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Anesthesiology
The Journal of the American Society of Anesthesiologists, Inc.

A Comparison of the Effects of Hypothermia, Pentobarbital, and Isoflurane on Cerebral Energy Stores at the Time of Ischemic Depolarization

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Issue: Volume 82(5), May 1995, pp 1209-1215

Publication Type: [Laboratory Investigation]

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Received from the Neuroanesthesia Research Laboratory, Department of Anesthesia. University of Iowa College of Medicine, Iowa City, Iowa. Submitted for publication November 1, 1994. Accepted for publication January 6, 1995.

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ISSN: 0003-3022
Accession: 00000542-199505000-00016

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Abstract

Background: In an accompanying article, we report that hypothermia (27-28 degrees Celsius) delayed postischemic cortical depolarization longer than did large-dose pentobarbital or isoflurane anesthesia, even though preischemic cerebral metabolic rates for glucose were similar in the three groups. To examine the mechanism that may underlie these differences, we measured the cerebral concentrations of high-energy phosphates (including adenosine triphosphate [ATP] and adenosine diphosphate) in normal conditions and at the moment of depolarization.

Methods: Rats were anesthetized with 0.8% halothane/50% N_2 O and prepared for measurement of the cortical direct-current potential by glass

Graphics

microelectrodes. Animals were assigned to one of four groups: (1) halothane/nitrous oxide anesthesia, pericranial temperature approximately 38 degrees Celsius; (2) halothane/nitrous oxide, approximately 28 degrees Celsius; (3) halothane/nitrous oxide anesthesia with pentobarbital added to achieve electroencephalographic isoelectricity, approximately 38 degrees Celsius; or (4) 2.4% isoflurane/50% N_2 O anesthesia (with electroencephalographic isoelectricity), approximately 38 degrees Celsius. The latter three groups were chosen on the basis of earlier work showing similar cerebral metabolic rates for glucose. In a subgroup of each, circulatory arrest was induced with KCl and the brain was frozen in situ (with liquid nitrogen) at the moment of cortical depolarization. In remaining animals, the brain was frozen without any ischemia. Tissue ATP, adenosine diphosphate, adenosine monophosphate, and phosphocreatine concentrations were measured by high-performance liquid chromatography.

Results: High-energy phosphate concentrations in nonischemic brain tissue were similar in all groups (e.g., ATP concentration 2.47-2.79 micro mol/g brain). With ischemia, depolarization occurred when ATP concentrations had decreased to 13-18% of normal. There were no significant differences in the concentration of any compound or in the energy charge among the groups, even though the time until depolarization was much longer in hypothermic animals (242 s) than in animals receiving large doses of anesthesia (119 and 132 s) or in normmothermic halothane/nitrous oxide animals (73 s).

Conclusions: The ATP/energy charge threshold for cortical depolarization was similar in all groups despite differing temperature or anesthetic conditions. Because hypothermia increased the time until depolarization, the rate of decrease in ATP concentration must have been slower in these animals than in the two groups receiving large-dose anesthetics, despite similar preischemic cerebral metabolic rates for glucose. This finding is similar to that of earlier studies and indicates that factors other than preischemic metabolic rate are responsible for controlling energy utilization after ischemia.

Key words: Anesthetics, intravenous: pentobarbital. Anesthetics, volatile: isoflurane. Brain: adenosine triphosphate; ischemic depolarization; metabolic rate. Temperature: hypothermia.

CEREBRAL ischemia results in the rapid depletion of energy stores in the brain. When the concentrations of high-energy phosphates decrease to a critical value, neurons lose their ability to maintain normal ionic gradients, and cellular depolarization occurs. [1-3] This in turn triggers a cascade of events that eventually result in neuronal damage or death. It has long been believed that reducing cerebral metabolic rate (CMR) increases the brain's tolerance to ischemia by slowing the consumption of the energy substrates necessary to maintain functional and structural integrity. However, data suggest that the protection provided by anesthetics and by hypothermia may involve mechanisms other than simply the slowing of energy depletion. [4-8].

In a companion study [9] we confirmed the finding by Astrup et al. that preischemic CMR (measured as the CMR for glucose [CMR sub G]) was inversely related to the time between the onset of ischemia and the appearance of ischemic cortical depolarization. [10] However, we also noted much greater delays until depolarization in hypothermic rats ([nearly equal] 27 degrees Celsius) than in normothermic animals anesthetized with large doses of isoflurane and pentobarbital, even when CMR_G s were similar in all three groups. There are several possible explanations for these differences, one of which is that hypothermia and anesthetics have differing effects on the concentrations of high-energy phosphates present at the time

of depolarization. We carried out the following experiment to examine this possibility.

Materials and Methods

These experiments were approved by the University of Iowa Animal Care and Use Committee. Male Sprague-Dawley rats, weighing 304- 403 g. were fasted overnight, with free access to water. Anesthesia was induced with 4% halothane in oxygen in a plastic box. After tissue infiltration with 1% lidocaine, a tracheotomy was performed and mechanical ventilation started with a tidal volume of 2.7-3.3 ml and a rate of 40-50 breaths/min. Throughout the preparation, anesthesia was maintained with 1-1.5% halothane in oxygen, balance air (fraction of inspired oxygen [nearly equal] 0.5). After skin infiltration with 1% lidocaine, a femoral vein and artery were cannulated for the administration of drugs or fluids, for arterial blood sampling, and for continuous blood pressure monitoring. Muscle paralysis was then achieved with 0.3 mg intravenous pancuronium bromide.

The animal was turned prone and the head fixed in a stereotactic frame (David Kopf Instruments, Tujunga, CA). After infiltration with 1% lidocaine, the scalp was incised and reflected laterally. A right-sided parietal craniectomy (2 x 2 mm) was performed using a high-speed electric drill under a microscope, and the drilling site was irrigated with saline to avoid injury to the brain. The dura was left intact. When surgery was complete, the inspired halothane concentration was reduced to approximately 0.8% (Anesthetic Agent Monitor 222, Datex Instrumentarium, Helsinki, Finland), and 50% N_2 O was added to the inspired gas mixture (fraction of inspired oxygen [nearly equal] 0.5). Platinum needles were inserted into the temporalis muscles bilaterally to permit the recording of a single biparietal electroencephalogram (EEG). Temperature was recorded in each animal in two locations: a needle thermistor (524, Yellow Springs Instruments, Yellow Springs, OH) was placed into the pericranial tissue adjacent to the craniotomy, and a probe (401, Yellow Springs Instruments) was inserted rectally.

Cortical direct-current potential changes were measured with a saline-filled glass micropipette (3-5 micro meter tip diameter) with an Silver-AgCl contact wire. The micropipette was inserted approximately 250 micro meter into the cortex with a micromanipulator and with the aid of a surgical microscope. The site of the craniectomy was filled with light mineral oil to prevent dehydration of the dura. The cortical electrode was referenced to a Ag-AgCl disk (Red Dot, 3M, St. Paul, MN) placed on shaved skin of the animal's back. The potential difference between the two electrodes was measured with an amplifier (7P122, Grass Instruments, Quincy, MA) equipped with a high-impedance input unit (H1P5, Grass) and recorded on paper with a polygraph (79, Grass).

Study Groups

After preparation was complete, animals were assigned to one of four primary groups in a fashion similar to that described by Nakashima et al. [9]:

- Normothermia (n = 15). Anesthesia was maintained with 0.8% halothane/50% N_2 O. Pericranial temperature was held at 38 plus/minus 0.2 degree Celsius (plus/minus SD) using a warming blanket and overhead warming lamp.

- Hypothermia (n = 12). Anesthesia was maintained with 0.8% halothane/50% N_2 O. After the completion of preparation, pericranial temperature was reduced to 28 plus/minus 0.2 degree Celsius using ice packs placed on and around the animal.

- Pentobarbital (n = 12). Anesthesia was maintained with 0.8% halothane/50% N_2 O. After preparation and without changing the concentrations of halothane or nitrous oxide, pentobarbital was infused at an initial rate of 5 mg *symbol* kg^1 *symbol*^{1} until burst suppression or isoelectricity was seen on the EEG. The infusion was thereafter decreased to 0.5-1 mg *symbol* kg^1 *symbol* min^1 to maintain the same EEG pattern. Pericranial temperature was kept at approximately 38 degrees Celsius.

- Isoflurane (n = 12). After preparation was complete, halothane was discontinued and replaced with isoflurane (still combined with 50% N_2 O). The isoflurane concentration was then adjusted to approximately 2.3-2.4% to achieve and maintain burst suppression or isoelectricity on the EEG. Pericranial temperature was held at approximately 38 degrees Celsius.

In all groups, saline was infused at a rate of approximately 2 ml/h. Mean arterial pressure was maintained greater than or equal to 80 mmHg by using small amounts of 6% hetastarch. Arterial blood gases were measured intermittently, and ventilation was adjusted to maintain arterial carbon dioxide tension between 36 and 42 mmHg and arterial oxygen tension at least 100 mmHg. All blood gases were measured at 38 degrees Celsius without temperature correction (alpha-stat management). Plasma glucose and hematocrit were measured shortly before energy metabolite measurements.

Protocol

After 60-80 min of stabilization, with at least 20 min at the target temperature or EEG pattern, animals in each group were randomly assigned to control or ischemia subgroups. In control animals, no other interventions were made until the brain was frozen in situ by pouring liquid nitrogen over the skull for approximately 3 min while ventilation continued. [11] In remaining animals (ischemia), circulatory arrest was induced by the intravenous injection of 1 ml saturated KCl. The cortical direct-current potential was carefully monitored, and as soon as the initial fast negative shift indicative of depolarization was seen, the brain was frozen in situ with liquid nitrogen. The delay until depolarization was calculated as the interval (in seconds) between KCl injection (which induced a circulatory arrest within [nearly equal] 2s) and the start of the negative direct-current shift.

After thorough freezing, the head was removed and immersed in liquid nitrogen. It was thereafter stored at -70 degrees Celsius. The brain was later chiseled out of the skull in a walk-in freezer while liquid nitrogen was repeatedly poured over the head to prevent thawing. Cortical samples were then dissected, weighed, and stored at -70 degrees Celsius.

Further sample preparation and high-energy phosphate measurements were performed (at the University of Minnesota School of Medicine) using a modification of methods previously described. [2,12,13] Ice-cold 0.42 M perchloric acid was added to the frozen preweighed samples and the tissue mechanically homogenized. The homogenate was centrifuged at 3,000 rpm for 10 min. Approximately 130 micro liter cold 2.0 M KOH was added to two 600-micro liter aliquots of supernatant, and the $KClO_4$ was allowed to precipitate for 10 min. The tubes were centrifuged for 1 min at 14,000 rpm. The pH of the resultant supernatant was 3.0-1.0 (checked with narrow-range pH paper). High-energy phosphate concentrations were measured by high-performance liquid chromatography. Adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), and phosphocreatine concentrations were expressed in micromoles per gram wet weight. The energy stores of the brain were assessed by the adenylate energy charge (EC), which was calculated by the following equation

[14]: Equation 1 Intergroup comparisons were performed using a one-way analysis of variance with a post hoc Scheffe's test. Statview 4.01 (Abacus Concepts, Berkeley, CA) for Macintosh (Apple, Cupertino, CA) was used for all statistical analyses.

$$EC = \frac{[ATP] + \frac{1}{2}[ADP]}{[ATP] + [ADP] + [AMP]}$$

Equation 1

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Results

Data from two ischemic animals (one normothermic and one hypothermic) were lost because of errors in sample handling. Baseline physiologic variables are shown in Table 1. Intergroup differences were similar to those seen by Nakashima et al. [9] Delays until ischemic depolarization in the various groups are also shown in Table 1. The shortest delay was in normothermic animals, and the longest was in hypothermic animals. There were no significant differences in latency times between the pentobarbital and isoflurane groups.

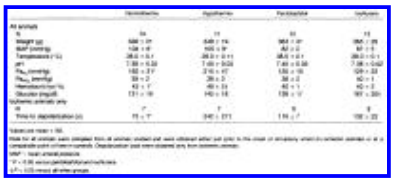

Table 1. Physiologic Data and Time to Depolarization

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Phosphocreatine, ATP, ADP, AMP, and EC concentrations for all groups (normothermia, hypothermia, pentobarbital, and isoflurane) and subgroups (control and ischemic) are shown in Table 2. There were no differences for any variable among the control subgroups. Values obtained at the moment of depolarization (ischemic subgroups) were markedly different from those in controls, but there were no differences between groups. Measured ATP concentrations at the time of depolarization were 13-18% of those seen in control animals (difference not significant).

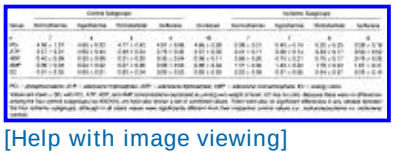

Table 2.

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Discussion

There is an inverse relation between preischemic CMR and the time between the onset of ischemia and the appearance of

cortical depolarization. [10] However, although it has been assumed that this is a cause-and-effect relation (a lower CMR resulting in a longer depolarization delay), several findings suggest that the relation is more complex. For example, Astrup et al. showed that although pentobarbital and hypothermia (28 degrees Celsius) could reduce the CMR for oxygen to a similar degree, they had different effects on the rate of extracellular Potassium[4] increase after the onset of circulatory arrest. [15,16] It is hence possible that both CMR and depolarization delay can be influenced independently by anesthetics and temperature.

This experiment was undertaken to aid in the understanding the results obtained by Nakashima et al. [9] In that study, we varied pericranial temperature over a wide range and observed the expected relation between preischemic CMR_G and the delay from cardiac arrest to terminal cortical depolarization. However, when CMR_G was reduced to equivalent degrees by hypothermia ([nearly equal] 27 degrees Celsius) or by deep pentobarbital or isoflurane anesthesia, the times to depolarization differed: much greater delays occurred in hypothermic rats. There are several possible explanations for this observation. Among the more likely, anesthetics and hypothermia may have different effects on the rate of Potassium sup + leak after ischemia (because depolarization is primarily a voltage-dependent event) or on the voltage threshold for depolarization. They also may differently influence the rate at which cellular energy stores are depleted or the ATP concentrations at which depolarization occurs. In the current experiment, we chose to examine one of these possibilities: does hypothermia or do some anesthetic agents differentially influence the ATP/EC threshold associated with the loss of transmembrane ionic homeostasis?

Several groups have shown that neither anesthetics nor temperature significantly alter the concentration of ATP or EC in the normal brain. [17-20] Ekholm et al. have also shown that during normothermia, depolarization occurs when tissue ATP concentration has decreased to less than 30% of normal. [21] Our results are consistent with these findings, although our ATP concentrations at the time of depolarization were lower. As early as 1958, Thorn et al. measured ATP concentrations during ischemia and concluded that the depletion rate was slowed by hypothermia (26 degrees Celsius). [22] Michenfelder and Theye [17] and Katsura et al. [20] have reported similar effects, showing that the depletion of EC was slowed by hypothermia (30-34 degrees Celsius). However, the concentrations of high-energy phosphates at the moment of depolarization have not been examined directly.

It may be intuited that hypothermia, by "stabilizing" the cell membrane or slowing the rate of Potassium sup + efflux, may result in lower ATP concentrations at the time of depolarization. Interpolation of the data of Katsura et al. suggests that cortical ATP concentration at the time of depolarization was approximately 63% of control in animals at 40 degrees Celsius compared with approximately 42% of control in animals at 34 degrees Celsius. [20] Reexamination of the data from Thorn et al. [22] and from Michenfelder and Theye [17] raises the possibility that during hypothermia, concentrations of ATP at depolarization may be greater than those during normothermia (perhaps because of hypothermic inhibition of Sodium-Potassium adenosine triphosphatase). Either of these possibilities would argue in favor of a dissociation between energy state and ion flux. However, our results do not support that argument. Ischemia produced the expected changes in high-energy phosphate concentrations, but there were no intergroup differences in the values seen at the time of depolarization: ATP concentrations were approximately 13-18% of normal, whereas EC was approximately 26-31% of normal. This finding implies that the ATP/EC threshold for membrane failure is relatively constant, regardless of the preischemic conditions, and in

turn suggests that the energy requirements of ion-pumping mechanisms are not influenced by preischemic CMR_G.

There is another implication of this result. Although in this experiment CMR_G was not measured directly, conditions were essentially identical to those of Nakashima et al., [9] and our current observed depolarization times were very similar. Therefore, if the CMR_G, depolarization time, and ATP/EC data from the two studies are combined, it becomes apparent that ATP/EC decreased more slowly in hypothermic animals than in pentobarbital and isoflurane groups (because a longer time was required to reach the same ATP concentration). Because prearrest CMR_G S were similar in the three groups, the rate of decrease in ATP concentration cannot have been determined entirely by preischemic CMR_G; if it were, we would anticipate lower ATP concentrations at the time of depolarization in hypothermic rats (depolarization time 244 s) than in pentobarbital or isoflurane rats (depolarization times 119-132 s). The rate of decrease in cellular EC must be determined by a mechanism other than simple preischemic carbohydrate and oxygen metabolism. This conclusion is essentially identical to that proposed by Michenfelder and Theye in 1970, although these authors did not correlate ATP concentrations with any functional parameter (e.g., depolarization). [17].

This partial dissociation may not be surprising. CMR_G/CMR for oxygen values are a better reflection of the rate of energy production. In normal brain, production and consumption of ATP are well balanced; this balance explains why drug- or temperature-induced reductions in CMR are not associated with changes in high-energy phosphate concentrations. Given the small carbohydrate and oxygen stores in brain, ischemia rapidly disrupts the normal production of ATP, but it may not simultaneously disrupt the processes that consume ATP. A similar argument was presented by Michenfelder in 1978. [23] He suggested that the different protective effects of hypothermia and barbiturates were related to their differing effects on energy-consuming activities, that is, on synaptic function versus the maintenance of cellular integrity. Barbiturates presumably reduce CMR (and hence energy consumption) only by depressing synaptic function, whereas hypothermia alters both synaptic and maintenance functions. If the EEG is rendered isoelectric by ischemia, barbiturates should have no protective value, while hypothermia may continue to influence cellular processes. It is not clear that the "synaptic function" argument is strictly correct. For example, in an earlier study by Verhaegen et al., CMR depression with small doses of isoflurane delayed the appearance of terminal depolarization (compared with halothane) but did not change the time until EEG isoelectricity (which presumably measures the cessation of synaptic activity). [5] In addition, Nakashima et al. found that hypothermia to 25 degrees Celsius increased the time to EEG electricity by only approximately 11 s while prolonging the time to depolarization by almost 250 s. [9] These findings suggest that both anesthetics and hypothermia have actions on ion homeostasis and energy consumption beyond those that can be accounted for by EEG-linked synaptic activity. They also indicate that a much larger fraction of postischemic energy consumption is related to nonsynaptic activity than perhaps heretofore believed. Nevertheless, Michenfelder's concept of subdividing energy utilization may explain our results. What remains to be understood is just what cellular energy-requiring functions are being slowed to a greater degree by hypothermia than by anesthetics. If these functions were identified, it might be possible to determine what processes should be targeted in our efforts to improve protection of the brain.

In summary, our current results indicate that neither normal cerebral concentrations of high-energy phosphates nor the concentrations associated with cortical depolarization are altered by deep barbiturate or isoflurane anesthesia or

by hypothermia (28 degrees Celsius). This finding suggests that the energy threshold for the loss of ionic- homeostasis is relatively constant. However, because it took longer for hypothermic rats to reach this threshold (as evidenced by the longer time until depolarization in hypothermic versus pentobarbital and isoflurane animals), the overall rate of ATP utilization appears to be lower in these animals, even though preischemic CMR_G was similar in all of the study groups. Clearly, there are factors other than preischemic CMR that define the rate of postischemic ATP depletion, and these factors are disproportionately influenced by temperature.

The authors thank William Gallagher, for his help in performing the high-energy phosphate assays, and Dr. William Lanier (Mayo Clinic, Rochester, MN), for his efforts to facilitate the completion of these experiments.

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