Influence of sympathetic blockade on the acute hypertensive response to aortic constriction

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Influence of sympathetic blockade on the acute hypertensive response to aortic constriction. Am. J. Physiol. 273 (Heart Circ. Physiol. 42): H2648–H2651, 1997.—The objective of the present study was to determine the contribution of the sympathetic nervous system to the hypertensive response to acute (45-min) aortic coarctation in conscious intact or sinoaortic-denervated (SAD) rats. Rats were treated chronically (5 wk) with guanethidine (50 mg·kg−1·day−1 ip) to induce sympathetic nerve degeneration or acutely with the α1-adrenergic receptor antagonist prazosin (1 mg/kg iv). Aortic coarctation elicited a prompt and sustained rise in mean carotid pressure that was significantly greater in SAD than in intact rats. The increase in pressure was associated with reflex bradycardia only in the intact rats, whereas the heart rate of SAD rats did not change. Guanethidine treatment did not affect the arterial pressure or heart rate responses to aortic coarctation of intact rats but blunted the hypertensive response of SAD rats to the same values exhibited by intact rats. Prazosin administered 10 min after the beginning of aortic coarctation reduced the hypertensive response of SAD rats to the same level as that of intact rats. In conclusion, the data obtained by means of the sympathetic nervous system, via the renal nerves, and sinoaortic denervation; sympathetic activity; reflex bradycardia; guanethidine; prazosin

PARTIAL AORTIC CONSTRICTION proximal to the renal arteries elicited a prompt and sustained (45-min) rise in carotid pressure associated with a stable reflex bradycardia in conscious intact rats (16, 17). This rise in arterial pressure has been attributed to the sudden increase in impedance to aortic flow and associated neurohumoral responses involving, particularly, angiotensin (16, 23) and vasopressin (5, 15, 17), whereas the stable reflex bradycardia is mediated mainly through vagal activation (8, 19, 20).

The model of abdominal aortic coarctation hypertension is somewhat similar to one-kidney, one-clip hypertension, since in both models the kidneys are under low perfusion pressure. In the latter model a sympathoexcitatory vasoconstrictor reflex (renal pressor reflex) has been shown to be triggered (2–4), suggesting that a similar reflex could be triggered by aortic coarctation. Moreover, there is a body of evidence indicating that the sympathetic nervous system, via the renal nerves, plays an important role in the pathogenesis of renovascular hypertension in humans and laboratory animals (12, 22). However, occlusion of the descending aorta in anesthetized cats inhibits almost completely sympathetic renal nerve activity (11). In addition, conscious rats submitted to an acute (45-min) aortic coarctation hypertension exhibited a marked decrease in plasma norepinephrine concentration that was attributed to reflexly mediated inhibition of the sympathetic outflow by the sinoaortic baroreceptors (18).

The objective of the present study was to evaluate the contribution of the sympathetic nervous system to the hypertensive response to acute (45-min) aortic coarctation in conscious rats with intact baroreceptors or with sinoaortic denervation to preclude any inhibitory influence of the baroreceptors on sympathetic activity.

METHODS

Experiments were conducted on male Wistar rats (280–320 g) receiving standard laboratory rat chow and water. Two days before the experiment the rats were anesthetized with pentobarbital sodium (40 mg/kg ip), and after laparotomy a pneumatic cuff was implanted around the aorta immediately below the diaphragm, as described elsewhere (17, 18). The tubing connected to the cuff was exteriorized through the animal’s back. On the day before the experiment the rats were anesthetized with ether and submitted to sham operation or sinoaortic deafferentation according to the technique described by Krieger (7), and polyethylene catheters were inserted into the femoral artery and left carotid artery for arterial pressure measurement. In some animals a catheter was inserted into the femoral vein for drug injection. The distal ends of the catheters were exteriorized through the animal’s back, together with the tubing connected to the cuff. The experiments were conducted with the animals unrestrained in individual cages in a quiet environment. Carotid and femoral arterial pressures were measured continuously with a pressure transducer (model P23Gb, Statham, Hato Rey, PR), and the signal was recorded with a thermal recorder (model 7848, Hewlett-Packard, Palo Alto CA). Heart rate (HR) was determined by counting arterial pulses at higher recorder speed.

Experimental protocol. After basal measurement of carotid pressure and HR, the balloon inside the cuff was filled with liquid to partially constrict the aorta and thus maintain the arterial pressure distal to the cuff (mean femoral pressure) precisely at 50 mmHg for 45 min. Aortic coarctation was performed (n = 7 in each group) in intact (sham-operated) and sinoaortic-denervated (SAD) rats treated or not with guanethidine (50 mg·kg−1·day−1 ip; Sigma Chemical, St. Louis, MO) for 5 days/week for 5 wk (6), which destroys sympathetic neurons. Sympathectomy induced by guanethidine was verified on the day of the experiment by the abolition of the pressor response due to the release of catecholamines from the nerve endings caused by tyramine (100 μg iv) (21). In another series of experiments the acute hypotensive effect due to the selective pharmacological blockade of α1-adrenergic receptors with prazosin (1 mg/kg iv) was examined in
intact (n = 5) and SAD (n = 6) rats 10 min after the beginning of aortic coarctation; during this period the increase in arterial pressure was already established and the effect of prazosin was observed over the next 15 min.

Values are means ± SE. Statistical analysis of the hypertensive response and of changes in HR in response to aortic coarctation was performed by two-way analysis of variance for repeated measures. If differences between groups were observed, the means for each period were compared by Duncan’s test. Differences were considered significant if P < 0.05.

RESULTS

Effect of chronic sympathectomy on the hypertensive response of SAD rats to aortic coarctation. The hypertensive response after sustained (45-min) aortic coarctation in untreated SAD and intact rats is shown in Fig. 1, top. Basal mean carotid pressure (MCP) measured before aortic coarctation did not differ between groups (107 ± 1 vs. 116 ± 4 mmHg in SAD rats). Five minutes after aortic coarctation, MCP had already reached a plateau and remained close to this level throughout the experimental period (45 min). However, the increase in MCP was much higher in SAD than in intact rats (170 ± 4 vs. 147 ± 2 mmHg 5 min after coarctation). The corresponding HR of both groups before and after aortic coarctation is shown in Fig. 1, bottom. The basal HR before aortic coarctation was higher in SAD rats (470 ± 13 beats/min) than in intact rats (369 ± 6 beats/min). However, whereas intact rats presented a conspicuous and maintained reflex bradycardia after coarctation, the HR of SAD rats did not change throughout the period of observation regardless of the increase in pressure elicited by aortic coarctation.

The hypertensive response to aortic coarctation of guanethidine-treated intact and SAD rats is shown in Fig. 2, top. Basal MCP measured before coarctation was similar in both groups (110 ± 3 vs. 107 ± 3 mmHg in SAD rats). Guanethidine treatment did not affect the hypertensive response of intact rats but significantly blunted the response of SAD rats, whose response did not differ from that of intact treated rats (152 ± 2 vs. 146 ± 4 mmHg in SAD rats 5 min after coarctation). Basal HR (Fig. 2, bottom) differed significantly between these groups (387 ± 6 vs. 425 ± 12 beats/min in guanethidine-treated SAD rats). However, whereas intact guanethidine-treated rats showed a significant reflex bradycardia during aortic coarctation, the HR of guanethidine-treated SAD rats did not change throughout the experimental period.
Effect of prazosin on hypertensive response of SAD rats to aortic coarctation. The effect of the α₁-receptor antagonist prazosin on the hypertensive response of SAD and intact rats to aortic coarctation is shown in Fig. 3, top. The increase in MCP after 10 min of aortic coarctation was significantly greater in SAD rats (from 116 ± 6 to 179 ± 4 mmHg) than in intact rats (from 108 ± 3 to 150 ± 2 mmHg). Prazosin injected intravenously did not affect the hypertensive response of intact rats, which remained stable up to the end of the experimental period. In contrast, after prazosin the MCP of SAD rats declined rapidly to values similar to those for the intact group. The corresponding time course of HR for these groups is shown in Fig. 3, bottom. As observed earlier, the basal HR was higher in SAD rats (418 ± 15 beats/min) than in intact rats (329 ± 11 beats/min). The reflex bradycardia of intact rats was not affected by prazosin, and the HR of SAD rats was not affected by the increase in MCP after aortic coarctation or by prazosin.

DISCUSSION

The present study confirms our previous reports showing that partial aortic constriction proximal to the renal arteries elicited a prompt and sustained (45-min) rise in MCP associated with a stable reflex bradycardia in conscious intact rats (16, 17). On the other hand, SAD rats presented a higher hypertensive response without reflex bradycardia. The maintenance of MCP at ~170 mmHg in SAD rats during a period of 45 min without any change in HR indicated total sinoaortic deafferentation. To compare the role of sympathetic activity in the hypertensive response to aortic constriction in SAD and intact rats, the experiments were performed on animals submitted to chronic (5-wk) sympathectomy with guanethidine or acute α₁-adrenergic receptor blockade with prazosin. Basal MCP and HR were not affected by 5 wk of treatment with guanethidine in intact or SAD rats, confirming previous reports (9). Chronically sympathectomized SAD rats showed a lower hypertensive response to aortic constriction than untreated rats; in fact, they exhibited a hypertensive response similar to that of intact rats but unaccompanied by reflex bradycardia. These findings suggest that the higher hypertensive response of SAD rats involves an effective contribution by sympathetic nervous activity. It is also noteworthy that chronically sympathectomized intact rats exhibited a hypertensive response and reflex bradycardia similar to those observed in untreated intact rats. It has been demonstrated that chronic administration of guanethidine to adult rats depletes only tissue catecholamines for several months after the end of the treatment (6). Therefore, the occurrence of reflex bradycardia in chronically sympathectomized rats indicates that baroreceptor afferents as well as vagal efferents were unaffected by guanethidine treatment.

In the model of abdominal aortic coarctation hypertension, the kidneys are under low perfusion pressure so that a sympathoexcitatory vasoconstrictor reflex (renal pressor reflex) can be triggered (2–4). As observed with stenosis of the renal artery in conscious rats, suprarenal aortic constriction may activate renal R₂ chemoreceptors (13, 14) by decreasing glomerular filtration rate and tubular fluid flow (1). This mechanism would trigger a renal pressor reflex, which causes sympathetic activation and a sustained increase in blood pressure, particularly in the absence of baroreflex. The fact that chronic sympathectomy blunted the enhanced hypertensive response to aortic constriction observed in the absence of the sinoaortic baroreceptors indicates that the sympathetic nervous system contributes to the hypertensive response of SAD rats.

The role of sympathetic activity during aortic coarctation in conscious SAD and intact rats was also examined by the acute administration of the α₁-receptor antagonist prazosin. Thus prazosin reduced the hypertensive response of SAD and intact rats to the same level, which is consistent with the findings obtained for chronically sympathectomized SAD rats. Likewise, the lack of effect of prazosin on the hypertensive response of rats with intact arterial baroreceptors supports the hypothesis of an efficient role for the arterial baroreceptors in buffering the pressor response to aortic coarctation by inhibition of the sympathetic nervous system.
We previously (18) demonstrated that conscious intact animals exhibited a significant decrease in plasma norepinephrine levels during 45 min of aortic coarctation. This finding indicated that sympathetic nervous activity was effectively attenuated by the arterial baroreceptors, with this vasopressor system playing no role in this model of hypertension when the arterial baroreceptors are intact. The similarity of the pattern of hypertensive response observed with chronic sympathectomy (guanethidine) and acute α1-receptor blockade (prazosin) precludes any secondary effect, e.g., fluid balance and altered vessel responsiveness to agonists, that might be caused by chronic guanethidine treatment.

In considering the pathophysiological implications of the data obtained in the present study, it is of interest that the sympathetic nervous system participates as a short-term regulator of arterial pressure and hypertension (10). In fact, it has been shown that young mildly hypertensive patients (10) and patients with established renovascular hypertension (22) display elevated sympathetic nervous system activity.

In conclusion, the data obtained in the present study by combining sinoaortic deafferentation with chronic sympathectomy with guanethidine or acute α1-receptor blockade (prazosin) indicate that the greater hypertensive response of SAD rats involves sympathetic activation, unmasked by the removal of the arterial baroreceptors, in the maintenance of the rise in pressure due to aortic coarctation. In addition, the results also highlight the importance of the arterial baroreceptors in preventing increases in sympathetic drive triggered by different stimuli such as low renal perfusion pressure.

The authors gratefully acknowledge the excellent technical assistance of Mauro de Oliveira.

This research was supported by Fundação de Amparo a Pesquisa do Estado de São Paulo Grant 1995/4685–8, the Conselho Nacional de Desenvolvimento Científico e Tecnológico, Financiadora de Estudos e Projetos Grant PRONEX-357/96, and the Coordenadoria de Aperfeiçoamento de Pessoal de Nível Superior.

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Received 5 March 1997; accepted in final form 12 August 1997.

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