ORIGINAL ARTICLE
α-Adrenergic Blockade with Phenoxybenzamine Enhances Cerebrovascular CO2 Reactivity
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Abstract. The influence of sympathetic nervous activity on cerebral circulation and cerebrovascular CO2 reactivity was investigated by an α-adrenergic blockade with phenoxybenzamine (PBZ). Cerebral oxygen and carbon dioxide tension (BrPO2, BrPCO2) and arterial blood pressure were continuously recorded before, during and after intracarotid infusion of 5 mg/kg of PBZ. The effects of 5% CO2 inhalation were measured before and after the infusion of PBZ. Following the intracarotid infusion of PBZ, BrPO2 and BrPCO2 did not change significantly. After the α-adrenergic blockade the degree of the increase in BrPO2 during 5% CO2 inhalation was significantly enhanced. The increase in the cerebrovascular CO2 reactivity produced by low dose PBZ suggests that the sympathetic nervous system modifies cerebrovascular CO2 reactivity. (Keio J Med 42 (2): 60-63, June 1993)

Key words: cerebrovascular system, α-blocker, cerebral oxygen tension, cerebral carbon dioxide tension

Introduction

Two types of adrenergic receptors exist in the walls of the peripheral blood vessels; postsynaptic α-adrenoceptors responding to stimulation by vasoconstriction, and β-adrenoceptors responding with vasodilatation. Cerebral blood vessels have been demonstrated to be richly innervated with sympathetic nerve fibers.1-3 However, the cerebral circulation is controlled mainly by metabolic factors,4 and under normal conditions the contribution of the sympathetic nervous system seems to be less extensive. Cerebrovascular CO2 reactivity and autoregulation of the cerebral circulation are considered to be influenced by different mechanisms.5-6 Phenoxybenzamine (PBZ), a potent long-acting adrenergic blocker, acts upon vessels by blocking their α-adrenergic receptors, resulting in vasodilatation without altering the function of other sympathetic or parasympathetic receptors.7 In the present study, we examined cerebrovascular effect of PBZ by administering a low dose of PBZ by intracarotid infusion to minimize the systemic influence of PBZ. Furthermore, we examined whether neurogenic influences play any part in cerebrovascular response to changes in arterial carbon dioxide tension.

Materials and Methods

Seven cats weighing 2.2-3.4 kg (mean 2.8 kg) were anesthetized with an intraperitoneal injection of α-chloralose (50 mg/kg) and urethane (500 mg/kg) and with 0.5% procaine hydrochloride for local anesthesia. After tracheostomy, the animals were immobilized with alcuronium chloride and a tracheal cannula was connected to a variable speed respirator pump (Harvard Model 662, Harvard, MA, USA). The respiration rate was set to 20 strokes/min and the stroke volume was set to between 25-40 ml depending on the size of the animal. Abdominal aortic pressure was measured with a pressure transducer (Statham P231 Db, Gould, Oxnard, CA, USA) connected to a polyethylene tube inserted into the abdominal aorta through the right femoral artery. The polyethylene tube, inserted retrogradely into the right lingual artery, was used for the injection of PBZ into the carotid artery. The rectal temperature of cats was kept at 37°C by means of heating blankets throughout the experiment.

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The skull was fixed in a stereotactic head holder (Type SN-1, Narishige, Tokyo, Japan) and the scalp and the dura over the parietal cortex region were removed. PO2 and Pco2 electrodes were attached gently by means of adjustable rods with springs on the exposed cerebral cortex. The PO2 electrode consisted of a platinum cathode and a silver-silver-chloride anode, and PO2 was measured by the polarographic principle. The method for measuring Pco2 was based on the change in the pH of a weak bicarbonate solution enclosed within a teflon membrane as CO2 diffused from outside the membrane. The output signal from the PO2 electrode was amplified by a gas analyzer (Beckman Model 160, Beckman Toshiba, Tokyo, Japan). The output signal from the Pco2 electrode was amplified by a pH meter (Radiometer Model 22, Radiometer, Copenhagen, NV, Denmark). These parameters were continuously recorded on a polygraph (Type R-56M3, Rikadenki, Tokyo, Japan). The calibration of the electrodes was performed by using 100% N2 and 5% O2 + 95% N2 for the PO2 electrode, 5% CO2 + 95% N2 and 10% CO2 + 90% N2 for the Pco2 electrode. Arterial blood PO2, Pco2, and pH were measured with a blood gas analyzer (Radiometer PHM71, Radiometer, Tokyo, Japan) before and after the administration of PBZ in 6 cats.

PBZ solution (5 mg/kg) was infused into the carotid artery for 5 min. Changes in Brain-Po2 (BrPO2), Brain-Pco2 (BrPco2) and blood pressure (BP) were observed for 12 min after the start of the infusion. Before and after the infusion of PBZ, inhalation of 5% CO2 in air for 2 min was performed. Cerebrovascular CO2 reactivity was estimated by changes in BrPO2 and BrPco2 (ΔBrPO2, ΔBrPco2). The data are shown as mean ± SD and analyzed by Student’s paired t-test. A P value of less than 0.05 was considered significant.

**Results**

*Effects of intracarotid infusion of PBZ on cerebral circulation*

Figure 1 summarizes the effect of intracarotid infusion of PBZ on each parameter during a period of 12 min from the beginning of infusion in 7 cats. Following intracarotid infusion of PBZ, BrPO2, BrPco2, and BP were not changed significantly. Arterial blood PO2, Pco2, and pH (Table 1) did not change significantly following PBZ infusion.

*Effects of 5% CO2 inhalation before and after PBZ*

Figure 2 demonstrates effects of CO2 inhalation before and after PBZ infusion on BrPO2, BrPco2, and BP.

![Figure 1](image_url)  
**Fig. 1** Summarized data demonstrating the effects of intracarotid infusion of phenoxybenzamine (PBZ, 5mg/kg). Following the infusion of PBZ, cerebral tissue oxygen tension (BrPO2), carbon dioxide tension (BrPco2) and mean arterial blood pressure (MABP) did not change significantly. N=7. Each point represents mean ± SD.

**Table 1** Comparison of Physiological Data before and after the Intracarotid Infusion of Phenoxybenzamine (PBZ)

<table>
<thead>
<tr>
<th></th>
<th>PO2 (mmHg)</th>
<th>Pco2 (mmHg)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>93.5 ± 4.6</td>
<td>32.4 ± 1.8</td>
<td>7.35 ± 0.03</td>
</tr>
<tr>
<td>After</td>
<td>93.0 ± 5.5</td>
<td>32.5 ± 1.8</td>
<td>7.35 ± 0.03</td>
</tr>
<tr>
<td>Delta</td>
<td>−0.4 ± 1.4</td>
<td>0.1 ± 2.1</td>
<td>0.01 ± 0.02</td>
</tr>
</tbody>
</table>

Each value represents mean ± SD. N = 6. Arterial blood PO2, Pco2 and pH did not change significantly by the infusion of PBZ.
Before the administration of PBZ, BrPO_{2} and BrPCO_{2} increased following CO_{2} inhalation. The same pattern of changes was seen after the administration of PBZ, but the increase in BrPO_{2} before PBZ (\Delta BrPO_{2} = 14.8 mmHg) was less than that after PBZ (\Delta BrPO_{2} = 15.6 mmHg). Figure 3 summarizes the changes in each parameter during 5% CO_{2} inhalation before and after the infusion of PBZ in 7 cats. Before the infusion of PBZ, the degree of increase in BrPO_{2} (\Delta BrPO_{2}) during 5% CO_{2} inhalation was 11.3 \pm 10.9 mmHg, which was enhanced significantly (P<0.05) after the infusion of PBZ (14.0 \pm 11.6 mmHg). There was no significant difference in the degree of the increase in BrPCO_{2} and mean arterial blood pressure (MABP) before and after the infusion of PBZ.

**Discussion**

In the present study the intracarotid infusion of PBZ did not change BrPO_{2} and BrPCO_{2} significantly. To minimize the systemic influence of PBZ we administered a low dose of PBZ by intacarotid infusion. Accordingly, we could selectively examine the cerebrovascular effect of PBZ without any changes of BP. Both histochmical and ultrastructural studies have established a rich adrenergic and cholinergic innervation of the cerebral vessels. Pharmacological studies also indicated the presence of both \alpha- and \beta-adrenergic receptors on cerebral vessels by administration of catecholamines, \alpha- and \beta-adrenergic blockers or stimulation of cerebral sympathetic nerves. However, the cerebral circulation is controlled mainly by metabolic factors (chemical control) while under normal conditions the contribution of the sympathetic nervous system seems to be less extensive. Our data suggest that low doses of PBZ do not change the resting tone of cerebral blood vessels which is consistent with the concept of the sympathetic nervous system regulation being less extensive. Weiss and Buchweitz have reported that PBZ does not change average cerebral blood flow in the rabbit, but the results of this kind of study have been conflicting.

After the infusion of PBZ, the degree of increase in BrPO_{2} during 5% CO_{2} inhalation was enhanced significantly without a significant change in BrPCO_{2} and MABP. This finding suggests an increase in the cerebrovascular CO_{2} reactivity by the administration of PBZ. From the observation that the smaller arteries with coarse or no sympathetic innervation respond to changes in arterial PCO_{2} and that the larger arteries with dense innervation respond to changes in BP, Gotoh et al postulated a dual control of the cerebral circulation which consists of chemical control functioning in the cerebrovascular response to local metabolic needs or to blood gas changes and neurogenic control operating in autoregulation. Arterial CO_{2} diffuses to the cerebral vessel wall and increases intracellular hydrogen ion concentration in smooth muscle fibers. This increase in [H^{+}] is responsible for the cerebral vasodilatation by...
CO₂. On the other hand, excitation of the autonomic nervous system by CO₂ induces not only peripheral vasoconstriction but also cerebral vasoconstriction. Under normal condition, direct cerebral vasodilatory action by CO₂ (chemical control) overcomes this vasoconstrictory action through a neurogenic mechanism. The inhibition of the neurogenic mechanism by the infusion of PBZ is thought to have produced the enhancement of cerebral CO₂ reactivity.

In conclusion, it is considered that the sympathetic nervous system modifies cerebrovascular CO₂ reactivity, although under normal conditions its contribution seems to be less extensive.

References