Chemical Renal Medullectomy and Arterial Pressure Response to Sinoaortic Denervation

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We investigated in conscious Wistar-Kyoto rats the effect of chemical renal medullectomy on the responses of mean arterial pressure, arterial pressure lability, and heart rate to sinoaortic deafferentation (SAD). Chemical medullectomy was obtained by the intravenous administration of 2-bromoethylamine hydrobromide (2-BEA) 2–3 weeks before SAD or sham SAD. Chemically medullectomized rats were compared with control rats treated with saline. In control rats, the increase in mean arterial pressure elicited by SAD was not significantly greater than that produced by sham SAD. In medullectomized rats, SAD significantly increased mean arterial pressure compared with sham SAD. No direct relation was observed between the response of mean arterial pressure to SAD and the grade (1, 2, or 3) of lesion of the renal papilla. In control rats, SAD increased significantly arterial pressure lability. Chemical medullectomy did not affect basal lability or the increased lability after SAD. No direct relation was observed between increased arterial pressure lability due to SAD and the grade of lesion of the renal papilla. SAD produced a conspicuous tachycardia in control rats. Chemical medullectomy did not affect basal heart rate or the tachycardia produced by SAD. No direct relation was observed between the extent of this tachycardia and the grade of lesion of the renal papilla. These data indicate that lesions of the renal papilla lead to a significant increase in mean arterial pressure after SAD, without affecting basal pressure or heart rate. In addition, SAD per se did not increase significantly the mean arterial pressure in control rats. In conclusion, chemical ablation of the renal medulla seems to render rats more sensitive to a hypertensive stimulus such as SAD, and the mechanism probably involves the lack of the suppressive effect of medullipin II on sympathetic activity.

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The kidney controls blood pressure by two major mechanisms, the renin-angiotensin system and the fluid-electrolyte balance. However, an opposing system of blood pressure control within the kidney working as a feedback to the renin-angiotensin system has been proposed by Muirhead. This is the medullipin system of blood pressure control. Homotransplants or autotransplants of renomedullary tissue as well as transplants of renomedullary interstitial cells grown in tissue culture exhibit a powerful antihypertensive action in several models of hypertension (compare Reference 2). The hormonal components of the medullipin system are medullipin I, which is secreted by the renomedullary interstitial cells of the renal papilla, and medullipin II, to which the former is converted within the liver. Medullipin II is a vasodilator that, in addition to causing diuresis/natriuresis, has a suppressive effect on sympathetic tone and on the central nervous system. Damage to the renal medulla induced by chemical means causes hypertension on its own and exacerbates two-kidney, one clip Goldblatt hypertension. On the other hand, there is no general agreement in the literature about whether sinoaortic deafferentation (SAD) causes a true and sustained hypertension, despite evidence that sympathetic activity may remain high. Nevertheless, there is general agreement that SAD causes a conspicuous variability of arterial pressure referred to as arterial pressure lability.

Because chemical renal medullectomy may cause the experimental subjects to become more sensitive to hypertensive stimuli, we investigated whether chemical lesion of the renal medulla with 2-bromoethylamine hydrobromide (2-BEA) affects the responses of mean arterial pressure (MAP), arterial pressure lability, and heart rate (HR) to SAD.
Methods

The studies were performed in conscious Wistar-Kyoto rats weighing 200–300 g. Ether anesthesia was used for all surgical procedures. The animals received either an intravenous (penile vein) injection of a fresh solution of 2-BEA (250 mg/kg; Sigma Chemical Co., St. Louis, Mo.) or 0.9% saline. Eight groups were studied. Group 1 (six rats treated with saline plus sham SAD) and group 2 (10 rats treated with saline plus SAD) were the control groups. Animals submitted to chemical renal medullectomy were separated into six groups based on the extent of damage to the renal papilla by 2-BEA according to the classification of Davies and Tange. Group 3 comprised eight rats with grade 1 lesions plus sham SAD, and group 4 comprised seven rats with grade 1 lesions plus SAD. Group 5 contained six rats with grade 2 lesions plus sham SAD, and group 6 contained eight rats with grade 2 lesions plus SAD. Group 7 was made up of six rats with grade 3 lesions plus sham SAD, and group 8 was made up of eight rats with grade 3 lesions plus SAD.

Polyethylene catheters (PE-10 connected to PE-50; Clay Adams, Parsippany, N.J.) were inserted into the abdominal aorta through the femoral artery for arterial pressure recording and into the femoral vein for drug administration. The cannulas were brought underneath the skin to exit at the nape. The experiments were conducted on conscious animals unrestrained in individual cages. Femoral arterial pressure was recorded continuously with a pressure transducer (model P23-Db, Statham, Hato Rey, Puerto Rico) attached to a thermal recorder (model 7848, Hewlett-Packard Co., Palo Alto, Calif.). MAP was electronically derived and simultaneously recorded with pulsatile femoral arterial pressure. MAP was sampled every 5 seconds during a 30-minute period to provide a measurement of arterial pressure lability. Arterial pressure lability is expressed as the standard deviation of MAP. HR was measured by counting arterial pulses at high recorder speed.

SAD was performed according to the technique described by Krieger. The efficacy of SAD was tested by evaluating the chronotropic baroreceptor reflex responses to an intravenous injection of 3–5 g/kg phenylephrine or 4–6 g/kg sodium nitroprusside (both from Sigma). Rats that presented reflex bradycardia with change of less than 24 beats per minute to an increase in MAP of 30–50 mm Hg or reflex tachycardia with change of less than 24 beats per minute to a decrease in MAP of 30–50 mm Hg were considered to have adequate SAD.

The experimental protocol consisted of an intravenous injection of 2-BEA or saline 2–3 weeks before the experiment. The day before the experiment, anesthetized rats were cannulated with the arterial and venous catheters. Twenty-four hours after cannulation, control measurements of MAP, arterial pressure lability, and HR were obtained for at least 30 minutes. The chronotropic baroreceptor reflex responses to an intravenous injection of phenylephrine or sodium nitroprusside were then evaluated. After the chronotropic baroreceptor reflex test, the rats were submitted to SAD or sham SAD. On the following day, the rats were submitted to another session of MAP, arterial pressure lability, and HR recording, followed by the chronotropic baroreceptor reflex test. At the end of the experiment the animals were killed under ether anesthesia; the kidneys were removed and examined macroscopically, incised and fixed by immersion in alcoholic Bouin’s solution, embedded in parafin and cut into 4-μm sections, stained with hematoxylin and eosin, and examined under the light microscope.

Statistical analysis. The results of MAP and HR are expressed as mean±SEM. The data were subjected to a specific statistical testaccording to the protocol. The effect of 2-BEA on MAP and HR was analyzed using Wilk’s test. The effect of SAD was compared with that of sham SAD using Student’s unpaired t test, whereas MAP and HR in the SAD rats were compared using the Kruskal-Wallis test. Finally, the arterial pressure lability data were subjected to the Newman-Keuls test. Differences were considered significant if p<0.05.

Results

The effects of chemical renal medullectomy (separated according to the grade of lesion) associated with SAD on MAP are presented in Figure 1. In control rats as well as in medullectomized rats, basal MAP did not differ significantly between SAD and sham SAD groups (range, 103±2 to 110±2 mm Hg). SAD alone did not significantly increase basal MAP (ΔMAP, 11±3 mm Hg) compared with sham SAD (ΔMAP, 4±3 mm Hg). Chemical medullectomy 2–3 weeks before the experiment did not affect basal MAP (range, 103±2 to 110±2 mm Hg) compared with the control groups. Regardless of the grade of lesion of the renal papilla, SAD significantly raised MAP (range of ΔMAP, 15±3 to 18±4 mm Hg) compared with sham SAD (range of ΔMAP, 3±2 to 4±3 mm Hg).

The effects of chemical renal medullectomy associated with SAD on arterial pressure lability and HR are presented in Figure 2. SAD significantly increased lability (range, 15±2 to 17±3 mm Hg) regardless of chemical medullectomy. Sham SAD did not affect arterial pressure lability (range, 3±0.4 to 4±0.6 mm Hg) in either control or medullectomized groups. In control rats, arterial pressure lability was increased approximately fourfold by SAD (17±1 mm Hg after versus 4±0.2 mm Hg before), whereas sham SAD did not affect lability (4±1 mm Hg before and after). Chemical renal medullectomy did not affect the increased arterial pressure lability produced by SAD nor did medullectomy per se affect the lability observed in sham SAD rats (range, 3±2 to 4±1 mm Hg).

Moreover, Figure 2 also shows that SAD produced a significant tachycardia regardless of chemical renal
medullectomy or the grade of lesion of the renal papilla. Whereas SAD per se produced tachycardia in the range of 75–104 beats per minute in control and medullectomized rats, sham SAD produced a chronotropic response in the range of 0–21 beats per minute.

Discussion

We demonstrated that chemical renal medullectomy elicited by 2-BEA 2–3 weeks before the experiment did not change the basal MAP, arterial pressure lability, or HR of conscious rats but allowed the response of MAP to SAD to increase significantly. On the other hand, SAD per se was unable to increase the basal MAP in control rats but elicited a conspicuous increase in both arterial pressure lability and HR.

Chemical renal medullectomy and SAD are important tools for investigation of the cardiovascular control and physiopathogenesis of arterial hypertension. SAD has been considered a model of neurogenic hypertension5,6 although there is evidence that it does not result in sustained hypertension.7 Recently, Persson et al10 demonstrated in dogs that receptors from the cardiopulmonary area buffer the long-term rise in pressure after SAD. A true hypertensive response due to deafferentation was achieved only after removal of the sinoaortic and cardiopulmonary baroreceptors. Even though data from the literature point to an acute hypertension associated with a disinhibition of the sympathetic drive after SAD, our results do not support such a conclusion. Among the effects of medullipin II are suppression of the sympathetic tone and a suppressive effect on the central nervous system.1,2 In our present study, the association of SAD with chemical renal medullectomy caused a significant increase in MAP in conscious rats. Because there is evidence that SAD promotes an increased sympathetic tone,8,9 the lack of medullipin II may play a role in the increased MAP response to SAD by facilitating peripherally the sympathetic drive to resistance vessels.3

In normal rats, medullectomy is initially associated with moderate arterial pressure elevation,13 probably linked to a significant tachycardia and an increase in cardiac output.14 Later, this hypertension is associated with increased peripheral resistance with no change in cardiac output.15 Moreover, this hypertension seems to be directly related to the extent of lesion of the renal papilla.15 However, Heckmann et al16 demonstrated that 1–3 weeks after the injection of 2-BEA, MAP is still unaltered. After this period, MAP increases gradually, reaching a maximum about the seventh week after injection. We obtained results similar to those obtained by Heckmann et al16 2–3 weeks after the administration of 2-BEA. It is worthwhile to point out that in our experiments, lesions (grades 1, 2, and 3) of the renal papilla were confirmed by histological procedures.

There is general agreement that SAD promotes an extreme arterial pressure lability. Although its mechanisms are not clear, lability does not appear to be related to MAP level or unbuffered changes in sympathetic drive, but rather seems to be produced by an interaction between neural (centrally mediated sympathetic discharge) and humoral (involving activation of vascular smooth muscle by a variety of
endogenous vasopressor substances) components.9 On the other hand, it is postulated that medullectomy elicits an increased sympathetic efferent activity.14 Our results demonstrated that SAD per se produces a fourfold to fivefold increase in arterial pressure lability, whereas chemical renal medullectomy alone does not affect the normal oscillations of arterial pressure. Moreover, the association of medullectomy with SAD did not affect the increased arterial pressure lability caused by SAD, indicating that the lack of medullipin II does not play a role in the mechanisms of increased arterial pressure lability.

Our results confirmed that SAD produces a conspicuous tachycardia in conscious rats12 but failed to demonstrate any positive chronotropic effect of medullectomy.14 As expected, treatment with 2-BEA did not affect the tachycardia produced by SAD.

Taken together, our data indicate that lesions of the renal papilla lead to a significant increase in MAP after SAD without affecting basal MAP or HR. In addition, SAD per se did not significantly increase MAP in control rats. In conclusion, chemical ablation of the renal medulla seems to render rats more sensitive to a hypertensive stimulus such as SAD. The lack of a suppressive effect of medullipin II on sympathetic activity may play a role in this mechanism.

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References


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