

Sympathetic Stimulation with Physostigmine Worsens Outcome from Incomplete Brain Ischemia in Rats

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Background: It has been suggested that anesthetics may protect the brain during incomplete cerebral ischemia by inhibition of sympathetic activity. This study evaluated whether physostigmine may increase plasma epinephrine and norepinephrine during carotid occlusion with hypotension and worsen ischemic outcome in rats and if this effect could be reversed by dexmedetomidine, an α_2 -adrenergic agonist.

Methods: Anesthesia was maintained with fentanyl ($25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) combined with 70% N_2O ventilation in oxygen. Ischemia was produced by right carotid ligation combined with hemorrhagic hypotension to 30 mmHg for 30 min. Plasma epinephrine and norepinephrine were measured during ischemia. Neurologic outcome was evaluated for 3 days after ischemia. There were three groups: control ($n = 10$), physostigmine (1 mg/kg intraperitoneal 3 min before the start of ischemia, $n = 10$), and physostigmine plus dexmedetomidine ($100 \mu\text{g/kg}$ intraperitoneally 15 min before the start of ischemia, $n = 10$). Brain tissue glutamate concentrations were measured by microdialysis in separate studies.

Results: Compared to control rats, physostigmine increased plasma epinephrine and norepinephrine 10-fold and worsened neurologic outcome. The increases in epinephrine and norepinephrine were blocked by dexmedetomidine before treatment, and neurologic outcome was improved. Outcome was not correlated with blood glucose during ischemia ($r = 0.11$). Ischemia increased brain tissue glutamate from $<100 \mu\text{M}$ to $400 \mu\text{M}$ during ischemia. This increase was not altered by physostigmine treatment.

Conclusions: These results suggest that physostigmine worsens ischemic outcome by a mechanism that is associated with increases in plasma epinephrine and norepinephrine. (Key words: Brain: ischemia. Sympathetic nervous system, α_2 -adrenergic agonists: anticholinesterase; dexmedetomidine; physostigmine. Sympathetic nervous system, catecholamines: epinephrine; norepinephrine.)

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DURING brain ischemia, brain extracellular dopamine, norepinephrine, glutamate, and other excitatory amino acids are increased.^{1–3} This may be associated with an increase in neuronal metabolism.^{4,5} An increase in neuronal metabolism will exacerbate the imbalance between oxygen demand and blood flow during ischemia and increase lactic acidosis. We previously showed that anesthetics and drugs that decrease sympathetic activity during incomplete brain ischemia will improve outcome in rats.^{6–8} However, it is unclear whether treatments that enhance sympathetic activation worsen ischemic outcome. Physostigmine has been used clinically to reverse sedation produced by midazolam.⁹ Central cholinergic stimulation is associated with enhanced sympathetic activity and increases in cerebral blood flow and brain metabolic demand.^{10–12} The purpose of this study was to determine whether physostigmine increases the sympathetic response to incomplete brain ischemia and worsens outcome in rats. The role of brain tissue glutamate release in this response was evaluated by microdialysis of the ischemic brain^{13,14} in sham- and physostigmine-treated rats.

Materials and Methods

These experiments were carried out after approval from the institutional animal care committee. Male Sprague-Dawley rats (350–450 g) were anesthetized with isoflurane in a bell jar. After tracheal intubation, the lungs were ventilated with 2% isoflurane in oxygen. Catheters were inserted into the left femoral vein, the right femoral artery, and the right jugular vein for pressure recording, drug infusion, and blood withdrawal. The right common carotid artery was isolated for later clamping. At the end of surgery, the isoflurane was withdrawn and the rat allowed 30 min for equilibration using one of the following randomly assigned treatments. Group 1 (control, $n = 10$) received a $10\text{-}\mu\text{g/kg}$ intravenous bolus of fentanyl followed by an infusion at a rate of $25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ and ventilation with 70%

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N₂O in oxygen. Group 2 (n = 10) received the same anesthetic treatment as group 1. These rats additionally were given an intraperitoneal injection of 1 mg/kg physostigmine 3 min before the start of ischemia. A previous study showed that this dose of physostigmine produced a significant increase in blood pressure, cerebral blood flow, and brain oxygen metabolism.¹⁰ Group 3 (n = 10) received the same anesthetic and an intraperitoneal injection of 100 µg/kg dexmedetomidine 15 min before ischemia, followed by an intraperitoneal injection of 1 mg/kg physostigmine 3 min before the start of ischemia. This dose of dexmedetomidine was shown to have a maximum anesthetic and brain protective effect in a previous study.⁷

Ischemia was produced by right common carotid clamping combined with hemorrhagic hypotension to 30 mmHg for 30 min. Arterial blood samples were taken under baseline conditions, during ischemia, and at the end of a 20-min recovery period for measurement of blood gas tensions, plasma glucose, and plasma catecholamine concentrations. Blood gas tensions and pH were measured using an Instrumentation Laboratories 1303 blood gas analyzer (Lexington, ME). Plasma glucose was measured using a Yellow Springs glucose analyzer (Yellow Springs, OH). Plasma epinephrine and norepinephrine were measured by radio enzymatic assay. The sensitivity and coefficient of variation of the assay was 48 pg/ml and 7.5%, respectively, for norepinephrine and 36 pg/ml and 10%, respectively, for epinephrine. Skull temperature was measured over the ischemic hemisphere by inserting a Yellow Springs thermistor needle between the temporal muscle and skull. Skull temperature was maintained at 37° C with an overhead heat lamp using servo-control. Arterial carbon dioxide tension was maintained between 35 and 40 mmHg. Arterial pH was maintained at 7.4 by bicarbonate infusion.

At the end of ischemia, the carotid clamp was removed and the blood reinfused. After recovery, the trachea was extubated and the rat returned to its cage. Each rat was monitored 15 min after extubation to ensure adequate ventilation. Neurologic outcome was evaluated by an investigator blinded to the treatment condition using an 18-point scale,¹⁰ starting 24 h after the end of ischemia and continuing every day for 3 days. A score of 0 represented no deficit, and a score of 18 indicated stroke-related death. The categories of neurologic evaluation included state of consciousness (4 points), walking (4 points), limb tone (1 point), response to pain (1 point), and performance of motor

tasks (7 points). Stroke-related death (18 points) was interpreted from progressive signs of stroke deficit determined after a minimum of 3 h of recovery from ischemia. Scores for each of the 3 days were added to produce a total neurologic score for each rat.

Brain Tissue Glutamate

Caudate tissue glutamate concentration was measured during ischemia using an on-line enzyme (glutamate dehydrogenase) analysis.¹³ These studies were performed in a separate group of rats from the neurologic outcome studies. Tissue microdialysis was performed using a CMA 12 probe (Bioanalytical Science, Indianapolis, IN). The integrity of each probe was determined by measuring its percent recovery. The probes were placed in a 150 mg/100 ml glucose solution, and glucose concentration in the perfusate was measured (perfusion rate 2 µl/min). The recoveries ranged from 10% to 25%. Each probe was used a maximum of three times.

Glutamate concentration was determined by fluorometric detection of NADH resulting from the reaction of glutamate with NAD (L-glutamate + NAD⁺ + water <glutamate dehydrogenase> 2-oxoglutarate + NADH + NH₄⁺). Quantitative oxidation of L-glutamate can be achieved by using an excess of NAD⁺ and scavenging the keto-acid with hydrazine. The reagent solution contained 5.4 U/ml glutamate dehydrogenase (0.34 mM/L NAD⁺, 0.29% hydrazine) and 1.5 mM/L adenosine diphosphate in TRIS buffer (100 mM, pH 8.5). Adenosine diphosphate is required in the reagent to activate and stabilize the enzyme during the assay. This solution was perfused through PE20 tubing at a rate of 8 µl/min and mixed by a Y-connector with dialysate of calibration solutions or brain dialysate infused at a rate of 2 µl/min. Calibration solutions for glutamate contained 200 or 400 µM/L glutamate in artificial cerebrospinal fluid (aCSF, composition in mM/L: NaCl 125, KCl 2.5, MgCl₂ 1.18, and CaCl₂ 1.26). Artificial cerebrospinal fluid also was used to perfuse the probes. The enzymatic reaction occurred in PE20 tubing over a period of 15 min. NADH was measured fluorometrically¹³ using a 10-µl flow cell and 340–450-nm excitation-emission wavelengths. For calibration, the probes were placed sequentially in aCSF, then in aCSF with 200 µM glutamate and 400 µM glutamate, followed by a return to aCSF. The calibration solutions were considered an approximation of extracellular glutamate concentrations. After calibration, the probe was placed in aCSF to re-establish zero control concentrations.

After the microdialysis probe was calibrated, rats were anesthetized and surgery was performed as described above. The rat was placed in a Kopf stereotaxic apparatus. The skull was exposed and a 2-mm hole drilled over the right hemisphere, 3 mm lateral to bregma. Microdialysis probes were lowered 7 mm from the brain surface into the caudate region. Upon insertion of the probe, glutamate concentration increased briefly and returned to baseline within 15 min. Brain microdialysis was performed continuously at a rate of 2 μ l/min with artificial aCSF during insertion of the probe, 1 h of equilibration, 30 min of ischemia, and 30 min of recovery. A sham saline or 1 mg/kg physostigmine intraperitoneal injection was given 3 min before the start of ischemia. This study was performed in eight sham-treated and nine physostigmine-treated rats.

Brain electrical activity was measured bilaterally in eight rats in which brain microdialysis was performed (four sham- and four physostigmine-treated rats). Brain electrical activity was analyzed using a Life Scan (Neuroometrics, San Diego, CA). A squared function of electrical amplitude was determined within the following frequency bands: σ = 0.5–3.0 Hz, θ = 3.1–8.0 Hz, α = 8.1–12.0 Hz, and β = 12.1–30 Hz. Data were averaged over 1-min epochs.

Statistics

Data are reported as mean \pm SD. Neurologic scores were compared using Kruskal Wallis tests. Physiologic

data were compared using analyses of variance and Tukey's *post hoc* test for comparison between treatment conditions and groups. Spearman rank-order correlations were used to evaluate the relation between either glucose or plasma epinephrine and norepinephrine and neurologic outcome.

Results

Arterial blood pressure, blood gas tensions, and plasma glucose are shown in table 1. Blood pressure and blood gases were similar between the treatment groups. Plasma glucose was increased during ischemia and was increased more in group 3 (dexmedetomidine + physostigmine) compared to the other groups. During ischemia, plasma epinephrine and norepinephrine increased with physostigmine compared to control rats (fig. 1, $P < 0.05$). These increases were attenuated by dexmedetomidine before treatment (group 3). Neurologic outcome was worse in physostigmine-treated rats (group 2, $P < 0.05$) compared to control rats (fig. 2). Dexmedetomidine before treatment significantly improved outcome in physostigmine-treated rats (group 2 compared to group 3, $P < 0.05$). With all rats considered together, the correlation between plasma glucose and neurologic outcome was not significant ($r = 0.11$, $P > 0.10$). The correlations between plasma epinephrine ($r = 0.48$) and norepinephrine (r

Table 1. Arterial Blood Pressure, Blood Gas Tensions, pH, and Plasma Glucose

Group	Treatment (min)	n	Blood Pressure (mmHg)	P _{aCO₂} (mmHg)	P _{aO₂} (mmHg)	pH	Plasma Glucose (mg/dl)
Control	Baseline	10	127 \pm 9	37 \pm 2	138 \pm 16	7.43 \pm 0.02	150 \pm 12
	Ischemia (15)		30 \pm 1*	37 \pm 2	143 \pm 12	7.42 \pm 0.02	—
	Ischemia (30)		30 \pm 1*	37 \pm 2	139 \pm 14	7.41 \pm 0.03	273 \pm 73*
	Recovery		115 \pm 7*	37 \pm 2	132 \pm 21	7.42 \pm 0.03	155 \pm 37
Physostigmine	Baseline	10	130 \pm 9	37 \pm 2	143 \pm 9	7.41 \pm 0.02	156 \pm 8
	Ischemia (15)		30 \pm 1*	34 \pm 2	148 \pm 19	7.42 \pm 0.02	—
	Ischemia (30)		30 \pm 1*	37 \pm 2	149 \pm 15	7.35 \pm 0.06†	335 \pm 50*
	Recovery		118 \pm 10*	38 \pm 2	142 \pm 12	7.33 \pm 0.06†	263 \pm 75*†
Physostigmine plus dexmedetomidine	Baseline	10	139 \pm 17	36 \pm 2	139 \pm 7	7.43 \pm 0.02	182 \pm 35†
	Ischemia (15)		30 \pm 1*	36 \pm 2	149 \pm 10	7.42 \pm 0.05	—
	Ischemia (30)		30 \pm 1*	36 \pm 2	129 \pm 12	7.39 \pm 0.04	428 \pm 126*†‡
	Recovery		102 \pm 18*	36 \pm 2	133 \pm 13	7.42 \pm 0.05	355 \pm 105*†

Values are mean \pm SD.

P_{aCO₂} = arterial carbon dioxide tension; P_{aO₂} = arterial oxygen tension.

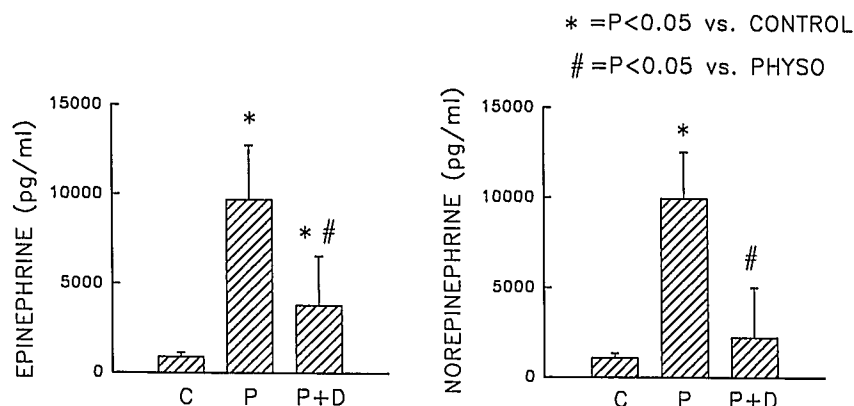
* $P < 0.05$ versus baseline.

† $P < 0.05$ versus control group at same treatment.

‡ $P < 0.05$ versus physostigmine-treated group at same treatment.

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Fig. 1. Plasma catecholamines during ischemia. Epinephrine and norepinephrine concentrations (\pm SD) are shown for each group: c = control; P = physostigmine-treated; P + D = physostigmine- and dexmedetomidine-treated. *P* values indicate difference between control and physostigmine groups, respectively.



= 0.55) and neurologic outcome were both significant ($P < 0.05$).

During measurement of brain tissue glutamate concentration, the initial probe placement increased glutamate concentration to $400 \mu\text{M}$ (range $200\text{--}600 \mu\text{M}$; fig. 3). Glutamate concentration decreased to the baseline of $80 \mu\text{M}$ (range $30\text{--}200 \mu\text{M}$) within 15 min and remained at this concentration during the equilibration period. Glutamate concentration increased during

ischemia to $400 \mu\text{M}$ (range $200\text{--}800 \mu\text{M}$) by the end of the ischemic period in both groups. During the 30-min recovery period, glutamate concentration decreased to the baseline in control rats but was still increased in physostigmine-treated rats. Brain electrical activity was depressed by ischemia in control and physostigmine-treated rats (fig. 4). Brain electrical activity increased during the 30-min ischemic period in control but not physostigmine-treated rats (analysis of variance,

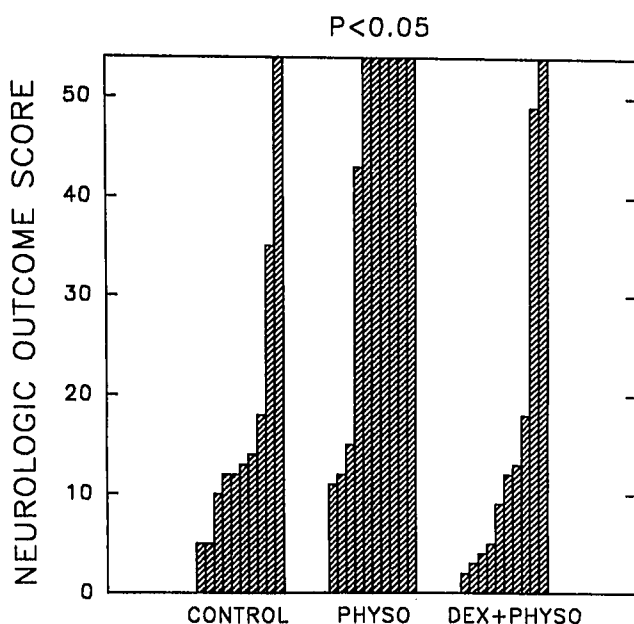


Fig. 2. Neurologic outcome scores for 3 days after ischemia. Each bar represents total score for each rat. PHYSO = physostigmine-treated; DEX + PHYSO = dexmedetomidine- and physostigmine-treated. The *P* value indicates that the physostigmine-treated group was significantly different from the control group.

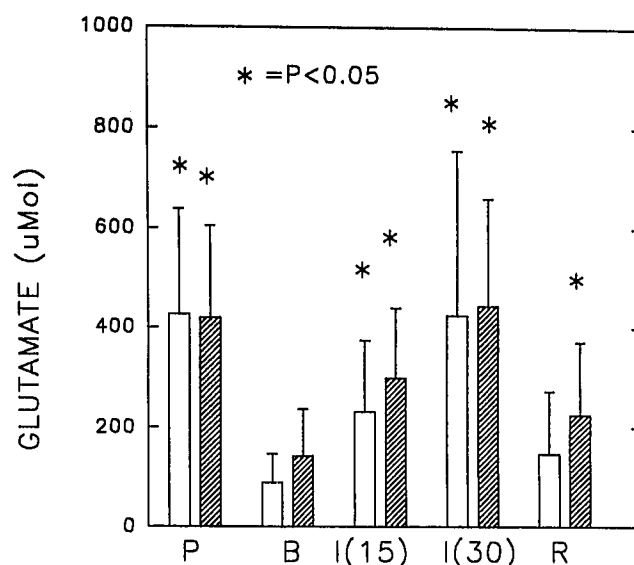


Fig. 3. Tissue glutamate concentrations in the ischemic striatum after insertion of the probe (P), during baseline (B), after 15 and 30 min of ischemia (I(15) and I(30), respectively), and after 30 min of recovery from ischemia (R). Open bars represents data (mean \pm SD) for the control group, and hatched bars show data for the physostigmine-treated group. The *P* value indicates the difference from baseline for each group ($n = 8$). There was no difference in response between groups ($P > 0.10$).

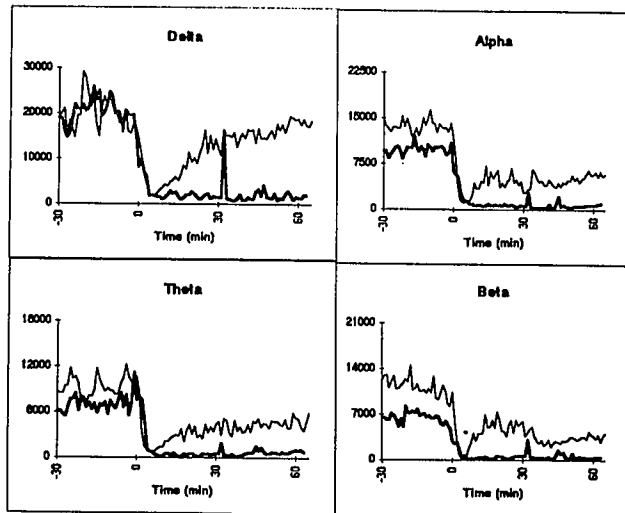


Fig. 4. Brain electrical activity during ischemia. The four figures show activity for four frequency bands (Hz): $\sigma = 0.5-3.0$, $\theta = 3.1-8.0$, $\alpha = 8.1-12.0$, and $\beta = 12.1-30.0$. The units of activity are presented as microvolts squared over 1 min. In each figure, the bold line shows the average of four rats treated with physostigmine, and the other line shows the average for four control rats. Time -30-0 represents baseline, 0-30 represents ischemia, and 30-60 shows recovery. Activity of each band differed between groups during ischemia and recovery ($P < 0.05$).

$P < 0.05$). This difference in brain electrical activity was maintained during the recovery period.

Discussion

In this study, physostigmine worsened outcome from ischemia, whereas dexmedetomidine reversed these changes. Despite the fact that we have observed a close relationship between neurologic outcome and plasma epinephrine and norepinephrine, the role of anesthetic depth is unknown. Physostigmine has been shown to reverse sedation produced by midazolam and diazepam^{9,15} whereas dexmedetomidine enhances anesthetic effects of isoflurane.¹⁶ If physostigmine and dexmedetomidine alter ischemic outcome by changing anesthetic depth, this may be mediated by changes in neuronal metabolism. However, dexmedetomidine administration does not decrease brain oxygen consumption.¹⁷ Newberg and Michenfelder¹⁸ proposed that anesthesia with inhalational anesthetics such as isoflurane protects the brain from hypoxic and ischemic injury by decreasing neuronal metabolism. However, Warner *et al.*¹⁹ found there is a poor correlation between depth of anesthesia or brain metabolism and

ischemic outcome during inhalational anesthesia. Anesthetic depth also may be defined by the ability to attenuate a stress response associated with ischemia. Plasma catecholamines would provide a marker for this effect. Our data show that plasma epinephrine and norepinephrine during ischemia are correlated with ischemic injury. This supports the suggestion that a critical level of anesthesia is necessary to protect the brain from incomplete ischemia. However, this level may depend on the ability of the drug to attenuate a central stress response and increases in plasma catecholamines rather than decrease brain metabolism.⁶⁻⁸ It is possible that these two effects occur at different anesthetic concentrations.

Physostigmine and dexmedetomidine may interact at a central site of action to modulate sympathetic activity. It was shown previously that the rostral ventral lateral region of the medulla oblongata contains adrenergic neurons that are important in sympathetic control.²⁰ This region may mediate the sympathetic response associated with ischemia.²¹ The rostral ventral lateral region contains cholinergic receptors that increase and α_2 -adrenergic receptors that decrease sympathetic activity.^{22,23} Our data are consistent with the conclusion that physostigmine and dexmedetomidine interact at a central site, possibly the rostral ventral lateral region, to modulate the sympathetic response to ischemia.

In this model of incomplete brain ischemia, decreasing plasma epinephrine and norepinephrine concentrations with hexamethonium improves outcome.⁶ However, Koide *et al.*²⁴ found that the ganglionic blocker trimethaphan decreased plasma catecholamines and worsened neuronal injury from near-complete ischemia. The worse outcome after trimethaphan could be reversed with intravenous epinephrine and norepinephrine infusion. This is consistent with the findings of Gustafson *et al.*²⁵ that catecholamines are important for neuronal recovery after near-complete forebrain ischemia. This controversy may be related to the role of catecholamines in ischemic injury and post-ischemic recovery. During incomplete brain ischemia, neuronal stimulation with catecholamines may increase ischemic injury. In the postischemic period following near-complete ischemia, catecholamines may be important for neuronal recovery.

Although it is known that brain extracellular dopamine and norepinephrine concentrations increase during ischemia,¹⁻³ there is controversy whether central catecholamine activity increases or decreases ischemic injury.^{26,27} Our data suggest that plasma catecholamine

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concentrations reflect changes in central sympathetic activity during ischemia, but this may not involve brain catecholamine pathways. Stress-related increases in plasma catecholamines are associated with increases in cerebral blood flow and neuronal metabolism.²⁸ However, brain metabolic stimulation during hypoxic stress is not inhibited by β -adrenergic blockade.²⁹ It is suggested that circulating epinephrine or norepinephrine may activate neuronal activity during hypoxia by stimulating receptors outside the blood-brain barrier.²⁸ However, other neurotransmitters that have not been identified may mediate sympathetic activation as well as neuronal stimulation.

One of the most puzzling problems is whether plasma epinephrine or norepinephrine can stimulate the brain and how this may occur. Studies show that increased plasma epinephrine and norepinephrine concentrations do not increase cerebral blood flow or brain metabolism if the blood-brain barrier is intact.³⁰⁻³² We have evaluated the blood-brain barrier in our model of ischemia and found an intact barrier during the ischemic period. § This suggests that circulating catecholamines do not have access to brain tissue. However, elevated plasma catecholamines will increase cerebral blood flow and brain metabolism if they are accompanied by a central stress response such as hypoxia or during electrical stimulation of the rostral ventral lateral region of the medulla oblongata.^{28,33} This suggests that circulating catecholamines may stimulate receptors outside the blood-brain barrier and facilitate neuronal activation induced by brain regions that may mediate the stress response to hypoxia or ischemia.^{21,28,33} This mechanism of brain activation would be deleterious under conditions of incomplete cerebral ischemia when cerebral blood flow and oxygen supply are limited. Anesthetics would modulate this metabolic mechanism of ischemic injury by attenuating the stress response. This may be mediated centrally by decreasing central excitatory neurotransmitter release or the sympathetic response to ischemia or both. It is likely that the ability of anesthetics to decrease a stress response occurs at lower drug concentrations than are necessary to decrease cerebral metabolic rate for oxygen, because as little as 0.5 minimum alveolar concentration of isoflurane will improve outcome from incomplete brain

ischemia, whereas higher concentrations are necessary to reduce cerebral metabolic rate.^{3,4}

Although physostigmine increased plasma epinephrine and norepinephrine in this study, this may not be the mechanism of enhanced ischemic injury. Cholinergic stimulation may increase brain metabolism directly or by an interaction with excitatory amino acids.³⁵ Excessive muscarinic stimulation also may produce pathologic changes in K^+ and Ca^{++} membrane fluxes *via* phospholipid breakdown, by altering activity of intracellular second messengers, or by aberrant phosphorylation of key regulatory signal transduction proteins.³⁵⁻³⁷ This suggests an alternative mechanism for physostigmine-induced ischemic injury other than by stimulating sympathetic activity.

Brain tissue glutamate concentration was measured in a separate series of experiments. At the time of probe insertion, there was an increase in extracellular glutamate concentration to approximately 400 μM , which decreased to the baseline of less than 100 μM within 15 min. This is consistent with movement of glutamate into the extracellular space due to cellular disruption and subsequent reestablishment of cellular integrity.³⁸ Baseline extracellular glutamate concentrations of 30–200 μM in our experiment agree with previous reports.^{3,13,39,40} Our results suggest an intra- to extracellular glutamate ratio of 50:1 during baseline measures. This would be consistent with the neurotransmitter action of glutamate.¹⁴ However, previous studies reported glutamate concentration in the dialysate rather than brain tissue.^{3,39,40} Our procedures calibrated glutamate concentration with respect to glutamate solutions in extracellular tissue. It is likely that probe insertion in brain tissue alters the ability of the probe to provide an exact measure of extracellular glutamate concentration with respect to calibration solutions.

Extracellular concentrations of glutamate increased during ischemia and decreased at the end of the ischemic period. These data agree with previous reports.^{13,14,38-40} Evidence indicates the neurotoxic nature of excitatory amino acids during hypoxia, ischemia, and hypoglycemia.⁴¹⁻⁴⁴ Increases in glutamate may enhance neuronal metabolism when blood flow is limited, exacerbating the degree of ischemia. However, the increase in extracellular glutamate during ischemia was similar between control and physostigmine-treated rats. This suggests that glutamate was not the primary factor for worsening ischemic outcome between the two treatment groups. Physostigmine may delay de-

§ Schultz JA, Hoffman WE, Albrecht RF: Unpublished results. 1992.

creases in glutamate after ischemia. This would prolong the neurotoxic effects of glutamate in the postischemic period.

Brain electrical activity measurements showed that activity of all frequency bands decreased during ischemia. During the recovery period, brain electrical activity was significantly greater in control compared to physostigmine-treated rats ($P < 0.05$). This is consistent with previous results in this model showing that recovery of brain electrical activity after ischemia is closely related to neurologic outcome.⁴⁵ It is expected that depression of brain electrical activity during ischemia and recovery is an indication of a more severe ischemic insult in physostigmine-treated rats and their inability to recover neuronal function.

It has been shown that glucose may be an important factor for ischemic injury. Increases in blood and brain tissue glucose will enhance anaerobic glycolysis and lactic acidosis during incomplete or complete ischemia.^{46,47} The increase in plasma glucose seen here during physostigmine treatment and ischemia are likely due to increased sympathetic activity. Although lactic acidosis may have been increased in physostigmine-treated rats during ischemia, this probably is not the primary mechanism of neuronal injury. Rats treated with physostigmine and dexmedetomidine had the highest plasma glucose concentrations during ischemia, but neurologic outcome was better than after treatment with physostigmine alone. Dexmedetomidine increases plasma glucose by stimulation of α_2 -adrenergic receptors in the pancreas and inhibition of insulin release.⁴⁸ Our results are consistent with a previous report that it is the ability of dexmedetomidine to inhibit sympathetic activity and not plasma glucose concentrations that is important in improving ischemic outcome.

These results show that physostigmine increased plasma epinephrine and norepinephrine during carotid occlusion and hypotension and worsened neurologic outcome. Both the increases in plasma epinephrine and norepinephrine and the poor neurologic outcome were reversed by dexmedetomidine. Although plasma glucose was increased during ischemia with physostigmine compared to control rats, increases in brain tissue glucose probably were not the primary mechanism of enhanced ischemic injury with physostigmine. Brain tissue glutamate concentrations also increased during ischemia. However, there was no difference in glutamate during ischemia between control and physostigmine-treated rats. These results suggest that increases

in plasma catecholamines are associated with a worse neurologic outcome during incomplete ischemia. This may be mediated by an interaction of circulating catecholamines with brain regions that mediate an ischemic stress response.

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