Effect of Sympathetic Nervous System Stimulation on Cerebrovascular CO₂ Responsiveness

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Cerebrovascular CO₂ responsiveness, following noradrenaline (NA) infusion, was studied in the cat by continuous measurement of cerebral tissue oxygen tension (BrPO₂), carbon dioxide tension (BrPCO₂), pH (BrpH), and blood pressure (BP). Intravenous infusion of NA (1 μg/kg/min) was done to stimulate the adrenergic nervous system. Inhalation of 5% CO₂+air was performed for 3 minutes before, during, and after NA infusion. Cerebrovascular CO₂ responsiveness was estimated from changes in BrPO₂, BrPCO₂, and BrpH. CO₂ inhalation increased BrPO₂, BrPCO₂, and BP, but decreased BrpH, in the respective 3 stages. Δ BrPO₂ decreased significantly during NA infusion, but recovered after cessation of NA. NA infusion caused a decrease in CO₂ responsiveness. This suggests that sympathetic hyperactivity can modify cerebrovascular CO₂ responsiveness.

(Key Words: Noradrenaline, Sympathetic System, CO₂ Responsiveness, Cerebral Circulation, Cerebral Metabolism)

INTRODUCTION

We have previously reported (8, 10) that in hypoglycemia the cerebral blood flow (CBF) decreases as the blood glucose level declines. Cerebrovascular CO₂ responsiveness is also impaired in hypoglycemia, but it can be restored by the administration of glucose. The impairment of CO₂ responsiveness during moderate hypoglycemia was assumed to be related to the following phenomena: hyperactivity of the autonomic nervous function, impairment of the chemical control mechanism, and damage of the walls of cerebral vessels. We have detected increases in blood catecholamine levels in hypoglycemia and suggested that excitation of the sympathetic nervous system may have occurred (8, 9).

However, the question of whether catecholamines exert direct effects on cerebrovascular CO₂ responsiveness is still unresolved. In the present study we examined the influence of plasma noradrenaline (NA) levels on cerebrovascular CO₂ responsiveness.

MATERIALS AND METHODS

Ten adult cats, weighing 3.0–4.0 kg, were anesthetized by the intraperitoneal injection of α-chloralose (50 mg/kg) and urethane (500 mg/kg). Operative sites were carefully infiltrated with procaine hydrochloride (0.5%). The femoral artery was exposed and a polyethylene catheter was inserted into the abdominal aorta via the femoral artery and connected to a Statham strain gauge (Model P231D) for recording blood pressure (BP). A second catheter was placed in the femoral vein for injection of drugs and sampling of blood. After tracheostomy, the animals were immobilized with an intravenous injection of alcuronium chloride (DialferinR 2–3 mg) and ventilation was maintained constant by a respirator (Harvard Model 662), so that arterial PO₂, PCO₂, and pH were kept at physiological levels. Body temperature was kept at 37°C by means of a heating blanket throughout the experiment.

The cats were fixed in a stereotactic headholder, the skull opened at the parieto-tempo-
eral region, and the dura incised. PO$_2$, PCO$_2$ and pH electrodes were gently placed on the exposed cerebral cortex using adjustable clamps (17). The output signal of the PO$_2$ electrode was amplified by a gas analyzer (Beckman PGA 160). The outputs of the PCO$_2$ and pH electrodes were amplified by pH meters (Radiometer PHM22). These parameters were continuously recorded on a polygraph (Rikadenki R56M3).

Inhalation of 5% CO$_2$ + air was performed for 3 minutes and cerebral tissue oxygen tension (BrPO$_2$), carbon dioxide tension (BrPCO$_2$), pH (BrpH), and BP were measured. An intravenous infusion of NA (1 μg/kg/min) was started to simulate hyperfunction of the adrenergic nervous system. During NA infusion CO$_2$ inhalation was repeated. Thirty minutes after the termination of the NA infusion, CO$_2$ inhalation was again repeated. Cerebrovascular responsiveness to CO$_2$ was estimated from the changes in brain PO$_2$, PCO$_2$, and pH (ΔBrPO$_2$, ΔBrPCO$_2$, ΔBrpH).

The data are expressed as means ± S.D. Student's t-test was used to compare differences between groups, with p<0.05 indicating significance.

RESULTS
(1) Control readings before CO$_2$ inhalation
The physiological levels of BrPO$_2$, BrPCO$_2$, BrpH, and MABP before CO$_2$ inhalation are shown in Table 1. MABP was 106.7 ± 28.3 mmHg before NA and increased to 128.5 ± 22.4 mmHg during NA (p<0.01). Thirty minutes after the cessation of NA infusion, the MABP had returned to 112.5 ± 25.0 mmHg. BrPO$_2$ was 30.0 ± 6.6 mmHg before NA, increased to 40.1 ± 12.6 mmHg during NA, and decreased to 33.3 ± 25.7 mmHg after NA. There was no significant changes in BrPCO$_2$ and BrpH.

(2) CO$_2$ inhalation before NA infusion
The data related to CO$_2$ inhalation before NA are shown in Figure 1. BrPO$_2$ increased from 29.7 to 36.4 mmHg; BrPCO$_2$ and BP also increased; however, BrpH decreased. These changes are summarized in Figure 4. ΔBrPO$_2$ reached its maximum (7.5 ± 2.3 mmHg) at 4 minutes.

(3) CO$_2$ inhalation during NA infusion
The values obtained following CO$_2$ inhalation during NA are shown in Figure 2. BrPO$_2$ increased from 38.7 to 44.5 mmHg, but the change is smaller than that recovered before NA. ΔBrPO$_2$ was decreased compared with that before NA, with its maximum change being 2.3 ± 3.3 mmHg. This reduction was statistically significant at 2, 3, 4, and 5 minutes. On the other hand, there were no significant changes in ΔBrPCO$_2$, ΔBrpH or ΔMABP. These data are summarized in Figure 4.

(4) CO$_2$ inhalation after NA infusion
The results of CO$_2$ inhalation after NA are shown in Figure 3. The decrease in CO$_2$ responsiveness caused by the administration of NA was restored after the cessation of NA. BrPO$_2$ increased from 34.8 to 43.6 mmHg after CO$_2$ inhalation. ΔBrPO$_2$ was greater than during NA, but remained slightly smaller than before NA. ΔBrPCO$_2$, ΔBrpH and Δ

<table>
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<th>Table 1 Cerebral tissue oxygen tension (BrPO$_2$), carbon dioxide tension (BrPCO$_2$), pH (BrpH) and mean arterial blood pressure (MABP) readings before CO$_2$ inhalation.</th>
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<td>before NA</td>
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<tr>
<td>BrPO$_2$ (mmHg)</td>
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<td>BrPCO$_2$(mmHg)</td>
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<td>BrpH</td>
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<td>MABP (mmHg)</td>
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mean ± S.D.  * : p<0.05  ** : p<0.01
MABP showed no significant changes. These results are summarized in Figure 4.

**DISCUSSION**

The present study demonstrates that cerebrovascular CO$_2$ responsiveness decreased during the infusion of NA, but then recovered after the cessation of NA.

The cerebrovascular action of CO$_2$ is thought to be due primarily to a direct action on the cerebral vessel wall, as described by Gotoh et al. (5, 16). Arterial CO$_2$ diffuses into the cerebral vessel wall and increases the intracellular [H$^+$] of the vascular smooth muscle through the action of carbonic anhydrase (4, 6). The increase in hydrogen ion concentration is responsible for the cerebral vasodilatation. In addition, sympathetic innervation of the cerebral vessels has been demonstrated both morphologically and functionally (2, 7, 9, 14, 19, 20, 22). Based on observations 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 (21), Gotoh et al. postulated a dual control of the cerebral circu-

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**Fig. 1** Graphic depiction of the effects of CO$_2$ inhalation **before** noradrenaline (NA) infusion on cerebral tissue oxygen tension (BrPO$_2$), carbon dioxide tension (BrPCO$_2$), pH (BrpH), and blood pressure (BP).

**Fig. 2** Graphic depiction of the effects of CO$_2$ inhalation **during** NA on BrPO$_2$, BrPCO$_2$, BrpH, and BP.
It was suggested that chemical reactions controlled the cerebrovascular response to local metabolic needs or to blood gas changes, and that a neurogenic control was operative in autoregulation (6). Excitation of the sympathetic system by CO₂ induces not only peripheral but also cerebral vasoconstriction. In the normal cerebral circulation, the direct vasodilatory action of CO₂ (chemical control) overcomes this vasoconstriction through a neurogenic mechanism.

BrPO₂ determined according to the balance between the amount of oxygen supplied by the CBF, and the amount of oxygen needed for cerebral energy metabolism. An increase in BrPO₂ is likely to occur with 1) an increase in oxygen content of the arterial blood, 2) an increase in oxygen supply induced by an increased CBF, and/or 3) a decrease in cerebral oxygen consumption (17).

**Fig. 3** Graphic depiction of the effects of CO₂ inhalation after NA on BrPO₂, BrPCO₂, BrpH and BP.

**Fig. 4** The effects of CO₂ inhalation before, during, and after NA infusion on the changes of cerebral tissue oxygen tension (ΔBrPO₂), carbon dioxide tension (ΔBrPCO₂), pH (ΔBrpH), and mean arterial blood pressure (ΔMABP). *p<0.05; **p<0.01.
In the present experiments, we undertook a pharmacological investigation of the role of sympathetic regulation of CBF function. Previously, we examined the effects of phenoxybenzamine (α-blocker) and clonidine (potent α2 adrenergic agonist and imidazole/imidazoline receptor agonist), measuring BrPO2 and BrPCO2 in the cat (11, 12). In those studies, phenoxybenzamine and clonidine significantly enhanced cerebrovascular responsiveness to CO2. That finding likely was due to inhibition of the neurogenic vasoconstrictory mechanism in cerebral vessels during CO2 inhalation, and enhancement of the direct dilatory response of cerebrovascular smooth muscle to CO2 (13, 18). Experimental hyperactivity of the sympathetic system elicited by stimulation of the cervical sympathetic ganglion (1, 15), or by catecholamine infusion (22, 23), caused cerebral vasoconstriction and decreased CBF. Intravenous administration of NA may not necessarily reflect its direct action on the cerebral vasculature, since the induced changes in BP, heart rate, and cardiac output would themselves modify CBF (3). Therefore, in the present experiment we administered very small doses of NA which did not cause any obvious accompanying changes in BP and heart rate. The results indicate a direct action of NA on the cerebral vessels rather than affecting changes in systemic variables. It is possible therefore that hyperactivity of the sympathetic system, induced by the infusion of NA, suppressed the normal cerebrovascular CO2 responsiveness. The decreased CO2 responsiveness during NA infusion distinctly improved after stopping the infusion of NA. This supports the view that the cerebrovascular dilatory action of CO2 was inhibited by stimulation of the sympathetic system by the infusion of NA.

In conclusion, the sympathetic system is believed to participate in cerebrovascular CO2 responsiveness, the full extent of which is still not clearly delineated.

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