Effect of Tetramethylpyrazine on Acute and Chronic Hypoxic Pulmonary Hypertension of the Rat

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Summary: The effect of tetramethylpyrazine (TMPZ) on acute as well as chronic hypoxic pulmonary hypertension has been studied in rats. TMPZ inhibited acute hypoxic pulmonary vasoconstriction and prevented chronic hypoxic pulmonary hypertension and hypertrophy of the right ventricle. In normal rats and those with chronic pulmonary hypertension, TMPZ dramatically increased the cardiac output and decreased the pulmonary arterial pressure and pulmonary vascular resistance. More marked changes in pressure and resistance were observed in rats with chronic pulmonary hypertension than in normal rats. Therefore, it may be suggested that TMPZ proves of use in the prevention and treatment of acute and chronic hypoxic pulmonary hypertension and cor pulmonale.

Key words: pulmonary circulation, pulmonary hypertension, hypoxia, tetramethylpyrazine

Tetramethylpyrazine (TMPZ) has been reported to be able to relax the spasm of systemic vascular smooth muscle and to increase myocardial contractility and cardiac output [1]. It is not yet known, however, whether it could dilate pulmonary vessels and alleviate pulmonary hypertension. This study was undertaken to probe the effect of TMPZ on hemodynamics in rats exposed to acute and chronic alveolar hypoxia and the role of TMPZ in the prevention of hypoxic pulmonary hypertension.

MATERIALS AND METHODS

41 Wistar inbred male rats weighing 390–600 g were randomly divided into four groups. Group I: 11 rats were confined to a hypobaric chamber which was decompressed to 380 mmHg 8 h daily, for 18 days, without medication. Group II and III: TMPZ phosphate (100 mg/kg) was given orally to 9 rats (group II), and TMPZ hydrochloride (80 mg/kg) intraperitoneally to 8 rats (group III), respectively, right before and after the daily decompression described for group I. Group IV: 13 rats kept in a normobaric room without medication served as controls. Three weeks after the beginning of the experiment, each rat was weighed and anesthetized with 2.3 ml/kg i.p. sodium pentobarbital. A polyethylene catheter (i.d. 1.5 mm) was introduced into the external jugular vein and another catheter (o.d. 1 mm) was inserted into the common carotid artery for monitoring the systemic blood pressure.

Right ventricular systolic and diastolic pressure (RVSP and RVDP) and mean carotid arterial pressure ($P_{ca}$) were transduced with strain gauge. The electrical outputs of the pressure transdu-
cers and ECG were processed through amplifiers and recorded on a SJ-41 polygraph. Cardiac output (CO) was calculated by differential impedance or admittance cardiogram, according to the method described by Dennison and Yu\(^{1,3}\). Pulmonary vascular resistance (PVR) was represented by RVSP (mmHg) \(\times 80/\text{CO} \,(1/\text{min})\). PVR thus calculated is higher than the actual PVR. In controls and in rats exposed to chronic hypoxia which had not been treated with TMPZ in the experiment, the hemodynamic changes induced by intravenous infusion of 80 mg/kg of TMPZ were studied.

The heart of each rat was dissected after the observation on hemodynamic changes and right ventricular hypertrophy was evaluated by a ratio of the weight of the free wall of the right ventricle to the weight of the left ventricle plus the weight of the interventricular septum, according to the method described by Suzuki\(^{14}\).

In a second series of experiments, 48 mongrel rats of both sexes weighing 340—550 g were used to determine pulmonary vascular response to acute hypoxia. Each rat was intubated with an endotracheal catheter, and pulmonary vascular response to hypoxia was tested by ventilating the rodent with 9 % O\(_2\) for 5 min. Hemodynamic changes were recorded before as well as 2, 3 and 5 min after the onset of hypoxia, respectively. In 11 of these animals, pulmonary vascular response to hypoxia was determined once more during an intravenous infusion of TMPZ hydrochloride in a dose of 80 mg/kg.

**RESULTS**

1. Hemodynamic changes in rats during acute alveolar hypoxia

5 min after the onset of hypoxia, RVSP and PVR increased significantly, accompanied by a decrease in CO and \(P_{CA}\) (table 1).

2. Effect of TMPZ on hemodyna-

| Table 1. Hemodynamic changes and effect of TMPZ on hemodynamics in rats during acute alveolar hypoxia (mean ± SD) |
|---|---|---|---|---|---|
| HR (b/min) | CO (mL/min) | RVSP (mmHg) | PVR (dyn-s·cm\(^{-3}\)) | SVR (dyn-s·cm\(^{-3}\)) | P\(_{CA}\) (mmHg) |
| Before | 35.9±14.3 | 55.6±2.8 | 29.0±1.8 | 106.0±2.1 | 106.0±2.1 |
| 5th min | 315.5±12.1 | 42.4±1.9 | 13.2±3.6 | -4.3±3.9 | 106.0±2.1 |
| Increment | <0.01 | <0.05 | <0.05 | <0.05 | <0.05 |

Hypoxia

\(\text{Before TMPZ} \quad \text{During TMPZ} \quad \text{P}^{*} \quad \text{P}^{**} \)

(Interaction) (Response to hypoxia) • compared with values before hypoxia, ** compared with values before TMPZ infusion