Sodium Nitroprusside and Cerebral Blood Flow in the Anesthetized and Unanesthetized Goat

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The effects of sodium nitroprusside (SNP) on total, ipsilateral cerebral blood flow (CBF) in the unanesthetized and anesthetized goat was evaluated under four conditions: 1) bolus injection of SNP into the cerebral circulation via the temporal artery; 2) continuous infusion of SNP into the temporal artery in amounts too small to affect the peripheral circulation (0.57–1.14 μg/kg/min); 3) intravenous infusion of SNP; 4) continuous intravenous infusion of SNP with a bolus injection of angiotensin. Small doses (20, 40, and 80 μg) of SNP injected directly in the cerebral circulation of the awake goat produced immediate increases of 21 ± 8, 36 ± 8, and 48 ± 10 per cent, respectively, in CBF lasting 1 to 3 min without causing peripheral cardiovascular changes. The effects of SNP were attenuated by 1.5 per cent halothane anesthesia. Continuous infusion of SNP into the temporal artery in amounts too small to cause peripheral cardiovascular effects produced sustained increases in CBF averaging 31 ± 8 per cent; CBF returned to preinfusion values upon cessation of infusion. Intravenous infusion of SNP in both anesthetized and unanesthetized animals in recommended clinical dosages (3–8 μg/kg/min) produced hypotension but did not significantly alter CBF. However, upon injection of angiotensin (1.43 μg/kg), both peripheral blood pressure and CBF increased sharply, suggesting that SNP may impair autoregulation of CBF. The results of this study indicate that SNP dilates the cerebral vascular system in a way that is probably similar to its effects on other vascular beds. (Key words: Brain, blood flow; Anesthetic techniques, induced hypotension; Pharmacology, nitroprusside.)

SODIUM NITRROPRUSSIDE is advocated for treatment of severe acute arterial hypertension and for induction of hypotension during neurosurgical procedures.1–4 Most reports indicate that the short-term use of nitroprusside is safe, nontoxic, and that the ensuing hypotension is easily controlled. However, while it is agreed that sodium nitroprusside produces hypotension by decreasing peripheral vascular resistance,5–8 with the exception of a single report,9 little is known concerning the effects of nitroprusside on the cerebral vasculature. No information is available regarding its effects on the cerebral autoregulatory mechanism in unanesthetized and anesthetized subjects. The present study evaluates the effects of sodium nitroprusside on the cerebral circulation.

Methods

The studies were performed in a model developed by Reimann et al. for continuous measurement of ipsilateral cerebral blood flow in the unanesthetized, unrestrained goat.10 Full anatomic descriptions of the arterial blood supply to the goat brain and the detailed methods employed to prepare the animal for study have been presented elsewhere.11,12 Briefly, total blood flow to each cerebral hemisphere is provided by a single external carotid artery (fig. 1). The external carotid artery bifurcates extracranially, forming the lingual and internal maxillary arteries. Two major vessels, the ramus anastomoticus and arteria anastomotica, arise from the internal maxillary artery and enter the cranial vault, where they empty into the rete mirabile. The rete mirabile consists of a compact network of intertwined, freely anastomosing arteries, permitting a high degree of contralateral communication across the midline of the brain. Blood leaves the rete by the right and left internal carotid arteries and empties into the circle of Willis. Branches from the internal maxillary artery also supply blood
FIG. 1. Diagram of the arterial blood supply in the goat’s head. Arrows on the left indicate direction of blood flow in the normal animal. Arrows on the right indicate direction of flow after deliberate thrombosis and ligation of extracerebral vessels. Also shown on the right are the positions of the temporal-artery catheter and electromagnetic flow probe.

to the extracerebral tissues via the buccinator, ethmoidal and ophthalmic arteries.

Eight mature female goats weighing 30–40 kg were surgically prepared for study as follows. Anesthesia was induced with halothane using a mask, the trachea intubated, and respirations mechanically controlled using an Ohio respirator with 1.5 per cent halothane in oxygen. An esophageal gastric tube was placed into the stomach to prevent vomiting and aspiration. A lateral incision was made along either the right or left mandible and a small portion of the mandible was removed to expose the internal maxillary artery, ramus anastomoticus, and the temporal and dental arteries. Ligatures were placed around the internal maxillary artery distal to the ramus anastomoticus and on the temporal and dental arteries. To obliterate extracerebral blood flow through the anatomically inaccessible ophthalmic, ethmoidal and buccinator arteries, 1,000–2,000 NIH units of thrombin (Thrombin—Parke Davis) were slowly injected in 0.5 ml of saline solution into the internal maxillary artery proximal to the site of ligation. The injected thrombin produced immediate clotting; elimination of extracerebral blood flow was evident by the appearance of thrombosed vessels in the sclera and by postsurgical ipsilateral blindness. After this, a 4-mm Statham electromagnetic flow probe was placed around the internal maxillary artery for continuous measurement of ipsilateral cerebral blood flow. Under direct vision, a small catheter was then placed into the temporal artery and advanced approxi-

FIG. 2. Effects of continuous intravenous infusion of sodium nitroprusside (2.89 µg/kg/min) on cerebral blood flow, cardiac output, and mean arterial pressure in the awake goat. CBF = ipsilateral cerebral blood flow (ml/min); CO = cardiac output (ml/min).
mately 0.5 cm to the juncture of the temporal and maxillary arteries. Care was taken to be sure that the tip of the catheter was not projecting into the maxillary artery. The catheter and leads from the electromagnetic flow probe were then externalized and secured to the goat's horn. In four animals a left thoracotomy was also performed and an 18-mm Statham electromagnetic flow probe was placed around the pulmonary artery for measurement of cardiac output. A long, firm catheter was introduced into the aorta through the femoral artery for blood-gas and arterial blood pressure measurements. A similar catheter was placed in the femoral vein for infusion of drugs. Incisions were then closed. In most cases, the animals were ready for study two weeks later.

The effects of sodium nitroprusside (Nipride—Roche) on the cerebral circulation were determined by intra-arterial administration and by peripheral intravenous infusion in awake and anesthetized animals. Small doses of sodium nitroprusside (20–80 μg) were injected directly into the cerebral vascular system via the previously implanted temporal arterial catheter during simultaneous monitoring of cerebral blood flow, cardiac output, heart rate, and blood pressure. Similarly, the effects of reduced peripheral blood pressure on cerebral blood flow caused by continuous infusion of sodium nitroprusside into the femoral vein were evaluated. In studies involving anesthetized animals, 1–1.5 per cent halothane in O₂ was used and ventilation controlled by an Ohio ventilator. Blood gases were determined at appropriate times throughout each experiment to ascertain whether sodium nitroprusside produced cerebral blood flow changes secondary to changes in blood gases.

Autoregulation of cerebral flow in awake animals was tested by peripheral intravenous injection of angiotensin (Hypertensin—CIBA) into awake, unrestrained animals and

![Fig. 3. Effects of intravenous injection of angiotensin (1.43 μg/kg) on cerebral blood flow and arterial blood pressure during intravenous infusion of sodium nitroprusside (SNP) (2.89 μg/kg/min).](attachment:fig3.png)

![Fig. 4. Effects of increasing arterial pressure on cerebral blood flow in the awake goat. Elevation of mean arterial pressure to 200 mm Hg by angiotensin infusion (1.43 μg/kg/min) produced only a slight increase in cerebral blood flow.](attachment:fig4.png)
into animals during intravenous infusion of sodium nitroprusside.

**Results**

The effects of continuous intravenous infusion of sodium nitroprusside on cerebral blood flow, arterial blood pressure, and cardiac output in the awake goat can be seen in figure 2. Cerebral blood flow remained constant as mean systemic arterial blood pressure fell to 50 mm Hg, suggesting intact autoregulation of cerebral flow. However, a bolus injection of angiotensin (1.43 μg/kg) caused immediate increases in mean arterial pressure and cerebral blood flow, indicating a loss of autoregulation of cerebral blood flow in the presence of rising arterial pressure (fig. 3). In the awake animal, intravenous infusion of angiotensin (1.43 μg/kg/min) increased arterial pressure, but cerebral flow remained essentially constant (fig. 3). Figure 5 depicts the effects of a bolus injection of 80 μg sodium nitroprusside directly into the cerebral circulation of an anesthetized goat via the temporal arterial catheter. An immediate increase in cerebral blood flow was observed, sometimes followed by a slight

**Table 1. Effects of Centrally Administered Sodium Nitroprusside (SNP) on Ipsilateral Cerebral Blood Flow (ICBF) in the Anesthetized and Unanesthetized Goat**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Anesthetized</th>
<th>Unanesthetized</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control ICBF (mL/min)</td>
<td>Increase after SNP* (Per Cent)</td>
</tr>
<tr>
<td>20 μg</td>
<td>98 ± 12</td>
<td>15 ± 7†</td>
</tr>
<tr>
<td>40 μg</td>
<td>95 ± 12</td>
<td>26 ± 5†</td>
</tr>
<tr>
<td>80 μg</td>
<td>101 ± 15</td>
<td>35 ± 10†</td>
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* Mean increase ± SD in ipsilateral cerebral blood flow above control values following sodium nitroprusside injection.
† Statistically significant change (P < 0.05, n = 8), based on t test for paired data.
transient decrease in systemic arterial pressure. The duration of increased cerebral flow was variable, lasting 1–3 minutes. Table 1 is a dose–response compilation of the effects of 20, 40, and 80 μg on cerebral blood flow following direct central injection in both unanesthetized and anesthetized goats. The effects of sodium nitroprusside on cerebral blood flow were less in animals anesthetized with halothane than in awake animals. Continuous infusion of sodium nitroprusside (0.57–1.14 μg/kg/min) into the temporal artery of eight awake animals produced sustained increases in cerebral blood flow averaging 31 ± 8 per cent above preinfusion levels, provided the dosage was adjusted so as to avoid depression of peripheral arterial pressure (fig. 6).

Changes in cerebral blood flow were not due to alterations in blood gases, since these remained unchanged during continuous infusion and during direct central administration of sodium nitroprusside.

Discussion

The results of this study indicate that sodium nitroprusside dilates the cerebral vascular system in a way that is probably similar to its effects on other vascular beds. Small doses of sodium nitroprusside (20–80 μg) injected directly into the cerebral circulation via the temporal-artery catheter in both awake and anesthetized goats produced an immediate decrease in cerebrovascular resistance and an increase in cerebral blood flow (fig. 5 and table 1). This effect could be sustained by continuous infusion unless there was sufficient accumulation of sodium nitroprusside in the blood to produce systemic hypotension (fig. 6). If peripheral systemic hypotension developed during either central or peripheral intravenous infusion of nitroprusside, blood flow remained essentially unchanged (fig. 2). However, a sudden increase in peripheral blood pressure following an intravenous injection of angiotensin produced a parallel and corresponding increase in cerebral blood flow (fig. 3). This suggests that angiotensin, which does not constrict cerebral vessels, by increasing peripheral vascular resistance displaces a portion of the blood volume into the cerebral circulation previously dilated by sodium nitroprusside, thus indicating that sodium nitroprusside by its action on cerebral vessels abolishes autoregulation of cerebral blood flow. Further, these data suggest that cerebral blood flow would remain constant during sodium nitroprusside infusion in the presence of decreased peripheral pressure, provided cardiac output remains constant and cerebrovascular resistance decreases at the same rate as peripheral vascular resistance. Kenney et al. failed to demonstrate changes in cerebral blood flow while studying the use of sodium nitroprusside during hypotensive anesthesia in baboons, probably because they did not test cerebrovascular autoregulatory capability during sodium nitroprusside treatment by increasing peripheral blood pressure.

The data from this study suggest that during surgical procedures involving the deliberate induction of hypotension with sodium nitroprusside, care should be taken to avoid sudden fluctuations in arterial blood pressure, since the patient may not be protected by a cerebral autoregulatory mechanism. Increases
in systemic blood pressure may be associated with precipitous increases in cerebral blood flow. In addition, patients who have central nervous system lesions might be poor candidates for induced hypotension with sodium nitroprusside because of the risk of cerebral blood flow "steal." Blood perfusing an infarcted, maximally dilated area of the brain might be diverted to other areas by the cerebral vasodilating action of sodium nitroprusside. This so-called "intracranial steal" phenomenon has been demonstrated in experimental situations where hypercarbia was induced to produce cerebral vasodilation.14

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References

Anticholinergic Drugs

ATROPINE AND GLYCOPYRROLATE

The effects of glycopyrrolate on pulse rate and pharyngeal secretions were compared with those of atropine. The drugs were used both as premedicants and in combination with neostigmine for reversal of neuromuscular blockade. Ninety-eight patients were studied; half received glycopyrrolate and half atropine in a double-blind fashion. The states of dryness of the pharynx prior to induction were similar with both anticholinergics. When used to antagonize the salivation stimulated by neostigmine, glycopyrrolate appeared significantly superior. Changes in pulse rate following premedication did not differ between the two drugs. When administered intravenously prior to use of neostigmine, a greater increase in pulse rate was observed two minutes after injection of atropine. However, by five minutes pulse rates were similar in both groups. Slowing of the pulse in response to administration of neostigmine seemed somewhat greater with atropine than with glycopyrrolate. (Oduro KA: Glycopyrrolate Methobromide. Comparison with Atropine Sulphate in Anaesthesia. Canad Anaesth Soc J 22: 466–473, 1975.) ABSTRACTER'S COMMENT: The author used 0.8 mg atropine or 0.4 mg glycopyrrolate to antagonize the effects of 2.5 mg neostigmine. Since only one dose of each drug was used (and perhaps a low dose at that), overall comparison of their safety and efficacy is difficult.