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RAPID COMMUNICATION

Vascular Reactivity in Isolated Lungs of Rats with Spontaneous Systemic Hypertension

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Summary

Pulmonary vascular reactivity to acute hypoxic challenges and to KCl was measured in isolated blood-perfused lungs of six rats with spontaneous systemic hypertension (SHR) and in six normotensive rats. Baseline perfusion pressure did not differ significantly between SHR (11.0±1.0 mm Hg) and normotensive controls (12.3±1.5 mm Hg). Reactivity to acute hypoxia was equal in both groups. In SHR the dose-response of perfusion pressure to KCl was shifted significantly towards lower perfusion pressures as compared with normotensive controls. These results suggest that, even though magnitude of hypoxic pulmonary vasoconstriction is not changed, the mechanism of the response may be altered in SHR.

Key words:
Spontaneously hypertensive rat – Pulmonary circulation – Hypoxic pulmonary vasoconstriction – Pulmonary vascular reactivity – Depolarization

Systemic vessels of spontaneously hypertensive rats (SHR) are generally hyperreactive to various stimuli (Triggle and Laher 1985). There is little information, however, concerning the reactivity of pulmonary blood vessels in SHR. The aim of the present experiments was to study pulmonary vascular reactivity of SHR to acute hypoxic stimuli and to depolarization caused by KCl administration.

Six male spontaneously hypertensive rats were compared with six normotensive male Wistar rats. Rats of both groups did not differ significantly in their body weight (300.0±19.2 g in SHR and 315.5±14.5 g in controls). The isolated perfused lung preparation was used as described in detail elsewhere (Hampl and Herget 1990). The lungs were prepared under thiopental anaesthesia (100 mg/kg BW, i.p.), placed in a thermostated (38 °C) chamber and perfused under constant flow (0.04 $ml.min^{-1}.g^{-1}$ BW). The blood for perfusion was obtained by a cardiac puncture from 2–3 normotensive rat donors.

After onset of perfusion, the isolated lungs were ventilated (65 breath/min) with normoxic mixture (all gas mixtures in this study contained 5 % CO_2 and were

balanced with N_2) for 15 min. Peak inspiratory and expiratory pressures were 9 and 2.5 cm H_2O, respectively. During the next 10 min the preparation was ventilated with mixture containing 3 % O_2. The same challenge was repeated after 10 min of normoxic ventilation. Responses to these two challenges were not evaluated. After another 10 min of normoxia the dose-response to acute hypoxia was measured. Lungs were ventilated with mixtures containing 10, 5 and 3 % O_2 in this order. The challenges were separated by 7-min intervals of normoxic ventilation. Each hypoxic challenge lasted 10 min. The highest value of perfusion pressure reached during hypoxic challenge minus perfusion pressure immediately before the challenge was considered a magnitude of response to a given degree of acute hypoxia.

During the measurement of dose-response to KCl, which followed 10 min after the last hypoxic challenge, the preparation was ventilated with air containing 5 % CO_2. Physiologic saline solution (0.1 ml) containing KCl was added into a blood in a reservoir in 5-min intervals. The amount of KCl in the solution was adjusted to result after mixing with perfusate (20 ml) in a cumulative concentrations of 0.1, 0.3, 0.6, 1.0 and 2.0 mM. The difference between maximal perfusion pressure reached in a 5-min interval after injection of the respective dose of KCl and basal perfusion pressure before the first dose of KCl was regarded a magnitude of response to a given cumulative dose of KCl.

Unpaired t-test and two-way ANOVA were used for statistical evaluation as appropriate (Steel and Torrie 1960). $P<0.05$ was considered significant. Results are presented as mean ± S.E.M.

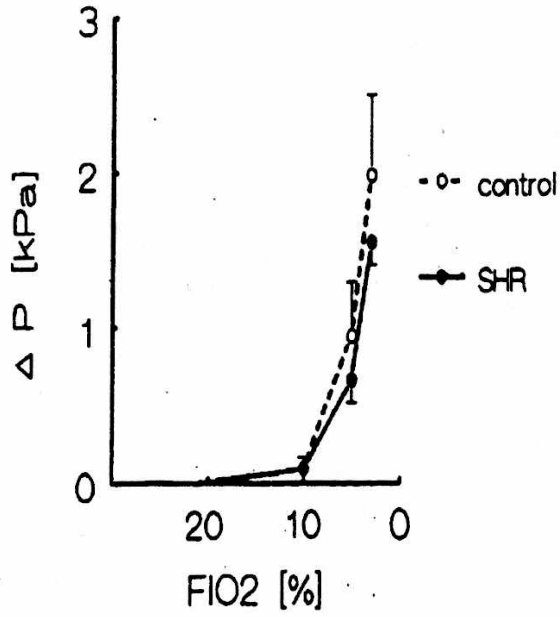

Fig. 1
Dose-response of perfusion pressure to acute hypoxia in isolated lungs. Vertical bars represent SEM. Two-way ANOVA indicates significant relation between the degree of hypoxia (FIO2) and an increase in perfusion pressure (ΔP). The difference between rats with spontaneous systemic hypertension (SHR) and normotensive rats (control) is not significant. In both groups, n=6.

Baseline perfusion pressure before the measurement of vascular reactivity of the isolated lungs to acute hypoxic stimuli was 1.64±0.20 kPa (12.3±1.5 mm Hg) in controls and 1.46±0.13 kPa (11.0±1.0 mm Hg) in SHR. The difference was not significant. The dose-response curves of perfusion pressure to hypoxia are shown in Fig. 1. All degrees of hypoxia elicited vasoconstriction, the magnitude of which was significantly dependent on the severity of the hypoxic stimulus. The dose-response curve to hypoxia of SHR was not significantly different from that of control rats.

Baseline perfusion pressure before the measurement of reactivity to KCl was similar ($p>0.05$) in SHR (1.46±0.17 kPa, 11.0±1.3 mm Hg) and in control rats (2.09±0.51 kPa, 15.7±3.8 mm Hg). These values do not differ significantly from the values of baseline perfusion pressure before the measurement of reactivity to hypoxia. The dose-response curves of perfusion pressure to KCl are in Fig. 2. The degree of vasoconstriction was proportional to the dose of KCl. The dose-response curves to KCl of SHR were significantly lower than those of controls.

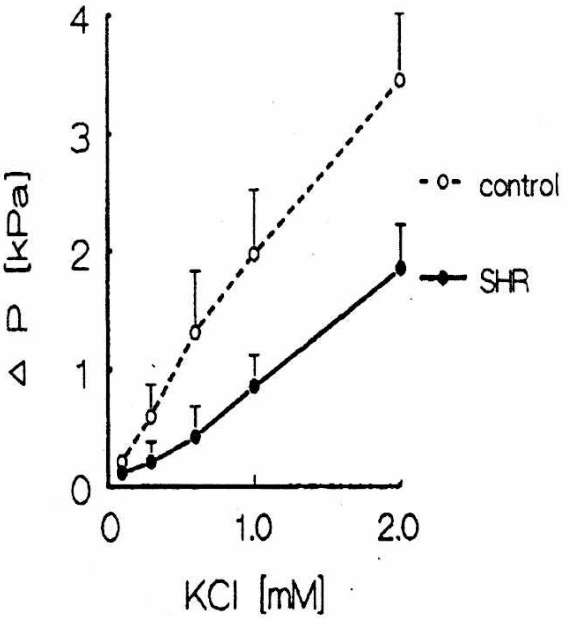

Fig. 2
Dose-response of perfusion pressure to KCl in isolated lungs. Vertical bars are SEM. Two-way ANOVA shows significant dependence of the increase in perfusion pressure (ΔP) on the dose of KCl. Rats with spontaneous systemic hypertension (SHR) are significantly less reactive than normotensive rats (control). In both groups, n=6.

Equal baseline perfusion pressures in lungs from SHR and normotensive rats in our study confirms previous observation of McMurtry *et al.* (1979). These authors also found that right ventricular systolic pressure did not differ between SHR and normotensive controls. In our experience, the groups of rats that have similar baseline perfusion pressures in the isolated lungs, also do not differ significantly in the pulmonary artery pressure *in vivo* (Hampl and Herget 1990). Thus, hypertension in SHR appears to be limited to the systemic circulation. McMurtry *et al.* (1979) also

demonstrated normal magnitude of hypoxic pulmonary vasoconstriction in SHR. Our study reproduced this finding. The original result of our present experiments is the pulmonary vascular hyporeactivity of SHR to KCl. It is in contrast to hyperreactivity to angiotensin II described by McMurtry *et al.* (1979).

Systemic vessels of SHR are hyperreactive to various vasoconstrictor stimuli including depolarization by KCl (Triggle and Laher 1985). Voltage-controlled Ca^{2+} channels are hypersensitive in smooth muscle cells of systemic vessels of SHR (Bohr and Webb 1988). Hyporeactivity to KCl of pulmonary vessels of SHR in the present study is, therefore, surprising. It shows that pulmonary and systemic vascular smooth muscle are functionally different.

Depolarization of the sarcolemma of pulmonary vascular smooth muscle is a substantial step in the mechanism of hypoxic pulmonary vasoconstriction (Madden *et al.* 1985, Harder *et al.* 1985). Based on this fact, the blunted pulmonary vascular reactivity to KCl would be expected to result in a decreased reactivity to hypoxia in SHR. This is not the case (Fig. 1). Hence, it can be concluded that, in addition to the reactivity to depolarization, also some other step in the mechanism of hypoxic pulmonary vasoconstriction is altered in SHR. The mechanism of hypoxic pulmonary vasoconstriction includes sensing of oxygen tension, transfer of information about hypoxia from sensor to effector, vascular smooth muscle membrane depolarization, Ca^{2+} influx, and vasoconstriction (Voelkel 1986). If we assume that the mechanism of pulmonary vasoconstriction is the same from the point of depolarization for hypoxia and for KCl, then it is obvious that the proposed alteration of mechanism of hypoxic pulmonary vasoconstriction in SHR must be localized "before" depolarization, i.e. at the level of oxygen sensing or transfer of information about hypoxia from sensor to effector. Augmented sensitivity of oxygen sensor could be expected to potentiate selectively the responses to less severe degrees of hypoxia. This did not occur in our results (Fig. 1). It may be concluded that the connection between sensor of hypoxia and pulmonary vascular smooth muscle depolarization is abnormal in SHR. We think that this defect may compensate for the hyporeactivity of their pulmonary vascular smooth muscle to depolarization so that the magnitude of hypoxic pulmonary vasoconstriction is normal in these animals. However, this hypothesis is far from being proved.

Patients with systemic hypertension and healthy lungs have augmented hypoxic pulmonary vasoconstriction (Guazzi *et al.* 1989). This discrepancy from our study may be the result of differences in pathogenic mechanisms between primary hypertension in humans and hypertension in SHR. Alternatively, systemic influences may contribute to hypoxic pulmonary vasoconstriction in intact humans but not in isolated rat lungs. Nevertheless, the finding of hypersensitivity of pulmonary circulation of hypertensive patients to hypoxia is in agreement with our conclusion that mechanism of hypoxic pulmonary vasoconstriction may be altered in subjects with systemic hypertension.

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Reprint Requests

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