Progressing Cerebral Infarction in Relation to Plasma Glucose in Gerbils

J. Vázquez-Cruz, MD, J.L. Martí-Vilalta, MD, I. Ferrer, MD, A. Pérez-Gallofré, PhD, and J. Folch, PhD

We studied neurologic morbidity and its evolution during hyperglycemia induced immediately after permanent unilateral common carotid artery ligation in Mongolian gerbils. A total of 60 animals were divided into five groups: one experiencing severe hyperglycemia for 1 hour after the onset of ischemia (brief hyperglycemia group, n=13), a normoglycemic control group for the brief hyperglycemia group (n=12), a group with severe hyperglycemia for 4 hours after the onset of ischemia (prolonged hyperglycemia group, n=11), a normoglycemic control group for the prolonged hyperglycemia group (n=13), and a hyperosmolar normoglycemic control group for the prolonged hyperglycemia group (n=11). Neurologic morbidity and mortality were higher in the two hyperglycemic groups than in the three normoglycemic control groups. The neurologic deficit progressed according to the duration of severe hyperglycemia. In the three normoglycemic control groups neurologic status stabilized 120 minutes after the onset of ischemia, in the brief hyperglycemia group stabilization occurred at 210 minutes, and in the prolonged hyperglycemia group neurologic deficit progressed for approximately 360 minutes, coinciding with the death of all but one gerbil, in which the neurologic deficit remained stable until death 23 hours after ischemia. We suggest that hyperglycemia is another cause of progressing cerebral infarction. (Stroke 1990;21:1621-1624)

Progressing cerebral infarction refers to that temporal clinical category for which progression or an increase in the severity of the neurologic signs has occurred within recent minutes.1 The mechanisms involved in clinical worsening are not uniform. The most common explanations for progression of ischemic stroke are extension of thrombus, brain edema, and systemic disorders.2 Other suggested causes, well-summarized by Price et al,3 are decreased cardiac output, systemic hypotension/postural hypotension, increased blood viscosity, hypoxia, seizures, and hemorrhage into an infarct.

There are no reports on progressing cerebral infarction to date that provide an analysis of plasma glucose level during the acute phase of the illness. Hyperglycemia during either global or regional brain ischemia is widely known to be detrimental.4-6 High brain glucose levels are thought to mediate their detrimental effect through accentuated tissue lactacidosis during and following ischemia.7-8 Hence, by controlling hyperglycemia during the acute phase of cerebral ischemia some progressing strokes could be arrested.

We examined the influence of hyperglycemia in the setting of progressing cerebral infarction. Specifically, we assessed neurologic morbidity and its temporal profile during hyperglycemia induced immediately after unilateral common carotid artery (CCA) occlusion in Mongolian gerbils.

Materials and Methods

We performed experiments on a total of 60 adult (50–80 g body wt) Mongolian gerbils (Meriones unguiculatus) (Shamrock, Henfield-Sussets, England) of either sex equally distributed among five groups: the brief hyperglycemia group (n=13), the prolonged hyperglycemia group (n=11), saline-treated normoglycemic control groups for both the brief (n=12) and the prolonged (n=13) hyperglycemia groups, and a hyperosmolar normoglycemic control group (n=11) for the prolonged hyperglycemia group. The gerbils were allowed water and food (A04 U.A.R. feed for rats and mice, Villemoisson, France) ad libitum before surgery. In the two hyperglycemic groups 3.5 g/kg i.p. glucose in 50% dextrose was given immediately after CCA ligation. In the pro-
TABLE 1. Mortality in Gerbils Subjected to Permanent Unilateral Common Carotid Artery Ligation

<table>
<thead>
<tr>
<th>Group</th>
<th>Mortality During surgery</th>
<th>Mortality After ischemia</th>
<th>n</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief hyperglycemia</td>
<td>0</td>
<td>8</td>
<td>1*</td>
<td></td>
</tr>
<tr>
<td>Saline-treated normoglycemic control</td>
<td>2</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Prolonged hyperglycemia</td>
<td>3</td>
<td>7</td>
<td>0†</td>
<td></td>
</tr>
<tr>
<td>Saline-treated normoglycemic control</td>
<td>1</td>
<td>7</td>
<td>0†</td>
<td></td>
</tr>
<tr>
<td>Hyperosmolar normoglycemic control</td>
<td>6</td>
<td>38</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.0001, 0.00001, respectively, different from prolonged hyperglycemia by Fisher's exact test.

Six of the 60 gerbils died during surgery (Table 1), and another 16 were rejected because they did not show neurologic signs of cerebral ischemia after CCA occlusion. Hence, 38 gerbils (Table 1) were valid for analysis. We failed to find significant differences among groups with respect to intraoperative mortality (Table 1) and the incidence of neurologic manifestations (data not shown).

Plasma glucose level and stroke index did not differ significantly among the three control groups. No gerbil in the prolonged hyperglycemia group survived 24 hours; seven died 4–6 hours and the other died 23 hours after CCA ligation. Mortality data are summarized in Table 1.

Stroke index in the brief hyperglycemia group was significantly higher than that in its control group (p < 0.05, Mann-Whitney U test) 210 minutes after CCA occlusion (Figure 1). Stroke index in the prolonged hyperglycemia group was significantly higher than that in its two control groups (p < 0.01, Mann-Whitney U test) at 210 minutes and between 240 and 360 minutes (Figure 1). We considered the time of death of the seven gerbils in the prolonged hyperglycemia group to be 6 hours after CCA ligation. The only gerbil in the prolonged hyperglycemia group to survive beyond 6 hours maintained a high stroke index until its death at 23 hours.

Evolution of neurologic morbidity differed among groups in relation to plasma glucose level after CCA ligation (Figure 1). In the three control groups stroke index...
Evolution of neurologic morbidity was related to the plasma glucose level (Figure 2). In the normoglycemic control groups stroke index increased only initially. In the brief hyperglycemia group plasma glucose level rose markedly early after CCA ligation but for only a short time. Stroke index in this group rose for a longer period and more than in the normoglycemic groups. In the prolonged hyperglycemia group plasma glucose level rose initially and remained high for 4 hours, while stroke index increased for a longer period and more, with a higher mortality than in the brief hyperglycemia group.

Furthermore, to determine the relation between plasma glucose level and stroke index, we correlated these two variables in 36 gerbils (Figure 3). One gerbil was excluded due to the lack of two determinations of plasma glucose level. The correlation between average plasma glucose level and mean stroke index was positive and very high (r=0.80, p<0.001, Student-Fisher t test).

Discussion

A variety of pathogenetic mechanisms may lead to progressive ischemic stroke. Anterograde, retrograde, or both forms of thrombus extension may increase the ischemic area by occluding collateral branches. Brain edema is another mechanism that may be implicated in some cases of neurologic worsening during cerebral infarction. Other proposed causes of clinical deterioration are systemic complications such as cardiac, pulmonary, hepatic, renal, infectious, acid/base, and water/electrolyte disorders.

In studies of progressing cerebral infarction to date, little attention has been focused on the effects of hyperglycemia. Hyperglycemia during brain ischemia is widely known to be detrimental. Experimental studies of global and regional cerebral ischemia have shown that hyperglycemia before or immediately after ischemia impairs functional and metabolic recovery and aggravates the neurologic manifestations and neuropathologic changes. Clinical studies suggest that hyperglycemia during the acute phase of ischemic stroke is associated with a worse neurologic outcome.

It has been proposed that excessive cellular lactacidosis accompanying anaerobic glucose metabolism adversely affects recovery after brain ischemia and hypoxia. Tissue acidosis may potentiate cellular edema and the production of injurious oxygen radical species, which in turn initiate lipid peroxidation and the consequent dissolution of cell membranes.

Our study shows that neurologic manifestations increased progressively, coinciding with high plasma
glucose concentrations after unilateral CCA occlusion in Mongolian gerbils. In normoglycemic animals neurologic manifestations stabilized soon after ischemia, while in hyperglycemic gerbils neurologic status worsened in relation to the duration of hyperglycemia after occlusion. Moreover, the severity of the neurologic disturbance was positively correlated with the plasma glucose level during ischemia.

We used this model of incomplete permanent regional brain ischemia because gerbils have small functional communicating arteries between the vertebrobasilar and carotid systems.29 Glucose reached the ischemic area during CCA occlusion. Cerebral edema,30,31 an increase in the extent and severity of cellular damage produced by lactic acidosis,32–33 or a combination of the two mechanisms gradually increased neurologic worsening and showed a clinical profile of progressing cerebral infarction.

In conclusion, we suggest that hyperglycemia during the acute phase of cerebral ischemia is another mechanism of progressing cerebral infarction, and we aim to test this hypothesis in clinical series. Prevention and treatment of increasing plasma glucose concentrations is not difficult and may have significant implications for the treatment of progressing cerebral infarction.

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