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Ganglionic Blockade Improves Neurologic Outcome from Incomplete Ischemia in Rats: Partial Reversal by Exogenous Catecholamines

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The authors investigated the effects of nitrous oxide (N_2O), ganglionic blockade, and combined infusion of epinephrine and norepinephrine (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ each) on neurologic outcome and brain histopathology in a model of incomplete cerebral ischemia in the rat. Thirty-eight Sprague-Dawley rats were assigned to one of four groups: group 1 (n = 10) received 70% N_2O in O_2; group 2 (n = 12) received 70% N_2O in O_2, plus ganglionic blockade; and group 3 (n = 10) received 70% N_2O in O_2, plus ganglionic blockade and catecholamine infusion. In groups 1–3, ischemia was produced by right carotid occlusion combined with hemorrhagic hypotension (35 mmHg) for 30 min. Group 4 (n = 6) received 70% N_2O in O_2 and hemorrhagic hypotension without carotid occlusion for 30 min. At the end of ischemic and nonischemic hypotension, the carotid artery was unclamped and the blood slowly reinfused. Neurologic outcome was evaluated for a 5-day period with a graded deficit score (0 = normal to 39 = stroke-related death). Brain histopathology was evaluated in coronal section at the level of the caudate nucleus according to a 6-point scale, from 0 = normal to 5 = total hemispheric infarction. Arterial blood gases, *p*H, and body temperature were kept constant in all groups. Compared to N_2O alone (group 1), treatment with ganglionic blockade (group 2) decreased plasma catecholamines by 75% and significantly improved neurologic outcome from incomplete cerebral ischemia ($P < 0.05$). Administration of exogenous epinephrine and norepinephrine in the presence of N_2O and ganglionic blockade (group 3) worsened neurologic outcome compared to group 2 ($P < 0.05$). Brain histopathology in rats surviving the 5-day examination period showed an entire range of brain tissue damage in the ischemic hemisphere. However, neurologic deficit did not predict histopathologic neuronal injury. No neurologic deficit or histopathologic damage was seen in rats treated with nonischemic hemorrhagic hypotension (group 4). The improvement of neurologic outcome after ganglionic blockade suggests direct involvement of the sympathetic nervous system in the modulation of ischemic brain damage.

(Key words: Brain: ischemia, neurologic outcome, histopathology. Anesthetics, gases: nitrous oxide. Sympathetic nervous system: ganglionic blockade; hexamethonium. Catecholamines: epinephrine, norepinephrine.)

THERE IS CONTROVERSY concerning the role of the sympathetic nervous system in mediating ischemic neuronal injury. Globus *et al.*[1–3] and Lavyne *et al.*[4] emphasized the detrimental role of central catecholamine pathways on ischemic injury: they attributed the damage to increases in cerebral metabolic rate and imbalance of cerebral blood flow (CBF) and metabolism. This suggestion was supported by Stein and Cracco,[5] who showed a direct toxic effect of topically applied catecholamines on neuronal tissue. In contrast, Blomqvist *et al.*[6] found less ischemic brain injury in the presence of intact central catecholamine pathways. Destruction of central noradrenergic projections resulted in increased ischemic neuronal damage. Consistent with this, Koide *et al.*[7] demonstrated improved postischemic brain histopathology in rats with normal adrenergic responses, as compared to animals treated with ganglionic blockade. They concluded that catecholamines modulate protection from ischemic brain injury.

To evaluate the role of catecholamines during brain ischemia, we studied the effects of nitrous oxide (N_2O), ganglionic blockade, and the administration of exogenous catecholamines on neurologic outcome and histopathology in a model of incomplete cerebral ischemia in the rat. N_2O was used as a background agent because it allows activation of the sympathetic nervous system.[8,9]

Materials and Methods

After approval from the Michael Reese Animal Care Committee had been obtained, 38 nonfasted male Sprague-Dawley rats (340–460 g) were anesthetized in a bell jar with isoflurane. After tracheal intubation, their lungs were ventilated with 1.4% isoflurane and 70% N_2O in O_2. Catheters were inserted into one femoral artery and into both femoral veins after surgical cutdowns for continuous blood pressure monitoring, blood gas sampling, and drug administration. This procedure did not produce limb ischemia. The right jugular vein was exposed and a catheter was inserted for blood removal during ischemia. The right common carotid artery was iso-

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lated and a loose ligature placed around it for later clamping. Vecuronium was given as a continuous infusion (0.1 $mg \cdot kg^{-1} \cdot min^{-1}$) to maintain paralysis. At completion of surgery, the wounds were infiltrated with 0.5% bupivacaine, and isoflurane was discontinued. After a 30-min equilibration period under 70% N_2O in O_2 the rats were randomly divided into four groups: group 1 (n = 10) received 70% N_2O in O_2 as a control treatment. Group 2 (n = 12) was given 70% N_2O in O_2, plus hexamethonium (8 $mg \cdot kg^{-1}$). The ganglionic blocking agent was injected 15 min prior to induction of ischemia to blunt the sympathetic response to ischemic hypotension. Group 3 (n = 10) received 70% N_2O in O_2, plus hexamethonium (8 $mg \cdot kg^{-1}$) and continuous infusion of epinephrine and norepinephrine (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ each). Catecholamines were infused starting 10 min after ganglionic blockade and were continued throughout the ischemic period. Group 4 (n = 6) received 70% N_2O in O_2 and hemorrhagic hypotension without carotid ligation to evaluate the effects of systemic shock on mortality and brain histopathology.

Cerebral ischemia was produced for 30 min by the combination of hemorrhagic hypotension and right carotid occlusion by means of a microvascular Heifetz clip. Mean arterial blood pressure was maintained at 35 mmHg with a range of 2 mmHg. The hypotensive level was increased from the 25 or 30 mmHg used in a previous study[10] to 35 mmHg, in order to reduce the ischemic injury so that differences could be shown among treatment groups. After 30 min of ischemia, the carotid artery was unclamped and the withdrawn blood reinfused over a period of 10 min. Administration of N_2O was discontinued 30 min after reinfusion of the blood. The catheters were removed, the incisions closed, and the trachea extubated within the recovery period. Rectal temperature was measured with a Yellow Springs thermistor probe and was maintained at 37° C by servomechanism with an overhead heat lamp. Arterial CO_2 partial pressure (Pa_{CO_2}) was kept between 35 and 40 mmHg by adjusting ventilation. Arterial *p*H was maintained at normal levels by bicarbonate infusion. Arterial blood gas (Instrumentation Lab 1303) and plasma glucose analyses (Yellow Springs Glucose Analyzer) were performed at control, during ischemia, and 15 min after reinfusion of the blood during recovery. Arterial blood samples were taken for radioenzymatic assay of plasma catecholamines (CAT-A-KIT,® Amersham) at the end of the ischemic period and were assayed as reported previously.[11]

Neurologic Outcome

Neurologic outcome scores were obtained once per day for a period of 5 days, starting 24 h after ischemia. The evaluator was blinded to the treatment condition of ischemia. Table 1 summarizes seven categories of performance obtained by neurologic examination. Stroke-related death (deficit score = 39) was determined after a minimum of 3 h after extubation only if the rat showed progressive signs of stroke impairment.

Brain Histopathology

Rats that survived 5 days were anesthetized with isoflurane. Then, after their chests were opened, they were killed by transcardial perfusion of 20 ml isotonic saline followed by 20 ml 10% buffered formalin. Volume overload was avoided by incisions of the right cardiac atrium. After removal, the brain was stored in formalin over 8 days for subsequent histologic examination. The forebrain was cut into coronal blocks and embedded in paraffin, and 7-μm sections were sliced and mounted on slides. The slides were stained with hematoxylin and eosin and examined in a blinded manner by a neuropathologist using light microscopy. Neuronal histopathology was evaluated in the coronal section at the level of the caudate nucleus. Brain tissue damage was graded on a six-point scale ac-

TABLE 1. Neurologic Deficit Scoring

Category	Score	Description
Consciousness	0	Normal
	2	Excitable
	4	Difficult to arouse
	6	Stuporous
	8	Seizures
	10	Coma
	12	Death
Walking	0	Normal
	1	Paw adduction
	2	Ataxia
	3	Unbalanced walking
	4	Circling to stroke side
	5	Unable to stand
	6	No movement
Rope platform	0	Climbs to platform
	1	Hangs on 5 s and pulls up rear legs
	2	Hangs on 5 s
	3	Hangs on <5 s
	4	No reflex grasp
Rotating screen	0	Grasps to 180° > 5 s
	1	Grasps to 180° < 5 s
	2	Grasps to 90°, not 180°
	3	Falls from vertical screen
Cranial nerves	0–2	Corneal reflex (present–absent)
	0–2	Gag reflex (present–absent)
	0–2	Swallowing reflex (present–absent)
Limb tone	0	Normal
	1	Spastic
	2	Flaccid
Pain reflex	0	Normal
	2	Hyperactive
	4	Hypoactive
	6	Absent

cording to the following markers: 0 = no observable neuronal death; 1 = scattered neuronal death; 2 = small focal infarcts in caudate and cortical areas; 3 = large infarcts involving 50% of the caudate; 4 = infarcts involving at least 50% of the total ischemic hemisphere; and 5 = total hemispheric infarction.

Statistics

Data are reported as mean ± SE. Nonparametric data, including neurologic outcome and histopathology, were evaluated by Kruskal-Wallis analysis of variance (ANOVA). Physiologic parameters were compared among groups and treatments with a two-way ANOVA and Tukey's tests for *post hoc* comparisons ($P < 0.05$). A Spearman rank-order correlation was used for correlations of neurologic outcome with other parameters. For correlations, all data were combined for groups 1–3.

Results

Cardiovascular Parameters, Blood Gases, Plasma Glucose, and Catecholamines

Table 2 summarizes the data for mean arterial blood pressure (MAP), plasma glucose, arterial O_2 partial pressure (Pa_{O_2}), Pa_{CO_2}, and *p*H at control, during ischemia (groups 1–3) or hemorrhagic hypotension alone (group 4), and during recovery. In group 2, infusion of hexamethonium decreased MAP from 134 ± 2 to 92 ± 3 mmHg ($P < 0.05$). In group 3, infusion of hexamethonium decreased MAP from 119 ± 3 to 87 ± 4 mmHg. Infusion of catecholamines after hexamethonium increased MAP to 129 ± 4 mmHg. According to the protocol, MAP was significantly decreased during ischemic (groups 1–3) and nonischemic hypotension (group 4), as compared to control. Total blood withdrawn to produce hypotension of 35 mmHg was 12 ± 1 ml in group 1, 8 ± 1 ml in group 2, 10 ± 1 ml in group 3, and 12 ± 1 ml in group 4. Significantly less blood was withdrawn in group 2 as compared to that drawn from group 1. Plasma glucose increased during ischemia in all groups and was higher in group 1 than in group 2 ($P < 0.05$). Arterial blood gases and *p*H remained within physiologic limits in all groups.

Plasma catecholamine concentrations at the end of the ischemic period (group 1–3) and at the end of nonischemic hypotension (group 4) are presented in figure 1. Ischemic (group 1) and nonischemic hypotension (group 4) produced similar plasma catecholamine concentrations. Epinephrine, norepinephrine, and dopamine were significantly decreased in the presence of hexamethonium alone (group 2), whereas additional infusion of epinephrine and norepinephrine (group 3) produced plasma concentrations not significantly different from those in group 1 or group 4.

Neurologic Outcome

Figure 2 shows neurologic outcome scores for all ischemic groups over a period of 5 days. Neurologic examination of animals in group 2 (N_2O in O_2 plus ganglionic blockade) showed a significant improvement in outcome when compared to group 1 (N_2O in O_2) and group 3 (N_2O in O_2 plus ganglionic blockade and exogenous cat-

Table 2. Mean Arterial Blood Pressure, Plasma Glucose, Blood Gas Tensions, and *p*H at Control, During Ischemia or Nonischemic Hemorrhagic Hypotension, and During Recovery

Group	Treatment	MAP (mmHg)	Glucose (mg/dl)	Pa_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	*p*H
1 (n = 10)	Control	136 ± 4	167 ± 4	146 ± 4	37.9 ± 0.9	7.44 ± 0.01
70% N_2O	15 min ischemia	35 ± 1*	—	147 ± 5	36.4 ± 0.9	7.39 ± 0.02
	30 min ischemia	35 ± 1*	384 ± 25*	140 ± 4	38.4 ± 0.7	7.38 ± 0.01
	Recovery	113 ± 3*	227 ± 36	122 ± 9	39.1 ± 0.7	7.37 ± 0.02*
2 (n = 12)	Control	92 ± 3†	180 ± 7	143 ± 6	39.1 ± 0.7	7.43 ± 0.01
70% N_2O/hexamethonium	15 min ischemia	35 ± 1*	—	142 ± 4	36.6 ± 0.7	7.40 ± 0.01
	30 min ischemia	36 ± 1*	279 ± 18*†	139 ± 5	35.8 ± 0.7	7.39 ± 0.01
	Recovery	109 ± 3*	150 ± 13	139 ± 6	37.9 ± 1.1	7.42 ± 0.01
3 (n = 10)	Control	129 ± 4	160 ± 7	132 ± 6	37.5 ± 0.9	7.41 ± 0.01
70% N_2O/hexamethonium/catecholamines	15 min ischemia	35 ± 1*	—	134 ± 4	37.5 ± 0.9	7.41 ± 0.01
	30 min ischemia	35 ± 1*	328 ± 27*	133 ± 3	35.6 ± 1.5	7.41 ± 0.01
	Recovery	92 ± 5*†	190 ± 23	127 ± 4	35.6 ± 1.5	7.41 ± 0.01
4 (n = 5)	Control	126 ± 2	171 ± 3	132 ± 8	39.1 ± 0.5	7.42 ± 0.01
70% N_2O	15 min hypotension	35 ± 1*	—	140 ± 9	37.2 ± 1.2	7.36 ± 0.01
	30 min hypotension	35 ± 1*	312 ± 31*	135 ± 8	40.5 ± 0.8	7.37 ± 0.01
	Recovery	120 ± 1	168 ± 14	126 ± 5	40.3 ± 0.5	7.42 ± 0.01

Data reported as mean ± SE.
Control measures were taken before induction of ischemia.
* $P < 0.05$ *versus* control within group.
† $P < 0.05$ *versus* group 1 at each respective treatment.

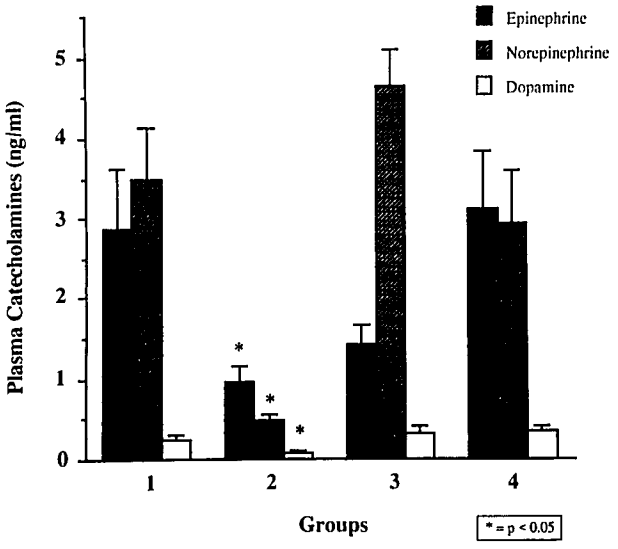

FIG. 1. Plasma catecholamine concentrations (mean ± SE) of groups 1–4. Treatment with ganglionic blockade significantly reduced catecholamines (group 2). Exogenous infusion of catecholamines in the presence of ganglionic blockade (group 3) resulted in catecholamine levels not significantly different from group 1 (*$P < 0.05$ *vs.* group 1).

echolamines). Neurologic outcome in group-3 animals improved as compared to that in group 1. Correlations between neurologic outcome and plasma glucose or plasma catecholamines were not significant ($P > 0.05$). All animals treated with hemorrhagic hypotension without cerebral ischemia (group 4) survived the 5-day examination period without evidence of neurologic deficit (score = 0).

HISTOPATHOLOGY

Due to stroke-related death in 90% of the N_2O-treated animals (group 1) and in 40% of catecholamine-treated animals (group 3), there were inadequate numbers of subjects for statistical comparison of histopathology among groups. None of the rats treated with N_2O and hypotension but not ischemia (group 4) developed neuronal damage. Because several rats in each of the ischemia-treatment groups showed large infarcts in the ischemic hemisphere, there was no significant correlation between histopathology and neurologic outcome ($P > 0.05$).

Discussion

Our results demonstrate that ischemia in rats with an intact sympathetic nervous system (group 1) produced severe neurologic damage: only one rat survived the 5-day examination period. This damage was due to cerebral ischemia, since hypotension without carotid ligation (group 4) produced no neurologic deficit or histopathologic damage. Ganglionic blockade produced significantly better outcome after ischemia (group 2 as compared to group 1). Additional treatment with intravenous catecholamines (group 3), compared to ganglionic blockade alone, worsened outcome, but was less injurious than was N_2O alone. Plasma glucose concentrations were increased during ischemia in all groups and were higher in group 1 as compared to those in group 2. However, plasma glucose showed a poor correlation to neurologic outcome. These results suggest that elevated sympathetic activity during N_2O ventilation worsens neurologic outcome from incomplete ischemia. This effect may be produced in part by elevated circulating catecholamines that act on cerebral vessels or move into the brain tissue through a leaky blood–brain barrier.[12,13]

The effect of sympathetic action on cerebral vascular resistance is controversial.[14,15] Catecholamines may produce vasoconstriction of both pial and parenchymal vessels after stimulation of the locus ceruleus or the stellate gan-

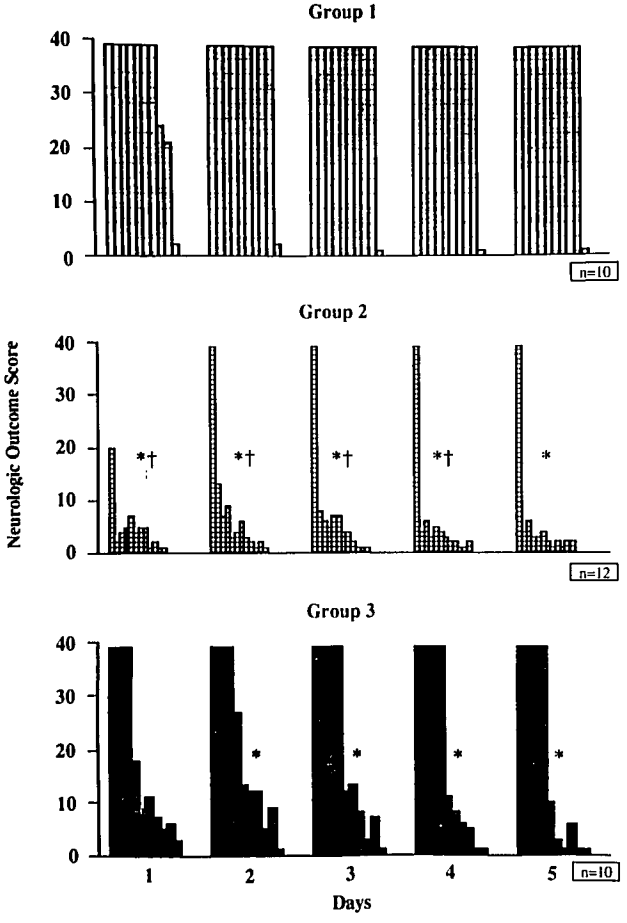

FIG. 2. Neurologic deficit scores after incomplete cerebral ischemia in groups 1–3 over a 5-day examination period. Each bar represents the neurologic score for each rat (*$P < 0.05$ *vs.* group 1; †$P < 0.05$ *vs.* group 3). The rats are ranked according to total outcome score in descending order.

glion.[16] Under normal conditions, parenchymal vessels may escape from constriction within 5 min, returning CBF nearly to control values.[17-19] However, decreases in CBF after sympathetic stimulation are prolonged under conditions of hypercapnia and hypoxia because of preexisting dilation of parenchymal vessels.[20,21] Consistent with this, Fitch *et al.*[22] and Busija[23] have shown that increased sympathetic activity is associated with reductions in CBF during hemorrhagic hypotension due to cerebral arterial vasoconstriction. If these mechanisms can be translated to the current model, ischemic hypotension would produce greater decreases in CBF in sympathetically intact rats as compared to ganglionic-blocked rats. We suggest that circulating catecholamines, given by intravenous infusion, may produce vasoconstriction in ischemic tissue.

Ischemic brain damage also may be enhanced by increases in brain metabolism mediated by central sympathetic neurons or circulating catecholamines. Several investigators reported increases in CBF and brain metabolism after activation of central and peripheral sympathetic pathways. MacKenzie and colleagues[24,25] demonstrated increases in cerebral O_2 consumption and glucose utilization when catecholamines gained access to brain tissue or after norepinephrine was released from intraneuronal stores. Under normal conditions, catecholamines do not cross the blood–brain barrier easily. Ischemia may increase the permeability of this barrier, but the time course of these changes is unclear with respect to monoamines.[12,13] Globus *et al.*[1] showed that central norepinephrine release is increased by ischemic stress. Other studies suggest that during ischemia, central sympathetic activity is associated with increases in brain metabolism and increased neuronal vulnerability.[16,26,27] Meyer *et al.*[28] correlated progression of brain infarction with abnormal release of central norepinephrine and increased cerebral O_2 consumption. This suggests that central and possibly circulating catecholamines produce inappropriately high metabolic rates in ischemic tissue, a condition that may worsen postischemic neuronal status.[3]

Previous reports indicate that N_2O, compared to other anesthetic agents, has detrimental effects on ischemic neuronal tissue.[10] N_2O has been reported to increase both CBF and brain metabolism, an effect attributed to stimulation of sympathetic activity.[8,29,30] From this it must be considered whether N_2O is directly responsible for a worse outcome during ischemia, or whether its association with increased sympathetic activity is the injurious mechanism. Our results indicate that increased sympathetic activity plays a major role in worsening neurologic outcome from incomplete ischemia.

Koide and co-workers[7] evaluated neuronal injury after treatment with N_2O ventilation and ganglionic blockade in a rat model of forebrain ischemia. In their experiment, all rats survived the ischemic challenge. Animals treated with trimethaphan showed worse brain histopathology as compared to animals receiving N_2O treatment alone. These authors therefore suggested that catecholamine induces protection from neuronal injury. This idea is supported by Blomqvist *et al.*,[6] who found that locus ceruleus lesions in rats decreased central sympathetic activity and worsened neuronal necrosis after complete cerebral ischemia. They attributed the beneficial effects of norepinephrine to its central inhibitory action.

In contrast, Grøgaard *et al.*[31] found that treatment of N_2O-ventilated rats with trimethaphan decreased mortality associated with forebrain ischemia from 100 to 12%. They suggested that hypotensive shock may be a factor that worsens short-term outcome. In contrast, the current data show that hemorrhagic hypotension without ischemia does not result in mortality or significant histopathologic brain injury. It is apparent that in our study and in that by Grøgaard *et al.*[31] markedly increased catecholamines associated with severe ischemia worsened neurologic outcome. However, increased catecholamines associated with modest ischemia in the study by Koide *et al.*[7] may not increase neuronal injury. We conclude that neuronal susceptibility to catecholamine-induced injury may increase with the severity of the ischemic insult.

Several studies suggest that increased plasma glucose may affect ischemic neuronal damage according to the ischemic model used. Increased plasma glucose concentrations may decrease infarct size in end-arterial territories[32-34] but may increase ischemic brain damage in collaterally perfused ischemic tissue.[32,35] In our model of collaterally perfused ischemia, catecholamines and plasma glucose concentrations were higher in group 1, which had a worse neurologic outcome than did group 2 (ganglionic blockade). This suggests that catecholamine-induced increases in plasma glucose may contribute to a worse neurologic outcome in this ischemia model. However, it seems unlikely that the injurious effects of catecholamines are exclusively mediated *via* stimulation of glycogenolysis, since there was only a poor correlation between plasma glucose and neurologic outcome.

One potential problem of the current study is that we did not measure brain temperature. The study of Busto *et al.*[36] suggests that brain temperature may vary from body temperature, depending on the way in which temperature homeostasis is maintained: they found that brain temperature and body temperature were closely correlated when temperature was maintained with a heat lamp.[36] We presume that a similar relationship would be found in our study, which also used a heat lamp. Busto *et al.*[36] used a model of near-complete ischemia. Under these conditions, brain temperature would not be maintained by circulating blood. In our model of incomplete ischemia, the brain receives a significant perfusion of blood during the ischemic challenge. This perfusion would be important

in maintaining brain temperature. Another problem of the current study is the possibility that differences in the amount of blood withdrawn to produce hypotension may influence the degree of ischemia. This effect seems unlikely, however, since the degree of ischemia in this model should be related to cerebral perfusion pressure rather than to circulating blood volume.

Brain histopathology did not correlate with neurologic outcome over all treatment conditions. This occurred in part because rats with severe neurologic deficits died before histopathology was performed. Large infarcts were present in all ischemic groups, even when neurologic deficit was moderate (group 2). This indicates that at this level of ischemia, neurologic outcome discriminates among treatment groups better than does histopathology. It is possible that histopathology performed in several forebrain sections rather than in the most severely affected areas would have produced a closer correlation with outcome. In previous studies using the same ischemic model, we found better agreement between neurologic outcome and histopathology when rats were killed 1–3 days after the ischemic insult.[10] This may be because neurologic deficits are most severe 2 days after ischemia, whereas histopathologic damage progresses for several days.[37]

We suggest that circulating catecholamines play a significant role in modulating ischemic brain damage during N_2O ventilation. In our study, outcome improved during suppressed catecholamine concentrations (group 2) and worsened after infusion of norepinephrine and epinephrine (group 3). Although the anatomic and enzymatic blood–brain barrier excludes circulating catecholamines from brain tissue,[38] the current results suggest that the blood–brain barrier may be impaired during the ischemic and early postischemic stages.[13] Alternatively, plasma catecholamines may act outside the blood–brain barrier, constricting large cerebral arteries and decreasing brain blood flow. It is likely that ischemic stress also activates central sympathetic pathways that produce cerebral vasoconstriction and central metabolic stimulation. Both increased circulating catecholamines and central sympathetic activity appear to be involved in worsening ischemic brain injury.

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