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Cardiovascular responses in spontaneously hypertensive rats with acute renal failure

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Cardiovascular status and reactivity have been investigated in spontaneously hypertensive rats (SHR) with glycerol-induced acute renal failure. SHR with acute renal failure had significantly lower mean arterial blood pressures and heart rates. The pressor responses to noradrenaline and the chronotropic responses to right cervical sympathetic and vagal nerve stimulation were diminished in uraemic SHR compared to control SHR. The cardiovascular depression observed in SHR with acute renal failure was similar to that previously noted in normotensive rats with acute renal impairment.

In a recent study of the normotensive rat we have shown that the induction of acute renal failure (ARF) by intramuscular injection of glycerol results in a significantly lower blood pressure and heart rate (Bowmer et al 1983). In anaesthetized rats with ARF, chronotropic responses to vagal and cervical sympathetic stimulation were smaller and responses to noradrenaline were diminished. Similarly reduced vascular responses to noradrenaline have been reported both in man and rats with chronic renal failure (Campese et al 1981; Rascher et al 1982).

We have now extended this study by using spontaneously hypertensive rats (SHR) of the Okamoto strain which have been reported to display vascular hyperreactivity towards vasoconstrictor agents. This vascular hyperreactivity appears to result from a structural alteration in the vascular wall (Folkow 1971) upon which is superimposed a specific hypersensitivity to noradrenaline (Lais & Brody 1975). By contrast, the cardiac reactivity of SHR was significantly lower than normotensive controls (Fujiwara et al 1972; Kunos et al 1978) which accords with the finding of a diminished density of β-adrenoceptors in the myocardial membranes of SHR (Limas & Limas 1978).

It was the aim of the present investigation to assess cardiovascular reactivity in SHR made uraemic by glycerol injection. Since people with essential hypertension (Kannel 1977) as well as SHR (Okamoto 1969) are prone to develop renal disease it seemed pertinent to study cardiovascular responses when ARF was induced in animals already hypertensive.

Methods

Acute renal failure was induced in male Okamoto spontaneously hypertensive rats (300–350 g) by i.m. injection of 50% v/v glycerol in sterile 0·9% NaCl w/v (saline). The glycerol solution was administered under ether anaesthesia, in divided doses in two sites in each of the hind limbs as described previously (Bowmer et al 1983). Control rats received an i.m. injection of sterile saline (8 ml kg^{-1}) only and were studied 24 h later. The procedure used to produce ARF in Wistar rats (Bowmer et al 1983) proved too rigorous for SHR resulting in high mortality but, the omission of the dehydration stage, the injection of 8 ml kg^{-1} of the glycerol solution and a shorter time interval before anaesthesia resulted in a mortality rate of 15%. The animals were studied 24 h later when they were anaesthetized with thiobutabarbitone (120–160 mg kg^{-1} i.p.), a tracheal cannula was inserted and artificial respiration was maintained with a Miniature Ideal Pump (Bio-Science) (ventilation rate 80 strokes min^{-1} and stroke volume 10 ml kg^{-1}). Cannulae were also inserted into the right femoral artery and vein. The cannula in the right femoral artery was connected to a Statham pressure transducer and then to a Grass Model 79 polygraph where the pressure wave was used to trigger a rate meter. Rectal temperature was maintained at 37 °C by means of a heating lamp.

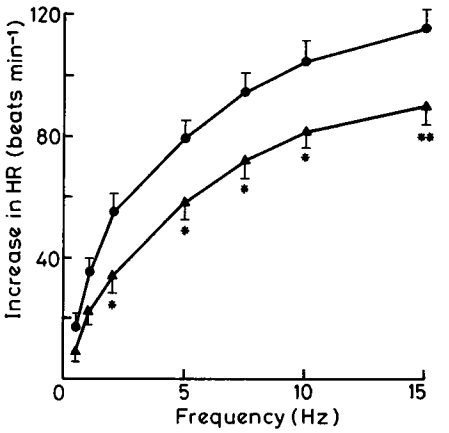

FIG. 1. The increase in heart rate (HR) with increasing frequency of right cervical sympathetic stimulation (8–10 V, 0·5 ms) in 6 control SHR (●) and 7 SHR with acute renal failure (▲) Values are mean ± s.e. mean. Significantly different from control values $*P < 0.05$, $**P < 0.01$.

* Correspondence.

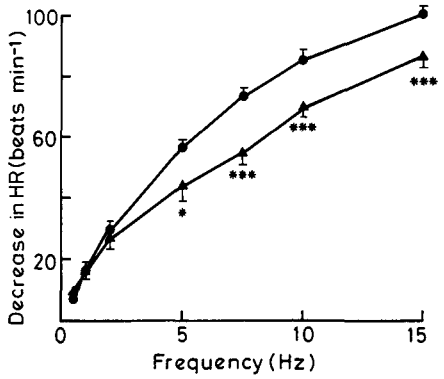

FIG. 2. The decrease in heart rate (HR) with increasing frequency of right vagal stimulation (8–10 V, 0·5 ms) in 10 control SHR (●) and 8 SHR with acute renal failure (▲). Values are mean ± s.e. mean. Significantly different from control values $^{*}P < 0{\cdot}05$, $^{***}P < 0{\cdot}001$.

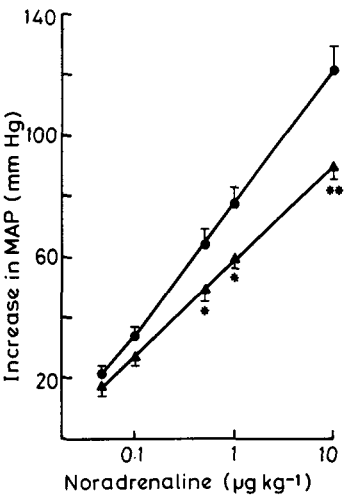

FIG. 3. The increase in mean arterial pressure (MAP) in response to i.v. doses of noradrenaline in 10 control SHR (●) and 8 SHR with acute renal failure (▲). Values are mean ± s.e. mean. Significantly different from control values $^{*}P < 0{\cdot}05$, $^{**}P < 0{\cdot}01$.

The right vagus and cervical sympathetic nerves were prepared for stimulation (Large 1975) to assess cardiac chronotropic responses. The vagus in the neck was doubly ligated and sectioned. The right cervical sympathetic nerve was left intact and placed on shielded bipolar platinum electrodes immersed in liquid paraffin. The nerve was stimulated with rectangular pulses, 0·5 ms duration, supramaximal voltage (8–10 V) and various frequencies. The frequency-response curves were obtained by applying a stimulus at a given frequency until a maximum response occurred (15–30 s). A further stimulus was applied after the heart rate had returned to control levels (2–3 min). The nerves were stimulated at frequencies ranging from 0·5–15 Hz.

After the periods of nerve stimulation the response of blood pressure was recorded to a series of bolus i.v injections of noradrenaline (0·1–5·0 μg). The dose of noradrenaline as a function of body weight (μg kg^{-1}) was determined and log-dose response lines constructed by linear regression. At the end of the experiment a heparinized blood sample was taken for the measurement of plasma urea concentration.

Plasma urea concentrations were measured by reaction with diacetyl monoxime using the reagents and procedure detailed in Sigma Technical Bulletin No. 535 (Sigma Chemical Co.). (−)-Noradrenaline bitartrate (Sigma Chemical Co.) was dissolved in 0·9% NaCl (w/v); the doses refer to the salt. All results are expressed as mean ± s.e. mean and statistical comparisons were made using a non-paired Student's *t*-test;

Results

The plasma urea concentrations of glycerol injected SHR (265 ± 23 mg 100 ml^{-1}; n = 11) were significantly elevated ($P < 0{\cdot}001$) when compared to control levels (59 ± 4 mg 100 ml^{-1}; n = 12). Both the mean arterial blood pressure (124 ± 3 mm Hg) and heart rate (358 ± 5 beats min^{-1}) of these uraemic rats were significantly reduced ($P < 0{\cdot}01$) when compared to controls (157 ± 5 mm Hg; 387 ± 7 beats min^{-1}).

The positive chronotropic response to right cervical sympathetic stimulation was diminished in uraemic SHR when compared with controls (Fig. 1). This difference was statistically significant at frequencies between 2 and 15 Hz. Furthermore, the negative chronotropic response to right vagal stimulation was also reduced in uraemic animals (Fig. 2), significant differences occurring at the higher frequencies (5–15 Hz).

The increase in mean arterial blood pressure in control and uraemic SHR in response to injection of noradrenaline is depicted in Fig. 3 which shows that, in uraemic rats, doses between 0·5 and 10 μg kg^{-1} produced significantly smaller pressor responses. The chronotropic responses to bolus i.v. injections of noradrenaline were variable and showed no dose-dependent relationship in either control or uraemic groups. At a dose of 10 μg kg^{-1} noradrenaline elicited an increase in heart rate of 40–70 beats min^{-1} in both uraemic and control SHR.

Discussion

The present findings in spontaneously hypertensive rats clearly show that the induction of acute renal failure is associated with a decrease in cardiovascular reactivity to a variety of stimuli.

Although the plasma urea concentration of control SHR (59 ± 4 mg 100 ml^{-1}) was not significantly different from the concentration we noted in normotensive control rats (50 ± 9 mg ml^{-1}; Bowmer et al 1983), the method employed to induce ARF in normotensive

animals (24 h dehydration, 10 ml kg^{-1} glycerol solution) proved too severe for SHR. As a result, we omitted the dehydration stage to reduce the degree of renal insult produced by glycerol as stated by Thiel et al (1967), and we reduced the dose of glycerol and used a shorter time interval before anaesthetizing the rats. Since SHR are prone to develop renal disease (Okamoto 1969) it is perhaps not surprising that a less severe procedure was required for inducing ARF. In the event, this procedure caused a 4·5 fold increase in plasma urea concentrations by contrast with the 7·5 fold increase measured in normotensive rats with the more rigorous procedure of Bowmer et al (1983).

The blood pressure and heart rate of uraemic SHR were significantly lower than their control counterparts although the differences (21 and 7·5%, respectively) were not as great as had been noted in our study of normotensive rats with ARF (35 and 12·5% respectively; Bowmer et al 1983). This suggests either that SHR are more resistant to the hypotensive and negative chronotropic effects of uraemia or, more probably, that the renal impairment was less marked in SHR due to the less rigorous method employed to induce ARF.

The pattern of the depression of chronotropic responses to vagal and cervical sympathetic stimulation noted in uraemic SHR (Figs 1, 2) is almost identical to that which we observed in normotensive rats (Bowmer et al 1983). In a similar manner the pressor responses to noradrenaline were also depressed in uraemic SHR (Fig. 3) although, unlike the findings in normotensive rats, at the lower doses of noradrenaline this depression was not statistically significant.

The mechanism responsible for decreased cardiovascular responses in renal failure is unclear. Diminished vascular responses have been reported both in humans and rats with chronic renal failure (Campese et al 1981; Rascher 1982) and in rats with ARF produced by bilateral ureter ligation (Ueda et al 1981). In the study conducted by Rascher et al (1982) the vascular response to vasopressin in uraemic normotensive animals was unchanged whilst that to potassium chloride and barium chloride was increased. They concluded that the decreased response to noradrenaline in renal failure was due to down-regulation of α-receptors in response to elevated noradrenaline concentrations. However, in a further study of vascular responses in normotensive rats with glycerol-induced ARF we have observed decreased vascular contractions to noradrenaline, angiotensin and potassium chloride (Bowmer et al 1984). This indicates that, at least in this acute model of renal failure, the depression of vascular response is non-specific and it may be that uraemia causes a basic defect in excitation-contraction coupling. Whatever mechanism is responsible for the diminished vascular response and for the reduced chronotropic response a similar pattern of depression of cardiovascular response occurs in SHR as in normotensive rats in the presence of ARF.

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REFERENCES

Bowmer, C. J., Clarke, C. A., Comer, M. B., Yates, M. S. (1984) Br. J. Pharmacol. 81: 69–73

Bowmer, C. J., Nichols, A. J., Warren, M., Yates, M. S. (1983) Ibid. 79: 471–476

Campese, V. M., Romoff, M. S., Levitan, D., Lane, K., Massry, S. G. (1981) Kidney Int. 20: 246–253

Folkow, B. (1971) Clin. Sci. 41: 1–12

Fujiwara, M., Kuchii, M., Shibata, S. (1972) Eur. J. Pharmacol. 19: 1–11

Kannel, W. B. (1977) in: Genest, J., Koiw, E., Kuchel, O. (eds) Hypertension. McGraw-Hill, New York pp 888–910

Kunos, G., Robertson, B., Kan, W. H., Preiksaitis, H., Mucci, L. (1978) Life Sci. 22: 847–854

Lais, L. T., Brody, M. J. (1975) Circulation Res. 36 & 37: (Suppl. 1) 1-216-1-222

Large, B. J. (1975) Br. J. Pharmacol. 54: 351–358

Limas, C., Limas, C. J. (1978) Biochem. Biophys. Res. Commun. 83: 710–714

Okamoto, K. (1969) Int. Rev. Exp. Pathol. 7: 227–270

Rascher, W., Schömig, A., Kreye, V. A., Ritz, E. (1982) Kidney Int. 21: 20–27

Thiel, G., Wilson, D. R., Arce, M. L., Oken, D. E. (1967) Nephron 4: 276–297

Ueda, S., Ayano, Y., Yano, S. Mutoh, S., Sakanashi, M. (1981) Arch. int. Pharmacodyn. 253: 257–265