (Fig. 1B). Qualitatively similar results were obtained by i.c.v. injection of l-carnosine (1.5 and 5 pmol/rat), at much lower doses than those used in i.v. treatment experiments (Fig. 1C). In contrast, mean arterial pressure, during the 45-min ischemic period, was not affected by i.v. (96 ± 3 mm Hg before ischemia; 93 ± 8 mm Hg at 45 min after ischemia) or i.c.v. (102 ± 3 mm Hg before ischemia; 100 ± 4 mm Hg at 45 min after ischemia) injection of l-carnosine, even at each higher dose (i.v., 15 nmol/rat; i.c.v., 5 pmol/rat).

**Effects of Intracerebroventricular Treatment with l-Carnosine on I/R-Induced Renal Dysfunction and Histological Damage.** As shown in Fig. 2, the renal function of rats subjected to 45-min ischemia showed a marked deterioration when measured 24 h after the reperfusion. Compared with sham-operated rats, vehicle-treated ARF rats showed significant increases in BUN, Pcr, urine flow, and FENa, and significant decreases in Ccr and Uosm. Intracerebroventricular injection of l-carnosine (1.5 and 5 pmol/rat) to ischemic ARF rats dose-dependently attenuated the I/R-induced renal dysfunction. Histopathological examination revealed severe lesions in the kidney of vehicle-treated ARF rats (24 h after the reperfusion). These changes were characterized by proteinaceous casts in tubuli in the inner zone of medulla (Fig. 3B), medullary congestion, and hemorrhage in the outer zone inner stripe of medulla (Fig. 3E), and tubular necrosis in the outer zone outer stripe of medulla (Fig. 3H). Intracerebroventricular injection of l-carnosine to ischemic ARF rats dose-dependently attenuated the development of all these lesions (Table 1). Typical photographs of the l-carnosine (5 pmol/rat)-treated ARF group are shown in Fig. 3, in comparison with sham-operated control and vehicle-treated ARF groups.

**Effects of Intracerebroventricular Treatment with Acetyl-l-Carnosine or l-Histidine on I/R-Induced Renal Dysfunction and Histological Damage.** The i.c.v. injection of acetyl-l-carnosine (5 pmol/rat) that is resistant to enzymatic hydrolysis by carnosinase did not affect the renal dysfunction and tissue injury in ischemic ARF rats. Conversely, l-histidine (5 pmol/rat), a metabolite cleaved from l-carnosine by carnosinase, ameliorated the I/R-induced renal dysfunction and tissue injury, to a degree similar to findings with i.c.v. injection of l-carnosine at the same dose (Fig. 4; Table 2).
Effects of Intracerebroventricular Treatment with Thioperamide on Renal Protection by Intravenous Treatment with L-Carnosine. We next examined whether renoprotective effects of L-carnosine on ischemic ARF would be affected by thioperamide, a selective H3 receptor antagonist. The i.v. injection of L-carnosine at a dose of 15 nmol/rat significantly improved the renal dysfunction and tissue damage, as demonstrated previously (Fujii et al., 2003b). Effectiveness of this i.v. injection was similar in extent to that seen with i.c.v. injection of L-carnosine to ischemic ARF rats at a dose of 5 pmol/rat. The L-carnosine (i.v. injection)-induced improvement was dose-dependently suppressed by i.c.v. injection of thioperamide (10 and 30 nmol/rat) before L-carnosine administration (Fig. 5; Table 3).

Effects of Intracerebroventricular Treatment with R-HA on I/R-Induced Renal Dysfunction and Histological Damage. From the aforementioned results obtained by a selective H3 receptor antagonist, it is likely that the acti-
vation of H3 receptors in the central nervous system is protective for ischemic ARF. Therefore, we next examined the effect of a selective H3 agonist, R-HA, on I/R-induced renal injury 24 h after the reperfusion. As shown in Fig. 6, i.c.v. injection of R-HA (5 pmol/rat) significantly prevented the I/R-induced renal dysfunction as well as l-carnosine did at the same dose. The R-HA treatment also attenuated the development of tissue lesions such as proteinaceous casts in tubuli (scores, 3.33 ± 0.21 versus 1.33 ± 0.21), medullary congestion, and hemorrhage (scores, 3.17 ± 0.17 versus 1.33 ± 0.42), and tubular necrosis (scores, 3.50 ± 0.22 versus 1.17 ± 0.31), compared with the vehicle treatment.

**TABLE 2**

Effects of i.c.v. treatment with acetyl-l-carnosine or l-histidine on histopathological changes in the kidneys of ARF rats 24 h after I/R. Values represent the mean ± S.E.M. (n = 6) of histopathological grade. Grade: no change (0), mild (1), moderate (2), severe (3), and very severe (4).

<table>
<thead>
<tr>
<th>Experimental Group</th>
<th>Proteinaceous Casts in Tubuli</th>
<th>Medullary Congestion</th>
<th>Tubular Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARF + vehicle i.c.v.</td>
<td>3.50 ± 0.22</td>
<td>3.33 ± 0.33</td>
<td>3.50 ± 0.34</td>
</tr>
<tr>
<td>ARF + acetyl-l-carnosine 5 pmol/rat i.c.v.</td>
<td>3.33 ± 0.21</td>
<td>3.33 ± 0.42</td>
<td>3.17 ± 0.31</td>
</tr>
<tr>
<td>ARF + l-histidine 5 pmol/rat i.c.v.</td>
<td>1.33 ± 0.42**</td>
<td>1.50 ± 0.43**</td>
<td>1.67 ± 0.21**</td>
</tr>
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</table>

**P < 0.01, compared with vehicle-treated ARF rats.**
TABLE 3
Effects of i.c.v. treatment with thioperamide on renal tissue protection by i.v. treatment with l-carnosine
Values represent the mean ± S.E.M. (n = 6) of histopathological grade. Grade: no change (0), mild (1), moderate (2), severe (3), and very severe (4).

<table>
<thead>
<tr>
<th>Experimental Group</th>
<th>Proteinaceous Casts in Tubuli</th>
<th>Medullary Congestion</th>
<th>Tubular Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARF + vehicle i.v. + i.c.v.</td>
<td>3.17 ± 0.40</td>
<td>3.33 ± 0.21</td>
<td>3.67 ± 0.21</td>
</tr>
<tr>
<td>ARF + l-carnosine 15 nmol/rat i.v. + vehicle i.c.v.</td>
<td>1.00 ± 0.37**</td>
<td>1.33 ± 0.42**</td>
<td>1.17 ± 0.31**</td>
</tr>
<tr>
<td>ARF + l-carnosine 15 nmol/rat i.v. + thioperamide 10 nmol/rat i.c.v.</td>
<td>2.83 ± 0.31</td>
<td>3.17 ± 0.31</td>
<td>3.33 ± 0.21</td>
</tr>
<tr>
<td>ARF + l-carnosine 15 nmol/rat i.v. + thioperamide 30 nmol/rat i.c.v.</td>
<td>3.33 ± 0.33</td>
<td>3.33 ± 0.33</td>
<td>3.83 ± 0.17</td>
</tr>
</tbody>
</table>

** P < 0.01, compared with untreated ARF rat.

Discussion

It has been pointed out that NE overflow into the renal vein can be useful to assess RSNA, since there is a significant linear relationship between the frequency of stimulation and NE concentrations in renal venous plasma, when renal nerves were electrically stimulated in anesthetized dogs (Oliver et al., 1980). Renal sympathetic nervous system and circulating catecholamines are considered to be involved in the pathogenesis of ARF (Baines, 1983; Iaina and Eliahou, 1983). Recently, one of our studies revealed that RSNA was significantly augmented during renal ischemia and that NE overflow into the renal vein was markedly increased immediately after the reperfusion following 45-min ischemia; the increased level lasted for 24 h after the reperfusion (Fujii et al., 2003a). The increases in the NE overflow were shown to be suppressed by i.v. treatment with RSNA of ischemic ARF rats (Fujii et al., 2003b). In the present study, we therefore investigated whether i.v. injection of l-carnosine could suppress the augmented RSNA during the ischemia period in anesthetized rats. Results clearly indicated that i.v. injection of l-carnosine was capable of suppressing the ischemia-enhanced RSNA. Thus, it is reasonable to consider that renoprotective effects of l-carnosine on ischemic ARF result from its suppressive action on the ischemia-enhanced RSNA followed by NE spillover from the nerve endings of the posts ischemic kidney.

In the present study, we observed that enhanced RSNA during the 45-min ischemic period was also suppressed by i.c.v. injection of l-carnosine to anesthetized rats. Interestingly, the suppressive effects were qualitatively similar to those obtained by i.v. injection of l-carnosine (1.5–15 nmol/rat), at doses less than or equal to 5 pmol/rat. The findings led us to investigate whether i.c.v. treatment with l-carnosine of ARF rats would prevent the I/R-induced renal injury. We obtained evidence that the i.c.v. treatment markedly overcomes I/R-induced renal dysfunction and histopathological damage, such as proteinaceous casts in tubuli, medullary congestion, and tubular necrosis. Therefore, these results indicate that l-carnosine's actions on the central nervous system may cause the suppression of enhanced RSNA during the ischemic period, and the effect would eventually improve the I/R-induced renal injury.

l-Carnosine possesses antioxidative and free radical scavenging functions (Dahl et al., 1988; Hartman et al., 1990). Stvolinsky et al. (2000) have indicated that l-carnosine administered intraperitoneally to rats at a dose of 150 mg/kg (the dose corresponds to approximately 660 μmol/kg; approximately 132–165 μmol/rat weighing 200–250 g) reduces the mortality of rats after global brain ischemia induced by occlusion of the carotid arteries and noted that this action of l-carnosine is due to its antioxidative effect. In the present study, we found that even at much lower doses (i.v. injection, 15 nmol/rat; i.c.v. injection, 1.5–5 pmol/rat), l-carnosine could efficiently prevent the I/R-induced ARF, accompanying the
suppressive action on ischemia-enhanced RSNA. It is therefore conceivable that l-carnosine exerts an inhibitory action on enhanced RSNA during the renal ischemia at much lower doses, independently of its antioxidative characteristic. However, a possibility that l-carnosine improves the I/R-induced renal injury, at least in part, via its antioxidative activity cannot be ruled out, because oxidative stress is definitely involved in the pathogenesis of ischemic ARF (Chatterjee et al., 2000; Takaoka et al., 2002).

l-Carnosine is decomposed to β-alanine and l-histidine by a carnosine-degrading enzyme, carnosinase, which is present in serum and several tissues (Lenney et al., 1985; Kunze et al., 1986; Jackson et al., 1991; Nagai et al., 2003). In rat brain, two types of carnosine-degrading enzymes are present: one enzyme is carnosinase, which preferentially hydrolyzes carnosine, and the other enzyme hydrolyzes β-alanyl-l-arginine considerably faster than carnosine, both of which do not degrade acetyl-l-carnosine (Kunze et al., 1986). The potential antioxidant activity of l-carnosine in vivo is limited by its susceptibility to hydrolysis by carnosinase. In contrast, acetyl-l-carnosine is resistant to enzymatic hydrolysis by carnosinase (Kunze et al., 1986; Babizhayev et al., 1996; Pegova et al., 2000) and is proposed to treat ocular disorders as an antioxidant (Babizhayev et al., 1996). In the present study, we made an attempt using acetyl-l-carnosine to clarify the mechanisms for the renoprotective effect of l-carnosine on ischemic ARF, and we found that i.c.v. injection of acetyl-l-carnosine could not improve renal dysfunction and degeneration in rats with I/R-induced ARF, very different from the case of l-carnosine. Taken together, it seems likely that preventive effects of i.c.v. treatment with l-carnosine on the I/R-induced renal injury are independent of its antioxidative activity and that a difference between l-carnosine and acetyl-l-carnosine in the effect on ischemic ARF is probably dependent on the enzymatic hydrolysis by carnosine-degrading enzymes in the brain. This view is supported by the observation that i.c.v. injection of l-histidine, a metabolite cleaved from l-carnosine by carnosinase, ameliorated the I/R-induced renal dysfunction and tissue damage to a degree similar to findings with i.c.v. injection of l-carnosine at the same dose.

In the present study, we obtained evidence that the renoprotective effect of i.v. treatment with l-carnosine on ischemic ARF is markedly suppressed by i.c.v. injection of a histamine H3 receptor antagonist thioperamide. Taken together with the results obtained by i.c.v. injection of l-histidine, it seems likely that peripherally administered l-carnosine is partly degraded by carnosinase, the resultant l-histidine is converted to l-histamine by histidine decarboxylase in the brain, and the produced l-histamine mediates the renoprotective effects of l-carnosine on ischemic ARF via the activation of H3 receptors, although there is no available evidence regarding the conversion of peripherally administered l-carnosine to l-histamine and the blood-brain barrier penetration of this peptide.

In the central nervous system, histamine H3 receptors are located on histaminergic nerve endings and act as presynaptic autoreceptors, which modulate the release of histamine (Arrang et al., 1983). Presynaptic H3 receptors are also present on nonhistaminergic nerves such as serotonergic, noradrenergic, cholinergic, and dopaminergic nerves (for review, see Hill et al., 1997). In the present study, we investigated the possible involvement of central histamine H3 receptors in the pathogenesis of ischemic ARF, and we obtained evidence that a selective H3 receptor agonist, R-HA, can efficiently prevent the I/R-induced renal dysfunction and tissue damage at a dose of 5 pmol/rat as well as l-carnosine did. The findings suggest that activation of the central histamine/H3 receptor system is protective for the development of I/R-induced renal injury. Thus, one possible mechanism whereby l-carnosine ameliorates renal dysfunction and degeneration in ischemic ARF is attributed to the suppression of enhanced RSNA during the renal ischemia, via the activation of H3 receptors in the central nervous system by l-histamine converted from l-carnosine. While the present work was in progress, Tanida et al. (2005) indicated that bilateral lesions of the hypothalamic suprachiasmatic nucleus, which is identified as origins of the autonomic nerves (Buïjs et al., 2003), eliminated effects of l-carnosine on RSNA in anesthetized rats, thereby suggesting that hypothalamic suprachiasmatic nucleus is involved in the effective mechanism of l-carnosine on RSNA. Therefore, it is possible that hypothalamic suprachiasmatic nucleus is responsible for the renoprotective effects of l-carnosine on ischemic ARF. Further studies are required to clarify the role of histamine or the site on which l-carnosine acts in the central nervous system, in the pathogenesis of ischemic ARF.

In conclusion, our results indicate that l-carnosine can suppress increased RSNA during the renal ischemia by its action on the central nervous system and that this suppressive effect is probably responsible for the renoprotection against I/R-induced renal injury. In addition, the renoprotective effect of l-carnosine on ischemic ARF seems to be induced by its conversion to l-histidine and l-histamine, and it is mediated through the activation of histamine H3 receptors in the central nervous system.

References


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