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Characteristics of the Arterial Hypertension by Subtotal Nephrectomy in the Rat

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The importance of the hemodynamic parameters in the hypertensive rats by subtotal nephrectomy and the role of the neurogenic tone in the maintenance of high blood pressure were studied. The baroreceptor sensitivity is significantly diminished in the hypertensive rats with respect to normal ones. The resistance of the hindquarters to perfusion with constant flows was decreased in the hypertensive animals. No differences were observed in the arterial pressure, cardiac output, heart rate, stroke volume and peripheral resistance between both groups of anesthetized animals. The pressure response to the phenylephrine injection was higher in the conscious hypertensive animals than in the normotensive rats but it was the same after the anesthesia and the blocking of ganglionic transmission. These results suggest that an increment of the neurogenic tone exists in the chronic phase of hypertension in this experimental model and it could be responsible for the elevated blood pressure.

Removal of about 70% of the total renal mass of the rat produces a significative increase in the blood pressure. The severity of the hypertension does not reach the levels obtained after clamping the renal artery. The purpose of this study was to study the contribution of cardiac output, heart rate, stroke volume and peripheral resistance to this model of hypertensive animal and to evaluate the role of the neurogenic tone in the maintenance of the high blood pressure.

Materials and Methods

General procedure. Male Wistar rats weighing approximately 200 g were used. The subtotal nephrectomy was done under ether anesthesia. One kidney was removed

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and both poles of the remaining kidney were excised. This amounted to about 70-75 % of the total renal mass. Bleeding was stopped by electrocoagulation (3). Blood pressure determinations were made, in unanesthetized rats, by an indirect tail-cuff method and the animals were considered hypertensive when the arterial pressure was higher than 140 mmHg. Some studies were performed in unanesthetized rats which were catheterized 24 h earlier under ether anesthesia. A catheter, filled with saline containing heparin (30 U/ml), was inserted, through the common carotid artery, into the aortic arch. The right jugular vein was also cannulated and the catheter tip positioned just above the right atrium. After cannulas were fixed, the free ends were passed subcutaneously to the back of the neck and brought through the skin. Direct arterial pressure determinations were recorded on a poligraph via a Statham P23AA pressure transducer All the experiments were performed four weeks after the subtotal nephrectomy.

Determination of baroreceptor system sensitivity. Baroreceptor activity was studied in unanesthetized rats according to SMYTH *et al.* (10). A quick intravenous injection of phenylephrine (6 μg/kg) produced an increase of the arterial pressure that was accompanied by cardiac slowing. There is a linear relationship between systolic blood pressure and pulse interval during the transient pressure changes produced by the phenylephrine injection. The reflex sensitivy was expressed as the slope of the regression line. At least twelve points were plotted to obtain these curves.

Perfusion of the hindquarters. The possibility of the existence of vascular alterations was tested by the perfusion of the hindquarters with different constant flows. The method used were previously discribed (6). Briefly, the rats were anesthetized with 1 g/kg urethane and kept with controlled breathing by means of a Harvard breathing pump. Through a midline incision the aorta was exposed and cannulated, below the renal arteries, in a peripheral direction. The common carotid was also cannulated in a central direction and blood was pumped from the carotid cannula to the hindquarters by a peristaltic pump, 25 cycles by minute, with different flows (0.48 to 1.9 ml/min). Perfusion pressure was recorded from a T tube and these values were considered representative of the peripheral resistance.

Hemodynamic parameters. Cardiac output was measured by the Fick method in anesthetized rats following the BLOOD *et al.* procedures (1) with slight modifications. The oxygen consumption was determined during a 30 minute period. After that, samples of blood were obtained from the carotid artery and the right atrium to determine the oxygen concentration. These determinations were carried out with an automatic analyzer (Radiometer). Heart rate was determined by recording pulsatile arterial pressure at a fast paper speed. Total peripheral resistance and stroke volume were calculated from the data obtained.

Response to the phenylephrine before and after anesthesia and hexamethonium. In both groups of animals the magnitude of the pressure increase in response to phenylephrine, 6 μg/kg, was evaluated before and after anesthesia and hexamethonium, 10 mg/kg. The values of arterial pressure and heart rate were also recorded in the different situations above mentioned.

Statistical evaluation. All data are expressed as the mean ± standard error and were compared by means of Student's t-test. To determine the baroreceptor reflex sensitivity, linear regression analysis was used correlating systolic blood pressure and pulse intervals. The 5 % probability level was used as a criterion for significance.

Results

Baroreceptor system sensitivity. The slope of the curve describing the magnitude of the reflex bradycardia obtained in response to the elevation of arterial pressure produced by phenylephrine was higher in control rats than in the hypertensive ones (fig. 1). This difference is statistically significant ($p < 0.005$). The magnitude of the increase of the mean arterial pressure was higher in the hypertensive rats, 54 ± 3 mmHg, than in the control animals, 44 ± 3 mmHg ($p < 0.05$).

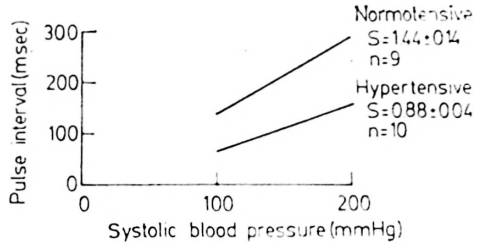

Fig. 1. *Comparison of the baroreceptor reflex response curves in unanesthetized normotensive and hypertensive rats.*
Each curve represents the average of the group. S = slope, n = number of experiments.

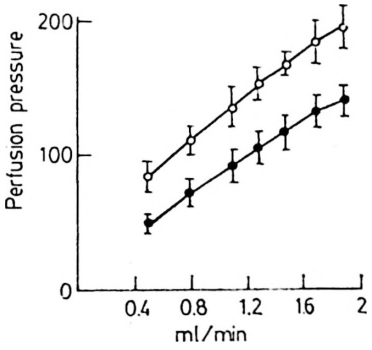

Fig. 2. *Perfusion pressures obtained when the hindquarters of the rat were perfused with different flows.*
Open circles: normotensive animals (n = 9). Filled circles: hypertensive animals (n = 8). Values were means ± SEM.

Peripheral resistance in the hindquarters. The values of the perfusion pressure when the hindquarters were perfused with different flows are showed in figure 2. The perfusion pressure was lower in the hypertensive animals than in the normal ones at all flows used ($p < 0.05$).

Hemodynamic parameters. In anesthetized animals no significative differences were observed in the arterial pressure, cardiac output, cardiac rate, stroke volume and peripheral resistance in both groups (fig. 3). The drop in arterial pressure produced by the anesthesia was greater in the hypertensive animals than in the normal ones. The anesthesia also annulled the difference in cardiac rate observed in both groups of conscious animals (fig. 4).

Effects of the abolition of ganglionic transmission on blood pressure, heart rate and response to phenylephrine.

The ganglionic blocking agent hexamethonium, administered to anesthetized animals, produced a decrease in the blood pressure (fig. 4). The magnitude of the decrease was greater in the hypertensive animals than in the normal ones. Similar results were observed in the heart rate. The difference in the response to phenylephrine observed in conscious animals between normotensive and hypertensive

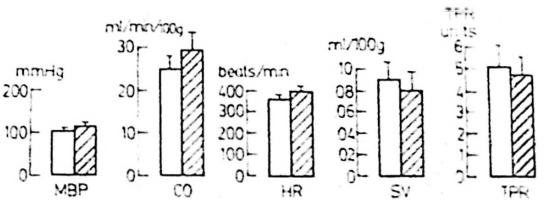

Fig. 3. *Hemodynamic parameters of the anesthetized normotensive and hypertensive rats.*
Open bars: normotensive animals (n = 7). Cross-hatched bars: hypertensive animals (n = 7). MBP: mean blood pressure. CO: cardiac output. HR: heart rate. SV: stroke volume. TPR: total peripheral resistance. TPR unit: MBP/CO. Values are means ± SEM.

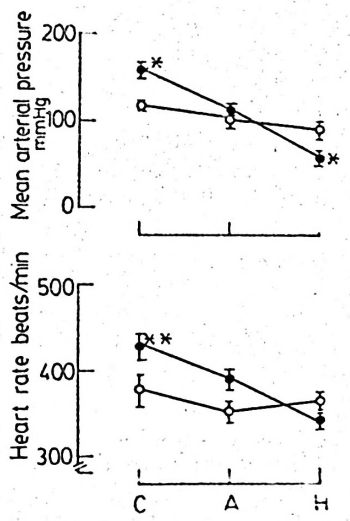

Fig. 4. *Changes in mean arterial pressure and heart rate in normotensive (open circles, n = 8) and hypertensive rats (filled circles, n = 8) produced by the anesthesia and the hexamethonium.*
C: conscious animals. A: anesthetized animals. H: hexamethonium treated animals. Values are means ± SEM. * $p < 0.001$; ** $p < 0.05$.

animals disappeared after the anesthesia and the abolition of ganglionic transmission; the increase of the arterial pressure was 62 ± 3 mmHg in control rats and 67 ± 4 in hypertensive animals.

Discussion

The baroreceptor sensitivity, expressed as the slope of the regression line, is significantly less in the rat than in man (10). It was also observed that this reflex is abolished by anesthesia (unpublished observations). This would suggest that the baroreceptor system of the rat does not play a role of great importance. Our results in the normal rats were similar to those reported by SNYTER *et al.* (11). Since the studies of MCCUBBIN *et al.* (8) that demonstrated that the baroreceptor reflex is reset in arterial hypertension, several studies have confirmed, in diverse species and by different methodology, that this reflex is altered in the hypertensive state. The data obtained demonstrated that in this model of hypertensive rats, at the fourth week, the baroreceptor system is reset and this fact can contribute to maintain the elevated blood pressure.

The magnitude of pressure rise in response to phenylephrine was higher in the hypertensive conscious animals than in normal ones. These results could be explained by structural changes in the arterioles that can alter the wall/lumen ratio. The results obtained with the perfusion of the hindquarters do not support this hypothesis. The lower values in the perfusion pressure observed in the hypertensive animals are difficult to explain. They could be due to a defect in the contraction process of the vascular smooth muscle produced by the decrease in the renal function. Previously, we have observed the existence of an alteration in the hydroelectrolytic composition of the aorta in this kind of hypertensive animals but without any relation to the development of maintenance of the arterial hypertension (7). The absence of increase in the peripheral resistance in the hindlimbs and the increased cardiac rate observed in conscious hypertensive rats support the hypothesis that the high arterial pressure was due to an increment of the cardiac output. It was measured in anesthetized animals since we could not obtain good reproductible results of the oxygen consumption in the conscious animal. The results obtained are comparable to those reported utilizing dye (4), thermo (5) or radioisotope dilution (2). The results of the cardiac output did not show differences between the control and hypertensive animals and the other parameters studied were also similar. On the other side, the total peripheral resistance was slightly decreased in the hypertensive animals and this is in concordance with the decrease in the peripheral resistance

observed when the hindquarters were perfused.

Only in the conscious animals differences were observed between both groups thus it is not unreasonable to suppose that the anesthesia annulled some neurogenic factors that play an important role in this model of hypertension. The first clear evidence of the participation of neurogenic mechanisms in the maintenance of high blood pressure in renal hypertension was provided by REED *et al.* (9). They observed that pentobarbital and yohimbine lowered the pressure of chronic hypertensive rats. A lot of evidences, that postulate an increase of the neurogenic tone in hypertension, have been described (12). The lower level of the arterial pressure reached in the hypertensive animals compared to normal ones after hexamethonium, supports this hypothesis. The absence of differences in response to phenylephrine between both groups of rats, after the abolition of ganglionic transmission, could be explained by a similar radius of the resistance vessels when the neurogenic tone is abolished.

In conclusion, the results observed make it possible to think that an increment of neurogenic tone exists in the chronic phase of hypertension in this experimental model, and this alteration could be responsible for the elevated blood pressure.

Resumen

Se estudia la importancia de los parámetros hemodinámicos en la rata hipertensa por nefrectomía subtotal y el papel del tono neurogénico en el mantenimiento de la presión arterial elevada. La sensibilidad del sistema presorreceptor está significativamente disminuido en los animales hipertensos. No se observaron diferencias en la presión arterial, volumen minuto, frecuencia cardíaca, volumen sistólico y resistencia periférica cuando los animales estaban anestesiados. La respuesta presora a la fenilefrina, en los animales despiertos, era mayor en los animales hipertensos, anulándose esta diferencia después de la anestesia y del bloqueo ganglionar. Estos resultados sugieren un incremento del tono neurogénico en este modelo experimental que podría ser el responsable de la elevación de la presión arterial.

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