

## Sympathetic Activity Enhances Glucose-related Ischemic Injury in the Rat

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**Background:** Studies have shown that increased sympathetic activity or increased blood and brain glucose concentration worsen posts ischemic brain damage. The authors evaluated the interaction of plasma glucose with epinephrine and norepinephrine during incomplete cerebral ischemia in the rat using ganglionic blockade.

**Methods:** Rats were anesthetized with  $25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  fentanyl and 70% nitrous oxide in oxygen. Ganglionic blockade was produced in 30 rats using 8 mg/kg hexamethonium intravenously. Three plasma glucose ranges, low < 150 mg/dl, moderate = 150–300 mg/dl, and high > 300 mg/dl, were produced in each group. Ischemia was induced by unilateral carotid ligation and hemorrhagic hypotension to 30 mmHg for 30 min. Plasma norepinephrine and epinephrine were measured by radioimmunoassay. Neurologic outcome was evaluated daily for 3 days after ischemia.

**Results:** Ganglionic blockade decreased blood pressure before the start of ischemia and plasma epinephrine and norepinephrine during ischemia ( $P < 0.05$ ). Neurologic outcome was significantly worse in rats with high glucose compared with low glucose concentrations with and without ganglionic blockade ( $P < 0.05$ ). Neurologic outcome and stroke-related mortality were worse in rats with increased plasma epinephrine and norepinephrine compared with rats with ganglionic blockade when plasma glucose was less than 300 mg/dl ( $P < 0.05$ ).

**Conclusions:** These results indicate that increased concentrations of catecholamines enhance glucose-related injury during incomplete ischemia in rats. (Key words: Anesthetics, intravenous: fentanyl. Brain: ischemia; neurologic outcome. Metabolism: glucose. Sympathetic nervous system, catecholamines: epinephrine; norepinephrine.)

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STUDIES indicate that increased plasma and brain tissue glucose worsen outcome from ischemia.<sup>1–3</sup> Glucose-related ischemic injury may occur at plasma glucose concentrations less than 200 mg/dl.<sup>4–6</sup> Sympathetic activity may worsen ischemic outcome by increasing blood glucose concentration or by increasing brain glucose metabolism.<sup>7–8</sup> This indicates that increased epinephrine and norepinephrine release may potentiate glucose-related ischemic injury. However, other studies indicate that catecholamines may improve neuronal recovery in the posts ischemic period.<sup>9–11</sup> The purpose of this study was to investigate the influence of plasma glucose on ischemic neurologic outcome in rats with elevated or low plasma catecholamines.

### Materials and Methods

This study was approved by the institutional animal care committee of Michael Reese Hospital. Sixty overnight-fasted and nonfasted male Sprague Dawley rats (320–480 g) were used. Rats were anesthetized with isoflurane in a bell jar. After tracheal intubation, the lungs were ventilated with 2% inspired isoflurane in 100% oxygen. Catheters were inserted into the right femoral artery, both femoral veins, and the right jugular vein for blood pressure monitoring, blood withdrawal, blood gas sampling, and drug administration. The right common carotid artery was isolated and a loose ligature placed around it for later clamping. Vecuronium was given as a continuous infusion ( $0.1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) to maintain paralysis. After surgery, isoflurane was discontinued. Fentanyl was given as a  $10\text{-}\mu\text{g}/\text{kg}$  intravenous bolus followed by a continuous infusion of  $25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ . The lungs were ventilated with 70% nitrous oxide in oxygen and rats were given the fentanyl infusion for 30 min. Skull temperature was measured by insertion of a 22-G stainless steel needle thermistor (Yellow Springs, Yellow Springs, OH) beneath the temporalis muscle on the right side, and was maintained at  $37^\circ \text{C}$  by servomechanism using an overhead heating lamp. Arterial carbon dioxide tension was

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maintained between 35 and 40 mmHg by adjusting ventilation. Arterial pH was maintained at normal levels throughout the study by bicarbonate infusion.

During the equilibration period, the rats were assigned to treatment groups with the following plasma glucose concentrations: low < 150 mg/dl, moderate = 150–300 mg/dl, and high > 300 mg/dl. Group 1 (low glucose) (n = 10) were fasted overnight. These rats received intraperitoneal saline (6 ml/kg) 15 min before the start of ischemia. Group 2 (moderate glucose) (n = 10) were fasted overnight and received 50% glucose (6 ml/kg intraperitoneally) 15 min before the start of ischemia. Group 3 (high glucose) (n = 10) were nonfasted and received 50% glucose (6 ml/kg intraperitoneally). In groups 4–6, hexamethonium (8 mg/kg intravenously) was given 15 min before the start of ischemia. Group 4 (low glucose) (n = 10) were fasted overnight. Rats in group 5 (moderate glucose) (n = 10) were fasted and received 6 ml/kg 50% glucose intraperitoneally. Group 6 (high glucose) (n = 10) were nonfasted and received 6 ml/kg glucose.

Cerebral ischemia was produced by the combination of right common carotid artery occlusion and hemorrhagic hypotension to a mean arterial blood pressure of 30 mmHg for 30 min. Blood was withdrawn from the jugular vein. A range of 2 mmHg was allowed for the target pressure. After 30 min of ischemia, the carotid artery was unclamped and the withdrawn blood slowly reinfused for 10 min. The  $P_{aCO_2}$ ,  $P_{aO_2}$ , pH, and plasma glucose (Yellow Springs Glucose Analyzer, Yellow Springs, OH) were measured at baseline, during ischemia, and 20 min after reinfusion of the blood during recovery. Arterial blood was drawn for plasma catecholamine determination at 30 min of ischemia. Plasma epinephrine and norepinephrine were measured by radioenzymatic assay.<sup>12</sup> 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. During the recovery period, the catheters were removed and the incisions closed. The fentanyl infusion and nitrous oxide administration were stopped. The trachea was extubated after 30 min of recovery on the establishment of spontaneous respiration. The animals were transferred to their cages and closely monitored for 3 h.

Neurologic outcome scores were evaluated every 24 h for a period of 3 days, starting 24 h after ischemia using an 18-point scale.<sup>12</sup> A score of 0 represented no detectable neurologic deficit, and a score of 18 represented stroke-related death. A score of 18 was deter-

mined a minimum of 3 h after extubation only if the rat showed progressive signs of stroke impairment. The evaluator was blinded to the treatment condition.

Those rats surviving the 3-day neurologic examination period were anesthetized with isoflurane and their chests opened. They were killed by transcardial perfusion with 20 ml isotonic saline followed by 20 ml 10% buffered formalin. After removal, the brain was stored in formalin for subsequent histologic examination. Separate coronal sections containing the caudate nucleus and hippocampus were obtained for each brain. Coronal sections were cut and embedded in paraffin. Brain slices (7  $\mu$ m) were mounted on glass slides and stained with hematoxylin and eosin. The caudate section was evaluated 1 mm posterior from the bregma landmark. The sections were evaluated in a blinded manner by a neuropathologist. The caudate nucleus is sensitive to ischemic injury in this model of ischemia. The section containing the caudate was scored as follows: 0 = no damage, 1 = scattered neuronal damage, 2 = small infarcts, 3 = infarcts involving 50% of the ischemic caudate, 4 = infarcts involving 50% of total ischemic hemisphere, and 5 = total hemisphere infarct.

Data are reported as mean  $\pm$  standard deviation. Nonparametric data, including neurologic deficit score and histopathology, were analyzed using a Kruskal-Wallis analysis. A Bonferroni correction was made for multiple comparisons. Spearman Rank-order was used to correlate nonparametric data. Physiologic data were analyzed using a two-way analysis of variance and Tukey tests for *post hoc* comparison among groups and treatments. Significance was assumed at a level of  $P < 0.05$ .

## Results

Arterial blood pressure was lower in hexamethonium-treated rats than in sham-treated rats before and after ischemia ( $P < 0.05$ ). Arterial blood gas tensions and pH did not vary significantly among the six treatment groups (table 1). According to the protocol, plasma glucose concentrations were greater in moderate- and high-glucose compared with low-glucose treatment groups ( $P < 0.05$ ). Plasma epinephrine and norepinephrine were significantly greater in groups without ganglionic blockade compared with groups with hexamethonium treatment (fig. 1).

Neurologic outcome scores were significantly worse in rats with high glucose compared with rats with low glucose with and without ganglionic blockade (fig. 2). With all plasma glucose concentrations considered to-

**Table 1. Mean Arterial Blood Pressure (MABP), Blood Gas Tensions, pH, and Plasma Glucose**

Group	Treatment	N	MABP (mmHg)	P <sub>aCO<sub>2</sub></sub> (mmHg)	P <sub>aO<sub>2</sub></sub> (mmHg)	pH	Glucose (mg/dl)
1, Sham (low glucose)	Baseline	10	130 ± 8	36 ± 1	122 ± 25	7.42 ± 0.02	154 ± 44
	Ischemia (15)		30 ± 1*	35 ± 2	136 ± 14	7.42 ± 0.03	
	Ischemia (30)		30 ± 1*	35 ± 1	132 ± 14	7.41 ± 0.04	121 ± 39
	Recovery		113 ± 9	36 ± 2	120 ± 12	7.41 ± 0.04	125 ± 42
2, Sham (moderate glucose)	Baseline	10	125 ± 8	37 ± 3	133 ± 14	7.40 ± 0.04	308 ± 81†
	Ischemia (15)		30 ± 1*	35 ± 1	140 ± 13	7.41 ± 0.03	
	Ischemia (30)		30 ± 1*	37 ± 2	140 ± 14	7.39 ± 0.04	255 ± 40†
	Recovery		110 ± 7	38 ± 3	130 ± 17	7.39 ± 0.04	223 ± 48*†
3, Sham (high glucose)	Baseline	10	127 ± 11	38 ± 2	133 ± 12	7.40 ± 0.02	224 ± 60†
	Ischemia (15)		30 ± 1*	37 ± 3	150 ± 15	7.41 ± 0.04	
	Ischemia (30)		30 ± 1*	37 ± 2	146 ± 16	7.39 ± 0.04	418 ± 82*†
	Recovery		100 ± 10	38 ± 2	136 ± 17	7.38 ± 0.03	292 ± 123*†
4, Hex (low glucose)	Baseline	10	91 ± 21†	36 ± 2	132 ± 18	7.40 ± 0.01	133 ± 27
	Ischemia (15)		30 ± 1*	36 ± 2	138 ± 18	7.42 ± 0.03	
	Ischemia (30)		30 ± 1*	38 ± 2	134 ± 13	7.42 ± 0.04	125 ± 26
	Recovery		68 ± 16*†	37 ± 4	134 ± 17	7.39 ± 0.05	124 ± 21
5, Hex (moderate glucose)	Baseline	10	86 ± 18†	36 ± 2	130 ± 15	7.43 ± 0.03	214 ± 58‡
	Ischemia (15)		30 ± 1*	37 ± 3	144 ± 12	7.40 ± 0.04	
	Ischemia (30)		30 ± 1*	37 ± 2	137 ± 14	7.40 ± 0.03	271 ± 39*†
	Recovery		85 ± 23†	38 ± 3	129 ± 15	7.41 ± 0.03	198 ± 40‡
6, Hex (high glucose)	Baseline	10	72 ± 11†	37 ± 3	129 ± 24	7.41 ± 0.03	259 ± 46‡
	Ischemia (15)		30 ± 1*	38 ± 3	148 ± 22	7.38 ± 0.04	
	Ischemia (30)		30 ± 1*	37 ± 2	142 ± 19	7.40 ± 0.03	397 ± 50*‡
	Recovery		74 ± 22†	37 ± 2	137 ± 22	7.40 ± 0.03	310 ± 66‡

Values are mean ± SD; the number in parentheses is the minutes of ischemia. Hex = hexamethonium.

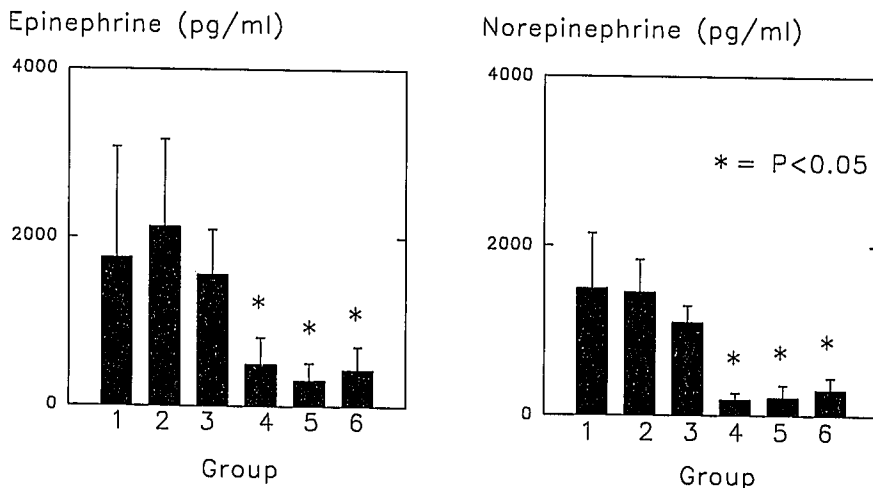
\* *P* < 0.05 versus baseline.

† *P* < 0.05 versus group 1.

‡ *P* < 0.05 versus group 4.

gether, neurologic outcome and mortality were worse in rats with elevated catecholamines (groups 1–3) compared with hexamethonium treatment (groups 4–6) (*P* < 0.05). This difference was significant in rats

with plasma glucose less than 300 mg/dl. With plasma glucose concentrations greater than 300 mg/dl, there was no significant difference in outcome between rats with and without ganglionic blockade. There was a sig-



**Fig. 1. Plasma epinephrine and norepinephrine concentration (mean ± SD) (n = 10 subjects per group). Groups 1–3 without hexamethonium, groups 4–6 with hexamethonium. \**P* < 0.05 compared with group 1.**

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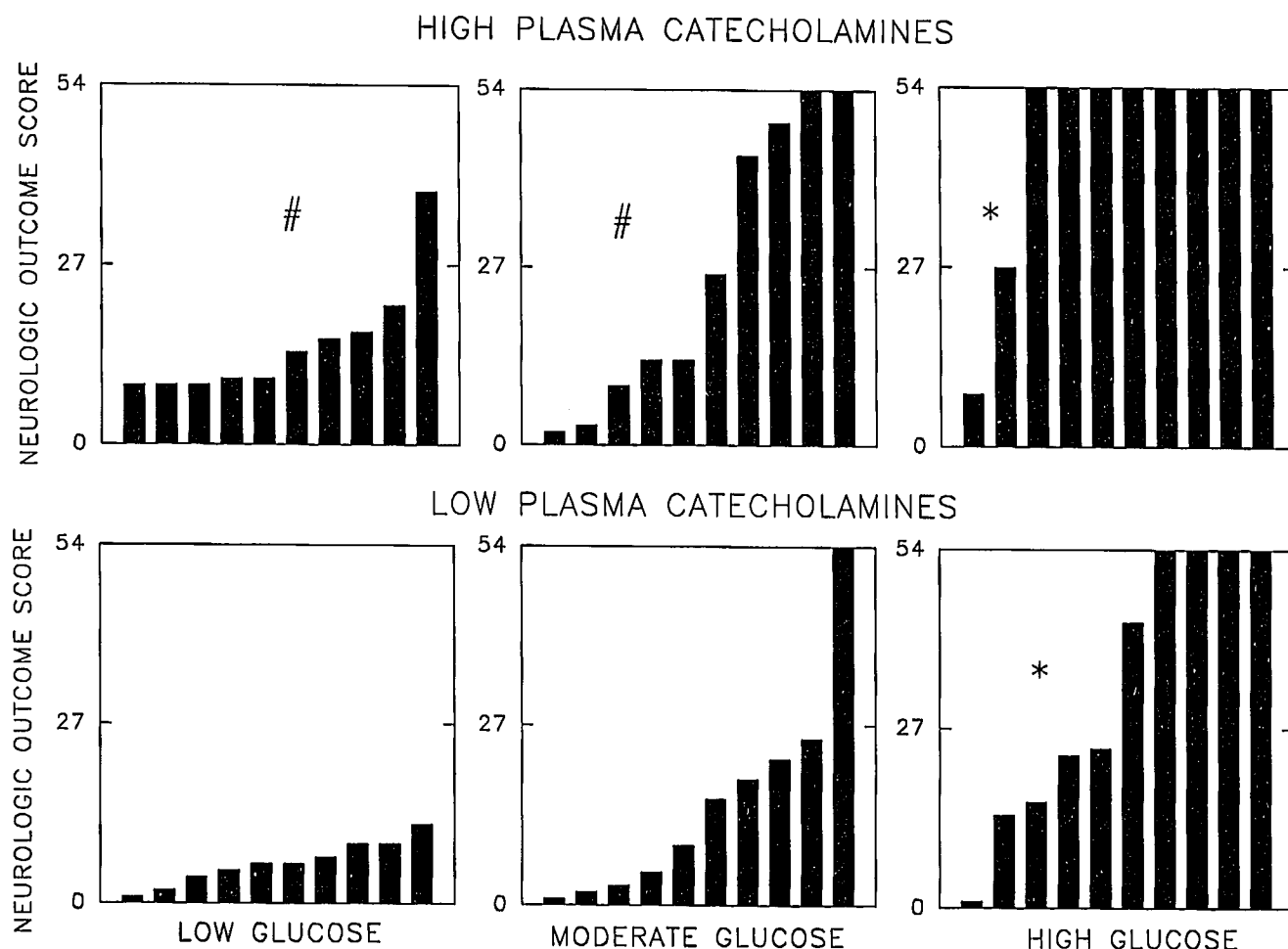


Fig. 2. Individual neurologic outcome scores (total for 3 days). Upper figures without hexamethonium, lower figures with hexamethonium. \* $P < 0.05$  compared with low glucose group with same hexamethonium treatment; # $P < 0.05$  compared with group with hexamethonium treatment at same glucose challenge.

nificant correlation between plasma glucose during ischemia and neurologic outcome with all groups considered together ( $r = 0.52$ ,  $P < 0.05$ ). There was no correlation between preischemic or postischemic glucose and neurologic outcome ( $P > 0.10$ ).

Histopathology was evaluated only in rats that survived for 3 days after ischemia. There were not enough animals in groups 3 and 6 for statistical comparison. There was a significant correlation between histopathologic scores and plasma glucose over all groups ( $r = 0.87$ ,  $P < 0.01$ ). Histopathology was also correlated to neurologic outcome ( $r = 0.71$ ,  $P < 0.01$ ).

### Discussion

Our results show that increases in plasma glucose concentration significantly worsen ischemic neurologic

outcome. This is consistent with previous reports.<sup>13,14</sup> Neurologic outcome and stroke-related mortality were worse in rats with increased concentrations of epinephrine and norepinephrine compared with rats with hexamethonium treatment in rats with plasma glucose less than 300 mg/dl. This agrees with reports that neuronal injury is greater when sympathetic activity is increased during ischemia.<sup>12,15-17</sup> Studies have shown that sympathetic activity increases glucose metabolism and lactic acidosis during ischemia.<sup>7,8</sup> Epinephrine and norepinephrine may potentiate glucose-related ischemic injury by enhancing lactic acidosis.

In this model of incomplete brain ischemia, decreasing plasma norepinephrine and epinephrine concentrations with hexamethonium were associated with a better neurologic outcome. However, other studies

have shown that blockade of central and peripheral sympathetic activity worsens neuronal injury in a model of near-complete cerebral ischemia in the rat. Blomqvist *et al.*<sup>9</sup> found that destruction of the central noradrenergic system before ischemia aggravated postischemic damage after cardiac arrest in rats. Koide *et al.*<sup>10</sup> showed 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.*<sup>11</sup> 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 postischemic recovery. During incomplete brain ischemia, neuronal stimulation with catecholamines increases ischemic injury. In the postischemic period after near-complete ischemia, catecholamines may be important for neuronal recovery.

Although hyperglycemia increases ischemic injury, controversy exists regarding whether there is a critical glucose concentration at which this occurs.<sup>4-6</sup> An increase in blood glucose above 250 mg/dl was found to worsen neurologic deficit in cats made ischemic by cardiac arrest,<sup>2</sup> and to increase neuropathology after four-vessel occlusion in rats.<sup>13</sup> Modest increases in blood glucose of 40 mg/dl were shown to worsen neurologic outcome after complete ischemia in monkeys.<sup>5</sup> This is consistent with a report that spinal cord injury is increased with modest increases in plasma glucose.<sup>6</sup> Our results support the contention that modest increases in plasma glucose will exacerbate ischemic injury. This effect is seen in rats with elevated epinephrine and norepinephrine. With ganglionic blockade, the ability of glucose to increase ischemic damage is attenuated. This indicates that epinephrine and norepinephrine potentiate glucose-related ischemic injury, particularly at low plasma glucose concentrations.

It is likely that the potentiation of neuronal injury produced by epinephrine and norepinephrine is mediated by an increase in brain glucose consumption during ischemia. Hypoxia or ischemia increases release of central catecholamines and excitatory neurotransmitters.<sup>18,19</sup> This stimulation is mediated by activation of epinephrine-containing neurons in the rostral ventral lateral region of the medulla oblongata.<sup>20,21</sup> This is associated with increased brain metabolism, which exacerbates the imbalance between ischemic tissue blood

flow and metabolic demand.<sup>22</sup> Circulating epinephrine and norepinephrine may also cross the blood-brain barrier, which is compromised by hypoxia or ischemia and increased oxygen consumption.<sup>23-25</sup> This effect is mediated by  $\beta$ -adrenergic receptors.  $\alpha$ -1-Adrenergic receptors, which may be stimulated by phenylephrine, do not have significant cerebral metabolic or cerebrovascular effects.<sup>26</sup>  $\alpha$ -2-Adrenergic stimulation decreases plasma norepinephrine and epinephrine and improves neurologic outcome in this model of incomplete brain ischemia.<sup>12</sup> This indicates that  $\beta$ -adrenergic receptors probably increase neuronal injury during ischemia by enhancing metabolic demand and worsening lactic acidosis.

Fasting may have a brain-protective effect by increasing utilization of ketone bodies.<sup>27,28</sup> However, it is unlikely that overnight fasting in our rats significantly increased brain ketone concentration. Moreover, Go *et al.*<sup>27</sup> showed that infusion of  $\beta$ -hydroxybutyrate does not improve survival in fed rats during ischemia. This indicates that brain ketone metabolism has little impact on ischemic neurologic outcome.

In our study, plasma glucose during ischemia, but not pre- or postischemic glucose, was significantly related to neurologic outcome. This indicates that plasma glucose during the prolonged ischemic challenge (30 min) is the important component for lactic acidosis and neuronal injury. This is probably because there is blood flow to the ischemic region (30–40 ml  $\cdot$  100 g<sup>-1</sup>  $\cdot$  min<sup>-1</sup>).<sup>29</sup> With more severe ischemia, preischemic blood glucose would become the important factor determining brain tissue glucose during ischemia.

Ganglionic blockade decreased blood pressure before and after ischemia, as well as lowering plasma epinephrine and norepinephrine during ischemia. It is unlikely that this was a factor that decreased neuronal injury. Blood pressure was controlled during ischemia to the same level in all groups (30 mmHg). After ischemia, a lower blood pressure may exacerbate postischemic hypoperfusion and worsen neuronal recovery. This indicates that the cardiovascular effect of ganglionic blockade was not a factor for the improved neurologic outcome seen with this treatment.

In summary, elevated plasma epinephrine and norepinephrine concentrations were associated with worse ischemic outcome at both high and low plasma glucose concentrations. Stimulation of central  $\beta$ -adrenergic receptors increase neuronal metabolism and may exacerbate lactic acidosis during hypoxia or incomplete

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ischemia. However, after near-complete ischemia, catecholamines may improve neuronal recovery in the postischemic period.

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