Short Communication

Captopril Enhances Cardiac Vagal but Not Sympathetic Neurotransmission in Pithed Rats

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Abstract. The effect of captopril on neurally evoked bradycardia and tachycardia was investigated in pithed rats. Captopril enhanced the vagal nerve stimulation-evoked bradycardia. Angiotensin I reduced the vagal bradycardia, which was reversed by subsequent administration of captopril. Bradykinin did not affect the neurally evoked bradycardia. Captopril and angiotensin I affected neither the exogenous acetylcholine-evoked bradycardia nor the sympathetic nerve stimulation-evoked tachycardia. These results suggest that the interruption of angiotensin II formation by captopril causes less presynaptic inhibition of acetylcholine release via angiotensin II receptors without affecting cardiac sympathetic neurotransmission.

Keywords: captopril, autonomic neurotransmission, rat heart

Angiotensin-converting enzyme (ACE) inhibitors such as captopril are useful for the treatment of hypertension. The hypotension induced by ACE inhibitors is not accompanied by a reflex tachycardia (1), although they do not impair a baroreflex function (2). Reflex tachycardia as a consequence of hypotension results from both increased sympathetic activity and decreased vagal one. We previously showed that angiotensin II receptor antagonists inhibited the facilitatory action of angiotensin II on the electrically stimulated norepinephrine release in perfused rat hearts (3), while they did not affect the tachycardia induced by sympathetic nerve stimulation in pithed rats (4). Although vagal efferent activity plays an important role in regulating heart rate change in a number of autonomic reflexes (5), there are few reports on effects of ACE inhibitors on the cardiac vagal neurotransmission. In the present study, we investigated the action of captopril on both bradycardia and tachycardia induced by vagal and sympathetic nerve stimulations, respectively, in pithed rats in order to elucidate the reasons why captopril is devoid of the reflex tachycardia.

Male Wistar rats (Nihon SLC Co., Shizuoka), weighing 300–400 g, were anesthetized with urethane + α-chloralose (0.6 g/kg + 0.06 g/kg, i.p.). The left femoral artery and both femoral veins were cannulated to measure blood pressure and to administer drugs, respectively. Both vagal nerves were cut in the neck, and both adrenals were removed. After tracheal cannulation, the rats were artificially ventilated with room air and were pithed according to the method of Hosono et al. (6) with minor modifications. Bradycardic and tachycardic responses were obtained by stimulating the peripheral end of the left vagal nerve through bipolar platinum electrodes and by stimulating the C7-T1 regions of the spinal cord through the pithing rod, respectively, with an electric stimulator (SEN-7103; Nihon Kohden, Tokyo). Stimulation parameters to produce bradycardia and tachycardia were 5 Hz, 0.2 ms, 30 V, 150 pulses and 2 Hz, 0.1 ms, 60 V, 60 pulses, respectively. The bradycardia and tachycardia induced by these stimulation conditions corresponded to about 50–60% of the largest and reproducible responses to electrical stimulations. In the present study, we investigated the action of captopril on both bradycardia and tachycardia induced by vagal and sympathetic nerve stimulations, respectively, in pithed rats in order to elucidate the reasons why captopril is devoid of the reflex tachycardia.

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pressure waves and was recorded on an ink-writing oscillograph (WI-640G, Nihon Kohden). Rectal temperature was maintained at 37 – 38°C. All rats were allowed 30 – 60 min to recover from preparatory surgery and then received (+)-tubocurarine (1 mg/kg, i.v.) to prevent muscle movement during electric stimulations. In bradycardia experiments, rats also received propranolol (1 mg/kg, i.v.) to exclude β-adrenoceptor-mediated effects. The vagal nerve stimulation (VNS) and the sympathetic nerve stimulation (SNS) were applied at 4- and 8-min intervals, respectively, until obtaining two reproducible responses, and the average of the two responses was regarded as the control value. Thereafter, drugs were intravenously injected or infused, and the VNS and SNS were further applied 7 and 4 times at the same interval as mentioned above, respectively, from 10 min after onset of drug administration. Each experiment was carried out with a separate rat. The studies were performed according to the guidelines of the Animal Care and Use Committee of Teikyo University. All drugs used in the present study were purchased from Sigma Chemicals (St. Louis, MO, USA). Statistical analyses were performed using ANOVA followed by Dunnett’s test for multiple comparisons. A value of $P<0.05$ was considered significant.

VNS decreased heart rate by 45 ± 1 beats/min (from basal value of 383 ± 4 to 338 ± 4 beats/min, n = 35). As shown in Fig. 1, a bolus injection of captopril (1 – 10 mg/kg, i.v.) significantly augmented the VNS-evoked bradycardia over seven successive stimulations in a dose-dependent manner. Intravenous infusion of bradykinin (1 μg/kg per min) did not affect the VNS-evoked bradycardia (Fig. 1). The dose of bradykinin was similar to that used by Dendorfer et al. (7). Angiotensin I infusion (200 ng/kg per min, i.v.) significantly inhibited the VNS-evoked bradycardia, which was significantly reversed by the subsequent administration of captopril (10 mg/kg, i.v.) (Fig. 2). Captopril, bradykinin, or...
angiotensin I caused no significant change in basal heart rate (data not shown). To evaluate whether the effects of captopril and angiotensin I on the VNS-evoked bradycardia occur by acting on the postsynaptic site, their effects on the bradycardia induced by exogenous acetylcholine (ACh) were studied. ACh was intravenously infused twice, for 5 min each time, at 5-min intervals, and SNS was applied at 8-min intervals until obtaining two reproducible responses. In each case, the average of the two responses was regarded as the control value. Thereafter, ACh infusion and SNS were applied 3 and 4 times, respectively, from 10 min after a bolus dose of captopril or onset of angiotensin I infusion. The control values of the ACh-evoked bradycardia in saline, captopril, and angiotensin I groups were 44 ± 6, 41 ± 3, and 36 ± 3 beats/min, respectively. The control values of the SNS-evoked tachycardia in saline, captopril, and angiotensin I groups were 82 ± 9, 91 ± 10, and 99 ± 15 beats/min, respectively. Values are expressed as means ± S.E.M. from five rats.

![Fig. 3. Effects of captopril and angiotensin I on the bradycardia evoked by intravenously infused acetylcholine (ACh) (A) and the tachycardia evoked by sympathetic nerve stimulation (SNS) (B) in pithed rats. ACh was intravenously infused twice, for 5 min each time, at 5-min intervals, and SNS was applied at 8-min intervals until obtaining two reproducible responses. In each case, the average of the two responses was regarded as the control value. Thereafter, ACh infusion and SNS were applied 3 and 4 times, respectively, from 10 min after a bolus dose of captopril or onset of angiotensin I infusion. The control values of the ACh-evoked bradycardia in saline, captopril, and angiotensin I groups were 44 ± 6, 41 ± 3, and 36 ± 3 beats/min, respectively. The control values of the SNS-evoked tachycardia in saline, captopril, and angiotensin I groups were 82 ± 9, 91 ± 10, and 99 ± 15 beats/min, respectively. Values are expressed as means ± S.E.M. from five rats.](image-url)

ACE is responsible for both angiotensin II formation.
and bradykinin breakdown. However, the blockade of bradykinin degradation by captopril is unlikely to be involved in its bradycardia-enhancing action because bradykinin infusion failed to affect the VNS-evoked bradycardia. Although serum acetylcholinesterase shares features common to peptidase which degrades substance P (10) and ACE breaks down substance P, cholinesterase inhibition is not responsible for enhancement of the VNS-evoked bradycardia by captopril because captopril did not alter the bradycardia induced by ACh which is sensitive to cholinesterase.

In contrast to their effects on the bradycardic response to vagal stimulation, neither captopril nor angiotensin I affected the SNS-evoked tachycardia. These results imply that the renin-angiotensin system does not influence cardiac sympathetic neurotransmission in pithed rats, as previously demonstrated by other investigators (11–13). The reason of the inability of captopril and angiotensin I to affect the SNS-evoked tachycardia is unclear. Pithed rats have a high activity of the renin-angiotensin system (14). If the activity of this system already reaches a maximal level in pithed rats, then angiotensin II formed from exogenous angiotensin I would exhibit no additional action. However, this is not true because angiotensin I inhibited the VNS-evoked bradycardia.

The present study suggests that angiotensin II converted from angiotensin I may inhibit ACh release toward the sinus node, presumably through presynaptic angiotensin II receptors on the vagal nerve endings and that captopril may enhance cardiac vagal neurotransmission by interrupting angiotensin II production. This action of captopril seems to contribute to the lack of reflex tachycardia. On the other hand, angiotensin II facilitates vascular sympathetic neurotransmission via presynaptic angiotensin II receptors (15). Thus, these presynaptic receptors on cardiac vagal and vascular sympathetic nerve endings have an opposite function in regulating neurotransmitter release, and stimulation of these presynaptic receptors by angiotensin II leads to tachycardia or high blood pressure.

In conclusion, the interruption of angiotensin II production by captopril causes less presynaptic inhibition of acetylcholine release through cardiac angiotensin II receptors without affecting cardiac sympathetic neurotransmission, the effect of captopril being contributory to the lack of baroreceptor-mediated tachycardia.

References