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Increase in Extracellular Potassium in the Brain during Circulatory Arrest: Effects of Hypothermia, Lidocaine, and Thiopental

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The effect of temperature (37°C, 28°C, and 18°C), 160 mg/kg lidocaine, and 40 mg/kg thiopental on the efflux of cellular potassium in the cerebral cortex during complete global ischemia was examined. Cerebral ischemia was induced in dogs on cardiopulmonary bypass circulation by stopping the pump. Potassium concentration was measured on the brain surface by a valinomycine-membrane electrode, which in its response corresponded well to an inserted microelectrode. Hypothermia reduced the ischemic potassium efflux rate to about 50 per cent at 28°C, and about 25 per cent at 18°C. At all temperature levels lidocaine caused an additional reduction in the potassium efflux rate of about 50 per cent, probably by reducing membrane ion permeability in accordance with its local anesthetic action. Thiopental had no effect on the potassium efflux during ischemia. This study opens the possibility that lidocaine, like hypothermia, may provide protection of the ischemic brain. (Key words: Anesthetics, intravenous: thiopental. Anesthetics, local: lidocaine. Brain: ischemia; oxygenation; protection. Hypothermia. Ions: potassium.)

FROM CLINICAL EXPERIENCE in open heart surgery it is evident that the infant brain can tolerate circulatory arrest for more than one hour if the temperature is lowered to 18°C.[1,2] Hypothermia reduces oxygen consumption in the brain[3,4] and causes a delay of the efflux of potassium from the cells in the brain cortex during ischemia.[5] The purpose of the present study was to investigate other interventions which similarly might cause a delay in the potassium efflux in the ischemic brain. Either alone or in combination, hypothermia, barbiturates, and lidocaine were studied in dogs undergoing cardiopulmonary bypass and subjected to standardized episodes of complete cerebral ischemia. The ultimate aim of the study was to explore new ways for providing cerebral protection during circulatory arrest.

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Methods

Thirty-eight mongrel dogs weighing 20–37 kg were studied. Anesthesia was induced with either 15–20 mg/kg thiopental (11 dogs) or 10 mg/kg ketamine (27 dogs) given intravenously. Ketamine was used in order to obtain a barbiturate-free preparation for the thiopental and lidocaine studies. Tracheal intubation was performed immediately afterwards, and in a few cases facilitated by the administration of 2 mg/kg succinylcholine, iv. Muscle relaxation was achieved by 5–8 mg/kg gallamine given intravenously initially and supplemented every half hour throughout the study in incremental doses. Anesthesia was maintained during surgery with halothane 1–1.5 per cent inspired in 50 per cent O_2 and N_2O. During cardiopulmonary bypass, halothane was discontinued and anesthesia maintained with ketamine given intravenously in an initial dose of 2 mg/kg, and repeated every half hour at temperatures above 28°C.

Cannulation of the femoral vessels on the right side was performed to obtain direct measurements of arterial blood pressure (BP) and central venous pressure (CVP). In addition, blood samples were drawn periodically from the arterial cannula for hemoglobin and blood gas measurements. Blood gases were measured at 37°C and corrected for animal temperature. The heart was exposed through a right thoracotomy. A multiperforated cannula was inserted in the right auricle allowing gravity drainage of the venous blood to a Rygg-Kyvsgaard bubble-oxygenator (Venoterm® 5000). The priming solution for the oxygenator consisted of 1000 ml Haemaccel® (Haemaccel® is a colloidal plasma substitute, 1 ml containing 35 mg polygetin, 8.5 mg NaCl, 0.38 mg KCl, 0.7 mg $CaCl_2$) 300 ml Ringer's solution, and 50 ml 50 per cent glucose. The oxygenated blood was returned by roller pump to the animal through a metal cannula in the left femoral artery. The ascending aorta was cross-clamped and cardioplegia was induced by the injection of several ml potassium chloride 1M, in the coronary circulation.

The whole body flow rate was 100 $ml \cdot kg^{-1} \cdot min^{-1}$. Heparin, 3 mg/kg, was given intravenously prior to bypass and repeated hourly in a dose of 1 mg/kg.

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Blood pressure was maintained in the range of 50–100 torr. This required occasional injections of 0.5–1.0 mg methoxamine or 1–2 mg chlorpromazine to the pump reservoir. Brain temperature was controlled by adjusting the temperature of the heat-exchanger in the oxygenator. During bypass, the hemoglobin concentration obtained was approximately 5 mM, and blood glucose was 20–25 mM. Metabolic acidosis was corrected using $NaHCO_3^-$ after the formula: base excess (BE) × body weight (kg) × 0.3.

The cerebral cortex was exposed prior to bypass through an enlarged burr hole over the right hemisphere. A potassium electrode was placed so that it just touched the brain surface. Two chlorinated silver wires placed on the cortex supplied the EEG signal. Brain temperature was monitored using a needle thermistor inserted into the brain tissue through a burr hole over the left hemisphere. Intracranial pressure was measured in 5 animals by an epidural transducer[6] placed over the left hemisphere.

The potassium surface electrode consisted of a polyvinyl-chloride membrane soaked with valinomycine (Radiometer Selectrode®). It was modified with a "built-in" reference (saline-silver chloride junction) (fig. 1). The electrode was calibrated in 2, 3, 5, and 100 mM KCl + 148, 147, 145, and 50 mM, NaCl respectively, using 100 mM KCl + 50 mM NaCl as the internal solution (fig. 2). Thiopental, 50 mg/l, or lidocaine, 1000 Mg/l, did not influence the calibration curve. Electrode resistance was 5×10^6 ohms and the response time was within several seconds. In four experiments, the response of the surface electrode was compared to the response of a double-barrelled potassium microelectrode inserted approximately 300 μm in the cortex.[7,8]

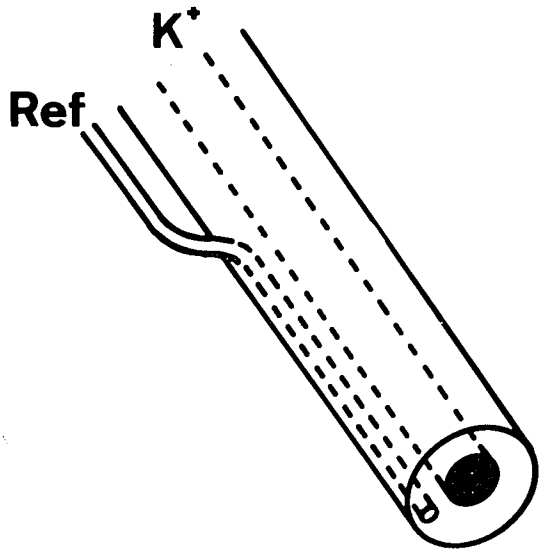

FIG. 1. The potassium selective surface electrode modified with a "built-in" reference electrode. The area of the potassium sensitive membrane was 4 mm².

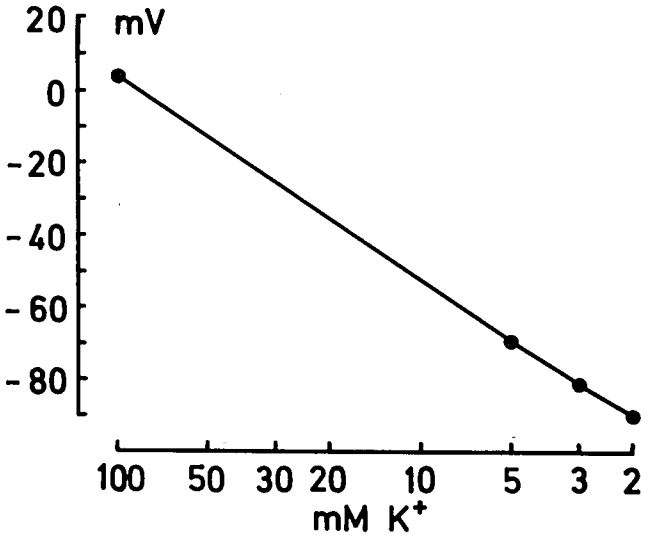

FIG. 2. Calibration curve. Outer solutions: 2, 3, 5 and 100 mM KCl + 148, 147, and 50 mM NaCl. Inner solution: 100 mM KCl + 50 mM NaCl. Room temperature. Calibrations were adjusted to brain temperature according to the Nernst equation.

Experimental Procedures

Two to eight circulatory arrest periods were performed in each animal, simply by stopping the pump. Recirculation was started when the potassium electrode depolarization reached about 40–50 mV corresponding to a potassium concentration of about 15 mM. During the arrest period the electrode position was lowered according to the degree of brain shrinking. During recirculation the electrode was lifted to allow brain re-expansion. The number of circulatory arrest periods was determined by potassium baseline return.

Thiopental, 40 mg/kg (injected in the pump reservoir). A sharp rise and subsequent fall in BP identified the biphasic response of the vascular bed to thiopental. Two min later, the pump was stopped. In 20 animals, 12 arrest periods were performed at 37°C, 6 at 28°C, and 10 at 18°C. The injection of 40 mg/kg thiopental was repeated prior to each subsequent arrest period. In five animals anesthesia was induced with thiopental, the others were induced with ketamine.

Lidocaine, 160 mg/kg (injected in the pump reservoir). Appearance of the drug in the systemic circulation was recognized by a fall in BP. Two min later, the pump was stopped. In 17 animals, 8 arrest periods were performed at 37°C, 7 at 28°C, and 7 at 18°C. In 5 of these animals the effect of lidocaine was tested after the

TABLE 1. Physiological Variables on Bypass Circulation Prior to Circulatory Arrest

	Brain Temperature (°C)	BP (torr)	Pa_{O_2} (torr)	Pa_{CO_2} (torr)	BE (mEq/l)	*p*H
Normothermia (n = 14)						
MEAN	37.0	64.3	355	41.3	−6.1	7.297
SD	0.15	14.3	115	10.0	4.1	0.102
Hypothermia (n = 15)						
MEAN	28.1	76.4	360	41.8	−5.9	7.294
SD	0.34	16.7	104	12.4	6.7	0.101
(n = 9)						
MEAN	18.0	49.2	588	31.0*	−7.9	7.359
SD	0.18	5.8	93	3.7	2.4	0.0069

* $P < 0.01$.

thiopental experiments had been completed. The reverse drug combination was not studied. After 60 min of recirculation, a second arrest period was performed without additional drug injection. In all animals anesthesia was induced with ketamine.

Brain temperature. As part of the experimental series described above, the effect of brain temperature alone was investigated. Seventeen arrest periods in 10 animals were performed at 37°C, 28 in 15 animals at 28°C, and 28 in 16 animals at 18°C. These arrest periods preceded the injection of thiopental or lidocaine.

Student's *t* test was used to calculate the level of significance.

Results

Table 1 summarizes physiological variables of the animals on bypass circulation prior to experimental procedures at the three different temperatures. The metabolic acidosis was corrected prior to circulatory arrest.

$[K^+]_s$ vs. $[K^+]_e$

The surface electrode and the inserted microelectrode were compared by simultaneous measurements on the same gyrus. The potassium concentration measured on the brain surface $[K^+]_s$ closely followed the concentration in the extracellular space $[K^+]_e$. The ischemic potassium efflux in the cortex appears on the surface in an only slightly delayed and attenuated fashion as shown in figures 3 and 4. These observations confirm the close correlation between surface and tissue measurements of potassium during spreading depression as previously reported by Crowe *et al.*[9]

EFFECT OF HYPOTHERMIA, THIOPENTAL, AND LIDOCAINE

Several circulatory arrest periods were induced in each animal. The EEG flattened after the first

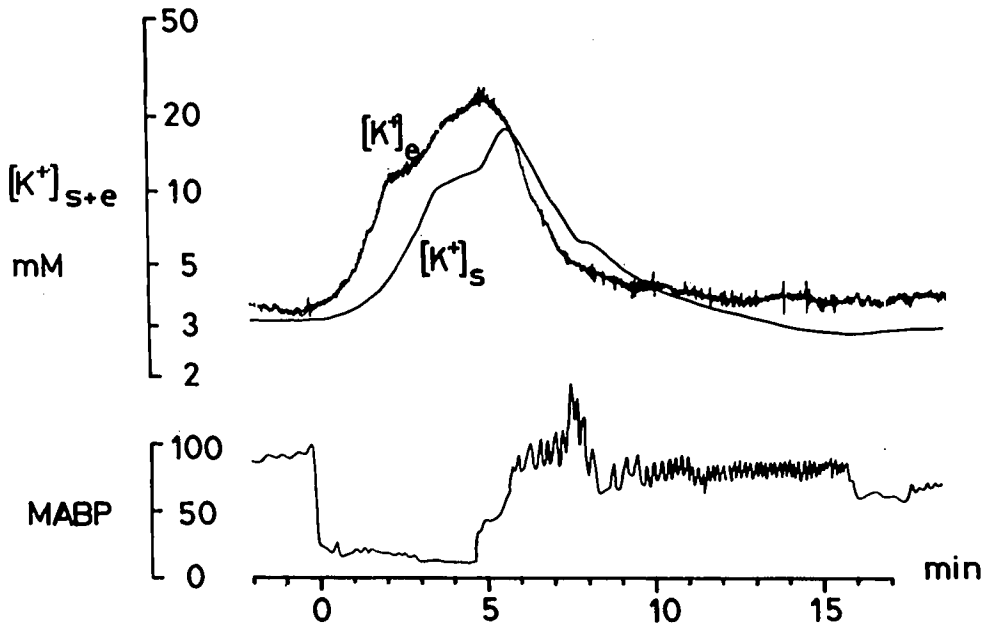

FIG. 3. Simultaneous measurement of $[K^+]_s$ and $[K^+]_e$ from the same gyrus. Note the slightly delayed and attenuated appearance of the ischemic potassium increase on the surface (37°C, no drugs).

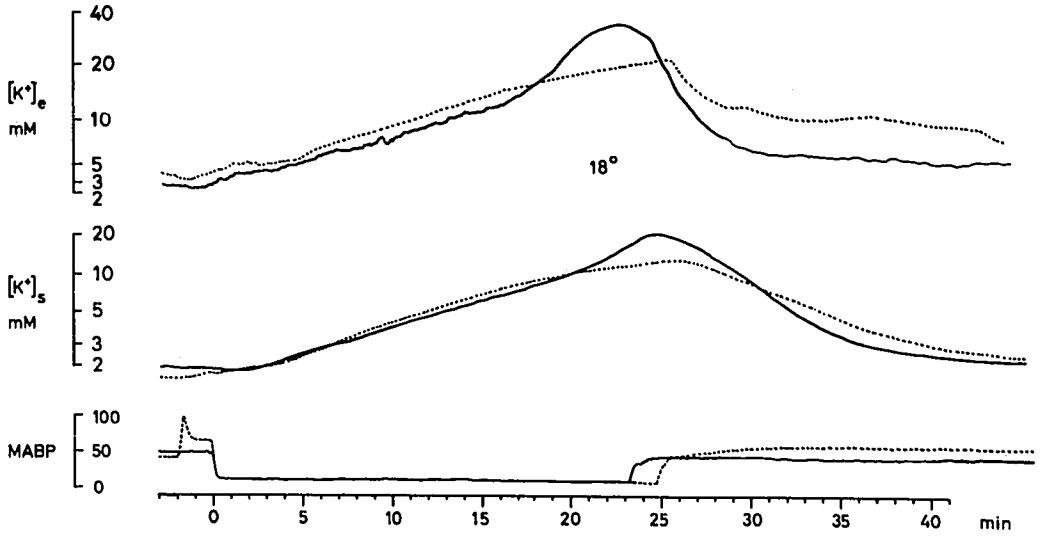

FIG. 4. Simultaneous measurement of $[K^+]_s$ and $[K^+]_e$ from the same gyrus. Potassium clearing during recirculation is delayed on the surface. This is probably explained by obstruction of microflow due to tissue compression by the electrode which in this experiment was left in position during recirculation. Measurement done at 18°C. Unbroken line: no drugs. Broken line: 2 min after 40 mg/kg thiopental. Thiopental has no effect on the ischemic potassium efflux.

arrest period and did not recover. The potassium efflux rate during the first arrest period was similar to the subsequent ones. The potassium curves were pooled and arranged according to brain temperature and the drug given (fig. 5).

It is evident that hypothermia effectively delayed the ischemic potassium efflux. This can be delayed further at all temperatures by 160 mg/kg lidocaine; however, the most effective delays are at 37°C and 28°C. Thiopental, 40 mg/kg, had no delaying effect either at normo- or hypothermia. Table 2 shows the time in min to the electrode depolarization of 10, 20, 30, and 40 mV. These data confirm the marked delaying effect of hypothermia and the additional delaying effect of lidocaine. The data indicate shortening of the 10 mV and 20 mV depolarization time by thiopental at 28°C and 18°C. This numerical result could not be substantiated by comparing the control arrest period without thoipental and the subsequent thiopental arrest period in individual animals (fig. 4). Neither does the visual presentation of data in figure 5 give evidence of an effect of thiopental on the initial depolarization rates. We conclude that thiopental has no overall effect, and certainly

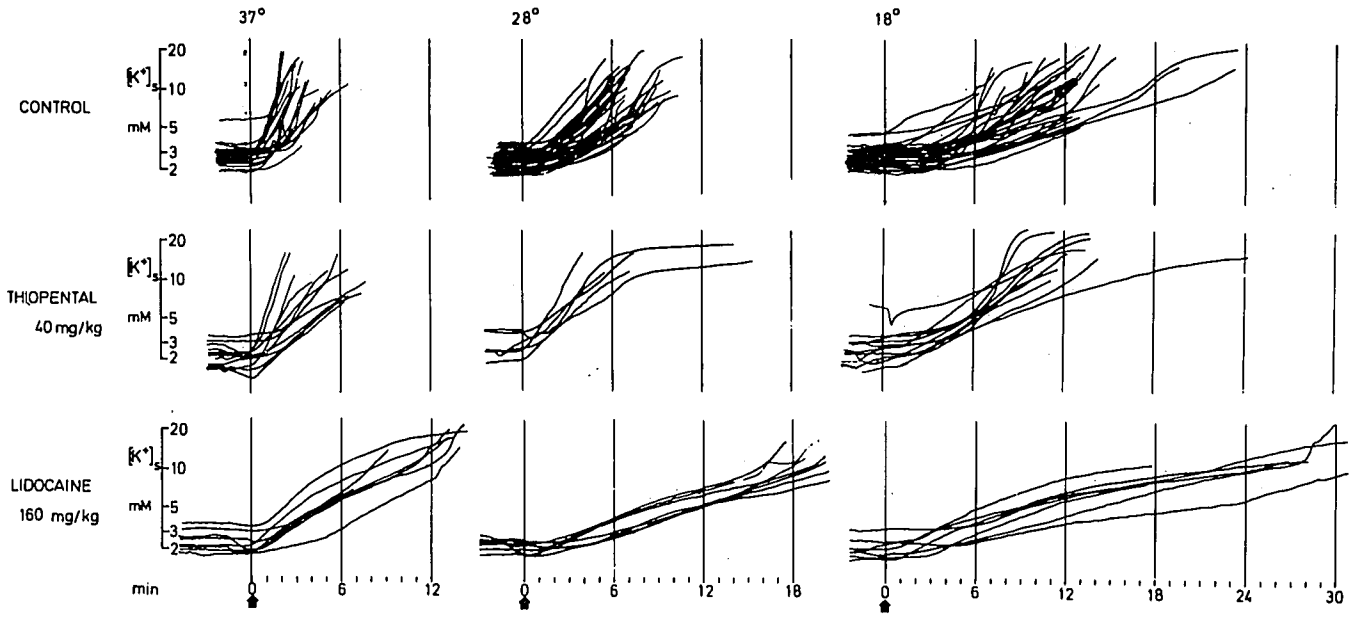

FIG. 5. All ischemic potassium curves grouped according to brain temperature and drug. Since the phase of recirculation is left out, the length of the curves from time zero indicates arrest duration.

TABLE 2. Potassium Electrode Depolarization Time Indicating Electrode Depolarization Rate and Hence Rate of Increase in $[K^+]_s$ According to the Calibration Curve Shown in Figure 2

	37°C				28°C				18°C			
Depolarization, mV	10	20	30	40	10	20	30	40	10	20	30	40
Electrode depolarization time (min)												
Control												
MEAN	2.0	2.7	3.3	2.9	3.6*	5.3*	6.5*	7.2*	6.9*	9.5*	10.9*	12.9*
SEM	0.2	0.3	0.3	0.2	0.2	0.3	0.3	0.3	0.5	0.5	0.7	1.3
n	17	17	15	8	28	28	25	19	28	28	20	12
Thiopental (40 mg/kg)												
MEAN	1.9	3.2	3.9	4.5	2.2*	3.7*	5.0	5.6	4.9*	7.4*	9.5	11.0
SEM	0.3	0.5	0.5	0.9	0.4	0.6	0.8	1.1	0.4	0.5	0.7	1.3
n	12	12	11	7	6	6	6	4	10	10	10	8
Lidocaine (160 mg/kg)												
MEAN	3.0	4.9*	7.4*	10.1*	6.0*	9.6*	14.2*	18.6*	6.2	10.9	16.2	22.8*
SEM	0.5	0.6	0.6	0.6	0.6	0.8	0.9	0.9	0.9	1.9	2.2	2.5
n	8	8	8	7	7	7	7	7	7	7	7	5

*$P < 0.01$.

not a delaying effect, on the ischemic potassium efflux.

EPIDURAL PRESSURE

During repeated episodes of arrested circulation and subsequent recirculation, the epidural pressure varied with BP but stayed low, indicating a sufficient cerebral perfusion pressure. This, together with clearing of potassium during recirculation, indicate sufficient reperfusion.

Discussion

The aim of this study was to explore possible interventions which like hypothermia, cause a delay in the potassium efflux in the brain cortex during ischemia. Hypothetically, such interventions could provide additional protection of the brain during prolonged periods of circulatory arrest during surgical correction of congenital heart diseases. The basic concept for this hypothesis dates back many years. During complete ischemica, the energy production from oxidative metabolism is almost instantaneously halted. The tissue stores of ATP are rapidly used up. The ion pump fails due to substrate depletion and the cells leak potassium and gain sodium. The cell membranes depolarize and chloride and water shift according to concentration gradients. Cortical polarity disappears. Tissue impedance increases, thus indicating shrinkage of the extracellular space. By monitoring any of the above mentioned events the metabolic changes in the brain cortex during ischemia can be followed. A delay in these events can also be recognized. The hypothetical question is whether a delay in the ischemic metabolic changes also implies a delay in the appearance of irreversible cellular damage. In 1957, Bures and Buresova[10] suggested that the delay in disappearance of cortical polarity seen during hypothermia indicated brain protection. It has been shown that the changes in cortical polarity[11] and impedance,[12] and the depletion of tissue ATP[13,14] in the ischemic brain are delayed by hypothermia. It is therefore not surprising that the increase in extracellular potassium concentration in the ischemic brain cortex also is delayed by hypothermia. Accordingly, the present study confirms previous results in the hypothermic rat brain.[5] Also, Bering[4] found a delay in ischemic potassium efflux during hypothermia, although his measurements of electrolyte concentrations in CSF sampled from cisterna magna introduced considerable attenuation of the response. These observations indicate that the ischemic metabolic changes in the brain are delayed by hypothermia. Similarly, hypothermia delays the development of irreversible cell damage in the ischemic brain as evidenced by the very considerable prolongation of acceptable circulatory arrest periods during cold ischemia.[1,2,15,16] The hypothesis mentioned above that a delay in the potassium efflux in the ischemic brain indicates protection is thus valid in the state of hypothermia. It remains controversial whether a drug-induced delay in the ischemic potassium efflux, either at normothermia or in combination with hypothermia, indicates protection.

The drugs studied in combination with hypothermia in the present study were thiopental, 40 mg/kg, and lidocaine, 160 mg/kg.

Thiopental

This drug was chosen due to its well-known effects on the brain. Like other barbiturates it reduces cerebral metabolic rate, and this effect is at a maximum when the EEG becomes isoelectric.[17] Furthermore, barbiturates may, at least in certain animal species, delay the ischemic metabolic deterioration. This is indicated by a delayed depletion of ATP in the rat[18] and mouse[19] brain during complete ischemia. Accordingly, the ischemic potassium efflux is delayed by barbiturate in the rat brain[5]. In the dog brain, however, thiopental seems without effect on the rate of ATP depletion during complete ischemia, although the preischemic metabolic rate is reduced markedly.[14,20] In the present study, the result of no effect of thiopental on the ischemic potassium efflux is thus in line with these metabolic studies of Michenfelder and Theye. The discrepancy between results obtained in the dog and in the rat is likely related to the considerable species difference in cerebral metabolic rates and hence in dynamics of the ischemic metabolic changes.

That barbiturates lack effect on the ischemic metabolic changes in the dog brain is consistent with the accumulating evidence that barbiturates are without significant clinical value as protectants in complete global cerebral ischemia, at least in dogs and primates (see *e.g.*, Rockoff and Shapiro[21]).

Lidocaine

As a local anesthetic, lidocaine blocks the sodium channels in the cell membrane.[22] We propose that lidocaine can block, at least partly, the leak of ions from the cells, and so to speak, save on the energy needed for maintaining the membrane potentials by ion pumping. Accordingly, lidocaine caused a marked delay in the ischemic potassium efflux. This action was additive to the effect of hypothermia. According to the hypothesis discussed above, this effect suggests the possibility that lidocaine could provide clinically useful protection of the ischemic brain, not only in combination with hypothermia, but even at normothermia.

Lidocaine readily crosses the blood-brain barrier and has been used for the treatment of status epilepticus due to its cerebral depressant action. The effect of lidocaine on the brain appears to be due to a dual action: a depression of function and metabolism at low and high dosages, and stimulation, *i.e.*, seizures at intermediate dosages.[23] Seizures are regularly induced at doses of 20–30 mg/kg.[23,24] Our dose of 160 mg/kg was selected with the intention of being well above the seizure dose which may vary considerably.[25] The selected dose was satisfactory in the sense that it caused a flat EEG without an intermediate phase of seizure activity. It may be possible to reduce the total lidocaine dose required to obtain a flat EEG by selective exposure of the brain immediately prior to stopping the pump. We did not attempt to revive the animals in this study. Further animal studies will be required to determine whether protection of the brain during prolonged circulatory arrest, as judged by recovery of neurological function can be realistically provided by lidocaine.

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References

1. Barrett-Boyes BG, Neutze JM, Seelye ER, et al: Complete correction of cardiovascular malformations in the first year of life. Prog Cardiovasc Dis 15:229–253, 1972
2. Behrendt DM: Deep hypothermia with circulatory arrest in infants, Second Henry Ford Hospital International Symposium on Cardiac Surgery. Edited by Davila JD. Appleton-Century-Crofts, New York, pp 119–124, 1977
3. Michenfelder JD, Theye RA: Hypothermia: Effect on canine brain and whole-body metabolism. Anesthesiology 29: 1107–1112, 1968
4. Bering EA: Effects of profound hypothermia and circulatory arrest on cerebral oxygen metabolism and cerebrospinal fluid electrolyte composition in dogs. J Neurosurg 39:199–205, 1974
5. Astrup J, Rehncrona S, Siesjö BK: The increase in extracellular potassium concentration in the ischemic brain in relation to the preischemic functional activity and cerebral metabolic rate. Brain Res 199:161–174, 1980
6. Beks JWF, Albarda S, Gieles ACM, et al: Extradural transducer for monitoring intracranial pressure. Acta Neurochir (Wien) 38:245–250, 1977
7. Astrup J, Heuser D, Lassen NA, et al: Evidence against H^+ and K^+ as main factors for the control of cerebral blood flow: A microelectrode study. Ciba Foundation Symposium 56:313–337, Excerpta Medica, Holland, 1978
8. Hansen AJ: Extracellular potassium concentration in juvenile and adult rat brain cortex during anoxia. Acta Physiol Scand 99:412–420, 1977
9. Crowe W, Mayevsky A, Mela L: Application of a solid membrane ion-selective electrode to *in vivo* measurements. Am J Physiol 233:C56–C60, 1977
10. Bures J, Buresova O: Die anoxische Therminaldepolarisation als Indicator der Vulnerabilität der Grosshirnrinde bei Anoxie und Ischämie. Pfluegers Arch 264:325–334, 1957
11. Benesova O, Buresova O, Bures J: Die Wirkung des Chlorpromazins und der Glykämie auf das elektrophysiologisch kontrollierte Überleben der Hirnrinde bei verschiedenen Körpertemperaturen. Arch Exper Path Pharmakol 231: 550–561, 1957

12. Collewijn H, Schadé JP: Conductivity of the cerebral cortex after circulatory arrest at body temperature from 37°C to 18°C. Arch Int Physiol Biochim 72:181–193, 1964
13. Kramer RS, Sanders AP, Lesage AM, et al: The effect of profound hypothermia on preservation of cerebral ATP content during circulatory arrest. J Thorac Cardiovasc Surg 56:699–709, 1968
14. Michenfelder, JD, Theye RA: The effects of anesthesia and hypothermia on canine cerebral ATP and lactate during anoxia produces by decapitation. ANESTHESIOLOGY 33: 430–439, 1970
15. Connolly JE, Boyd RJ, Calvin JW: The protective effect of hypothermia in cerebral ischemia: Experimental and clinical application by selective brain cooling in the human. Surgery 52:15–23, 1962
16. Smith MC, Adams JE, Leake TB, et al: Occlusion of blood supply to the brain of the goat. Protective effect of deep hypothermia. J Neurosurg 20:46–59, 1963
17. Michenfelder JD: The interdependency of cerebral function and metabolic effects following massive doses of thiopental in the dog. ANESTHESIOLOGY 41:231–236, 1974
18. Nordström C-H, Siesjö BK: Influence of phenobarbital on changes in the metabolites of the energy reserve of the cerebral cortex following complete ischemia. Acta Physiol Scand 104:271–280, 1978
19. Gatfield PD, Lowry OH, Schulz DW, et al: Regional energy reserves in mouse brain and changes with ischemia and anesthesia. J Neurochem 13:185–195, 1966
20. Michenfelder JD, Theye RA: Cerebral protection by thiopental during hypoxia. ANESTHESIOLOGY 39:510–517, 1973
21. Rockoff MA, Shapiro HM: Barbiturates following cardiac arrest: Possible benefit or Pandora's box? ANESTHESIOLOGY 49:385–387, 1978
22. Strichartz G: Molecular mechanisms of nerve block by local anesthetics. ANESTHESIOLOGY 45:421–441, 1976
23. Sakabe T, Kaekawa T, Ishikaka T, et al: The effects of lidocaine on canine cerebral metabolism and circulation related to the electroencephalogram. ANESTHESIOLOGY 40: 433–441, 1974
24. Munson ES, Tucker WK, Ausinisch B, et al: Etidocaine, bupivacaine seizure thresholds in monkeys. ANESTHESIOLOGY 42:471–478, 1975
25. Rosenbaum KJ, Sapthavichaikul S, Skovsted P: Sympathetic nervous system response to lidocaine induced seizures in cats. Acta Anaesth Scand 22:548–555, 1978