The Importance of Brain Temperature in Cerebral Ischemic Injury

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Averting the injurious consequences of brain ischemia, long sought by cerebrovascular investigators, remains a tantalizing though often elusive goal. Current advances in the neurosciences have raised the hope that pathophysiological approaches directed at specific mechanisms of tissue injury may find eventual clinical application.1 In this brief survey, we call attention to another avenue that, in our view, may hold promise and deserves careful scrutiny: the therapeutic modification of brain temperature.

Observations of cerebroprotection by hypothermia are not new, though traditional approaches have tended to employ overall reductions of whole-body temperature of rather sizable magnitude. In contrast, our laboratory first suspected several years ago that small fluctuations of brain temperature might account in part for variability in the extent of tissue injury encountered in animal models of reversible ischemia. (For example, we observed less histologic injury in animals whose heads may have been inadvertently cooled by scalp tissue removal for electroencephalographic monitoring.2) These casual observations provided the impetus for a large controlled study employing reversible forebrain ischemia in rats, in which 1) brain temperature was directly monitored by an implanted thermocouple; 2) brain temperature was allowed to vary independently of rectal (core) temperature, which was held constant at 37° C; and 3) careful histopathologic endpoints of ischemic injury were blindly assessed.3

When no effort was made to control it, brain temperature tended to fall gradually by 5-6° C during high-grade forebrain ischemia. By regulating brain temperature at various levels (by means of a fan and warming lamp), we observed that the histological consequences of ischemia were markedly influenced by the level of intraischemic brain temperature. For example, hippocampal pyramidal neurons of the CA1 layer showed grades 2-3 histologic damage (many or all neurons affected) in 100% of hemispheres held at 36° C during ischemia but in only 20% of those held at 34° C, in 0% of those held at 33° C, and in 0% of those held at 30° C. Similarly, ischemic injury to the dorsolateral striatum, another selectively vulnerable zone, was reduced by approximately 80% at 33-34° C and was completely eliminated when intraischemic brain temperature was 30° C.3 This marked dependence of ischemic injury on intraischemic brain temperature clearly suggests that the failure to monitor or control brain temperature, or allowing body temperature to change during ischemia and/or administration of therapeutic agents, might be expected to introduce unacceptable variability into the outcome of experimental ischemia studies.

We have shown that this pronounced protective effect of mild-to-moderate brain hypothermia is not explicable on the basis of alterations in cerebral blood flow, energy metabolites, or free fatty acids during ischemia.3,4 Further studies employing intracerebral microdialysis, however, have shown that as intraischemic brain temperature is lowered from 36° to 33° C, the (normally expected) sevenfold increase in the release of the excitatory neurotransmitter glutamate into the brain’s extracellular space is almost totally suppressed, and the extracellular release of dopamine is reduced by 60%.5 Furthermore, moderate intraischemic hypothermia has been shown in autoradiographic studies to enhance early postischemic glucose utilization and blood flow.6 The therapeutically relevant issue is whether postischemic induction of moderate brain hypothermia
Halothane-anesthetized Wistar rats were subjected to 10 minutes of forebrain ischemia by bilateral common carotid artery occlusion plus systemic hypotension (45–55 mm Hg). In the 36-36-36 ischemic group, brain temperature was maintained at 36°C throughout the preischemic, ischemic, and postischemic periods. In the 36-36-30 group, postischemic brain temperature was lowered to 30°C for 3 hours, beginning 5 minutes into the recirculation period. Three days later, brains were perfusion-fixed for histology, and numbers of normal-appearing neurons were counted at 100× magnification from standardized zones of the hippocampal CA1 sector. Cell counts represent mean±SEM. Statistical significance was assessed by a one-way analysis of variance followed by the Scheffé and Dunn tests.

\*p<0.01, 0.05, respectively, significantly different from non-ischemic controls.

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