

Short communication

SYMPATHOADRENAL DYSFUNCTION IN RATS WITH CHRONIC NEUROGENIC HYPERTENSION

PETER DOMINIAK *, FRIEDER KEES and HORST GROBECKER

Department of Pharmacology, University of Regensburg, University-Street 31, D-8400 Regensburg, F.R.G.

Received 20 September 1984, accepted 29 October 1984

P. DOMINIAK, F. KEES and H. GROBECKER, *Sympathoadrenal dysfunction in rats with chronic neurogenic hypertension*, European J. Pharmacol. 107 (1985) 263–266.

Compared to sham-operated controls 5 weeks after surgery neurogenic hypertensive rats with sino-aortic baroreceptor deafferentation had higher blood pressure, higher plasma noradrenaline and adrenaline levels, lower heart noradrenaline concentrations, higher adrenomedullary adrenaline levels and increased cardiac intraventricular pressure (dp/dt_{max}).

Sinoaortic baroreceptor deafferentation	Neurogenic hypertension	Adrenomedullary catecholamines
Plasma catecholamines	Heart catecholamines	

1. Introduction

Neurogenic hypertension is produced by total surgical sino-aortic deafferentation (Krieger, 1964). In the rat, neurogenic hypertension develops immediately and persists chronically (Krieger, 1964; Alexander et al., 1976; Chalmers, 1975). Both the peripheral (Alexander et al., 1976) and central (Chalmers, 1975) sympathetic systems have been proposed to be involved in the development of this model (Alexander et al., 1976). There is increasing evidence that, in addition to sympathetic nerves, the adrenal medulla has a role in neurogenic as well as in other animal models of hypertension and in selected cases of human essential hypertension (Grobecker et al., 1982; Dominiak and Grobecker, 1982). We undertook the study of plasma, adrenal and heart catecholamine levels in conscious, unrestrained rats with chronic neurogenic hypertension and their sham-operated controls. We compared these levels with basic haemodynamic parameters (systolic and diastolic blood pressure, heart rate and intraventricular

pressure (dp/dt_{max}). Our results suggest that peripheral sympathetic nerves and adrenal medulla are involved in the development of neurogenic hypertension in the rat.

2. Materials and methods

Total sino-aortic deafferentation was performed in atropinized (1.4 mg/kg i.p.), ether-anaesthetized rats by section of the sympathetic trunk, stripping and painting the carotid sinus (10% phenol in 95% ethanol) and resection of 1 cm of the cervical sympathetic trunk and superior laryngeal nerves (Krieger, 1964). Sham operation was performed by isolating the sympathetic trunk and the carotid sinus on both sides without resection. We used male Sprague-Dawley rats (SIV 50) from Dr. Ivanovas, Kisslegg, Germany, weighing about 250 g and housed individually in plastic cages (Makrolon®) in an air-conditioned, light-dark-cycled (12 h) room, with lights on from 6 a.m. to 6 p.m. Food (Altromin® standard diet) and tap water were available ad libitum.

Four and a half weeks after sino-aortic deaf-

* To whom all correspondence should be addressed.

fermentation, an indwelling catheter (PE-50, Clay Adams, Parsippany, NJ, U.S.A.) was placed into the thoracic aorta through the right carotid artery, and heparin (125 I.U.) injected twice daily. Three days after catheter implantation, the blood pressure, increase in intraventricular pressure (dp/dt_{max} , paper speed: 100 mm/s) and heart rate were recorded in conscious rats for 5 to 10 min with a Statham pressure transducer (P 23 Db), 5 min after connecting the pressure transducer twice daily (8 a.m., 5 p.m.) over a period of 6 days. The blood pressure of the rats was measured throughout the experiments in a quiet room, without handling. At the end of the 5th week and immediately after blood pressure measurement blood samples (0.3-0.5 ml) were taken from the catheters in conscious rats, without handling, for determination of the plasma catecholamine concentrations. The animals were then killed by decapitation under ether anaesthesia and the adrenal glands and hearts were removed and placed immediately in liquid nitrogen. Plasma and organs were kept frozen at -70°C until they were assayed.

Plasma catecholamines were assayed according to Da Prada and Zürcher (1976). Tissue catecholamines were determined by high performance liquid chromatography (HPLC) (Kissinger et al., 1981).

The data were evaluated statistically using the unpaired Student's *t*-test and standard linear regression analysis. The results are expressed as means \pm S.E.M.

3. Results

Blood pressure and dp/dt_{max} were significantly increased in neurogenic hypertensive rats when compared with sham-operated controls. However, no significant changes in heart rate between both groups of rats investigated could be observed (fig. 1).

Plasma noradrenaline and adrenaline concentrations were raised significantly (fig. 1). There was no difference in circulating dopamine between the two groups of rats.

The heart weight of neurogenic hypertensive rats was significantly higher than that of sham-op-

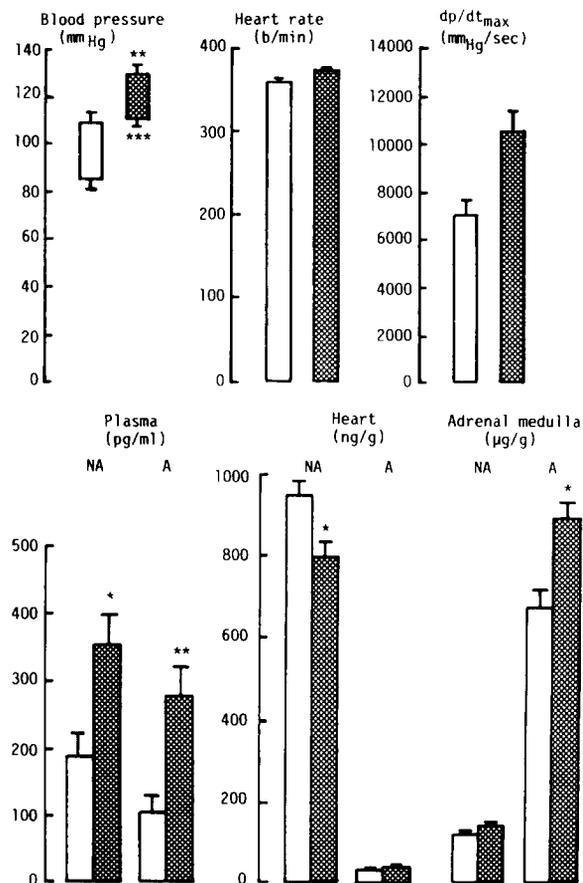


Fig. 1. Haemodynamic parameters (upper panel) in sham-operated normotensive (white columns) and neurogenic hypertensive rats (hatched columns) 5 weeks after total sino-aortic deafferentation (for details see Methods). Circulating plasma catecholamines and tissue catecholamines (lower panel) under the same conditions as described for the upper panel. NA = noradrenaline, A = adrenaline. Significance levels: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$; groups of 6-14 rats.

erated rats. In addition there was a significant difference ($P < 0.05$) between the heart/body weight ratio of neurogenic hypertensive rats (302×10^{-5}) and control rats (273×10^{-5}).

The noradrenaline content of the heart in neurogenic hypertensive rats was significantly ($P < 0.05$) decreased when compared with sham-operated control animals (fig. 1). There was no difference in adrenaline and dopamine contents between the two groups of rats.

The adrenal glands of rats with sino-aortic deafferentation had a significantly increased adrenaline content ($P < 0.01$; fig. 1). However, no changes in dopamine and noradrenaline contents between the two groups of rats could be observed. The wet weight of adrenal glands (55.2 ± 3.7 mg, hypertensive animals and 61.9 ± 4.3 mg, sham-operated animals) was similar.

Rats with neurogenic hypertension showed a positive linear correlation between circulating plasma noradrenaline concentrations and dp/dt_{\max} ($r = 0.91$, $P < 0.05$). We did not find a similar correlation in sham-operated rats.

4. Discussion

Our results confirm that chronic neurogenic hypertension occurs in rats 5 weeks after total sino-aortic deafferentation (Krieger, 1964). A significant elevation of blood pressure and an increase in dp/dt_{\max} were demonstrated 5 weeks after baroreceptor deafferentation. An increase in heart/body weight ratio as an index for hypertrophy was also observed as had been reported for genetic hypertensive rats by Bürger and Strauer (1981). We observed a positive correlation between plasma noradrenaline concentration and dp/dt_{\max} . The noradrenaline content in heart was significantly diminished probably as a result of an increased release elicited by stimulation of presynaptic β_2 -receptors through high circulating adrenaline concentrations (Rand et al., 1983).

Elevated circulating plasma noradrenaline and adrenaline concentrations (fig. 1), as well as the increased adrenaline content in the adrenal medulla (fig. 1), indicate that enhanced peripheral sympathetic activity probably in addition to increased heart work contributed to elevated blood pressure. The results are in agreement with observations of Alexander et al. (1980) and Chalmers et al. (1979).

In contrast to our results, Alexander et al. (1980) reported that rats showed no change in circulating noradrenaline and adrenaline 3 and 6 weeks after baroreceptor deafferentation when compared to the controls. However, their basal values for noradrenaline and adrenaline in the controls were much too high (approximately 400 pg/ml). This

may have been due to inadequate blood sampling (noise, handling etc.). Enhanced formation of catecholamines by the adrenal medulla during the development of hypertension in genetic and experimental (DOCA-salt) hypertensive rats has been reported recently (Grobecker et al., 1982). High circulating adrenaline levels can contribute to the maintenance of high blood pressure in rats (Rand et al., 1983). An increased level of circulating adrenaline has also been observed in young patients with essential hypertension (Dominiak and Grobecker, 1982).

From our results we conclude that deafferentation of baroreceptors resulted in enhanced sympathoadrenal activity/reactivity, leading to increased cardiac work and possibly vasoconstriction, thereby elevating blood pressure.

Acknowledgements

We thank Dr. Juan M. Saavedra for helpful discussions during the preparation of the manuscript.

References

- Alexander, N., M.T. Velasquez, M. Decuir and R.F. Maronde, 1980, Indices of sympathetic activity in the sinoaortic-denervated hypertensive rat, *Am. J. Physiol.* 238, H521.
- Bürger, S.B. and B.E. Strauer, 1981, Left ventricular hypertrophy in chronic pressure load due to spontaneous essential hypertension. I. Left ventricular function, left ventricular geometry, and wall stress, in: *The Heart in Hypertension*, ed. B.E. Strauer (Springer Verlag, Berlin, Heidelberg, New York) p. 13.
- Chalmers, J.P., 1975, Neuropharmacology of central mechanisms regulating pressure, in: *Central Action of Drugs in Blood Pressure Regulation*, eds. D.S. Davies and J.L. Reid (Pitman Med. Publ. Ltd., Kent) p. 13.
- Chalmers, J.B., M.A. Petty and J.L. Reid, 1979, Participation of adrenergic and noradrenergic neurones in central connections of arterial baroreceptor reflexes in the rat, *Circ. Res.* 45, 516.
- Da Prada, M. and G. Zürcher, 1976, Simultaneous radioenzymatic determination of plasma and tissue adrenaline, noradrenaline and dopamine within the femtomole range, *Life Sci.* 19, 1161.
- Dominiak, P. and H. Grobecker, 1982, Elevated plasma catecholamines in young hypertensive and hyperkinetic patients: effect of pindolol, *Br. J. Clin. Pharmacol.* 13, 381S.
- Grobecker, H., J.M. Saavedra and V. Weise, 1982, Biosynthetic enzyme activities and catecholamines in adrenal glands of

- genetic and experimental hypertensive rats, *Circ. Res.* 50, 742.
- Kissinger, P.T., C.S. Brüntlett and R.E. Shoup, 1981, Neurochemical applications of liquid chromatography with electrochemical detection, *Life Sci.* 28, 455.
- Krieger, E.M., 1964, Neurogenic hypertension in the rat, *Circ. Res.* 15, 551.
- Rand, M.J., H. Majewski and L.-H. Tung, 1983, Activation of prejunctional β -adrenoceptors by adrenaline acting as a co-transmitter. A possible cause of hypertension, *Drugs* 25 (Suppl. 2), 64.