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Inhibition of Cerebral Oxygen and Glucose Consumption in the Dog by Hypothermia, Pentobarbital, and Lidocaine

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The effect of lidocaine, 160 mg/kg, and pentobarbital, 40 mg/kg, on cerebral oxygen and glucose consumption was examined at brain temperatures of 37°C, 28°C, and 18°C. Cerebral metabolic rate was measured in dogs on cardiopulmonary bypass circulation by using the sagittal sinus outflow technique. When studied separately, both drugs suppressed synaptic transmission and inhibited metabolism, and a maximum effect was obtained when the EEG became flat. Using halothane 1–1.5 per cent as the control condition, this function-metabolism coupled inhibition was about 30 per cent. When the drugs were studied in combination, it was found that when lidocaine was given after pentobarbital, it caused an additional metabolic inhibition of 15–20 per cent, while pentobarbital given after lidocaine had no effect. It is concluded that pentobarbital has no inhibitory effect on cerebral metabolism in the absence of synaptic activity, while lidocaine —in addition to the effect related to suppression of synaptic transmission—has a specific "membrane stabilizing" effect. In analogy to its local anesthetic action, lidocaine blocks the Na^+ channels and restricts the Na^+-K^+ leak fluxes. The load on the ion pump is reduced and metabolism is decreased accordingly. This specific effect of lidocaine was evident also at brain temperatures of 28°C and 18°C. The study supports the possibility that lidocaine, like hypothermia, may provide protection for the ischemic brain. (Key words: Anesthetics, intravenous: pentobarbital. Anesthetics, local: lidocaine. Brain: blood flow; electroencephalography; metabolism; oxygen consumption; protection. Hypothermia.)

LIDOCAINE delays the efflux of potassium in the ischemic brain.[1] Presumably, lidocaine reduces the leak fluxes of sodium and potassium ions in the brain by lowering the membrane permeability primarily for sodium. In the ischemic brain this action appears as a delay in the rate of potassium efflux. We assume that in the nonischemic brain this action appears as a reduced oxygen and glucose consumption. If ion leak fluxes are diminished, the ion pump is relieved of part of its load. Accordingly, the energy demand for ion pumping will be proportionally reduced. In order to find evidence for this assumption we have measured the effect of lidocaine on cerebral oxygen and glucose consumption in the dog on cardiopulmonary bypass circulation using the venous outflow technique.[2,3]

The overall purpose of the study was to explore conditions of very low cerebral metabolism. Such conditions may improve the hypothermic protection of the brain during the often long intervals of circulatory arrest in open heart surgery in infants.

Methods

Twenty-five mongrel dogs weighing 23–40 kg were anesthetized by thiopental, 13–27 mg/kg (mean 19.6 mg/kg), intravenously. Endotracheal intubation was performed after muscular relaxation using gallamine, 2–8 mg/kg. Respiration was controlled by mechanical ventilation. Anesthesia was maintained with halothane 1–1.5 per cent inspired in 20–25 per cent oxygen and 75–80 per cent air. During cardiopulmonary bypass circulation this gas mixture was diverted to the bubble-oxygenator at constant gas flow. Halothane anesthesia thus represents the control condition for the present studies. The femoral vessels on the right side were cannulated for blood pressure (BP) and central venous pressure measurements. Blood gases and hemoglobin concentration were repeatedly measured. The blood gases were measured at 37°C and corrected for brain temperature. Metabolic acidosis was corrected with bicarbonate according to the formula: base excess (BE) × body weight (kg) × 0.3. Ventilation or alternate gas flow through the bubble-oxygenator was adjusted to ensure normocapnia or slight hypocapnia at normal body temperature. Due to the constant gas flow, Pa_{CO_2} decreased during hypothermia.

The heart was exposed through a right thoracotomy. The left femoral artery was cannulated using a metal cannula. A multiperforated cannula was inserted in the right auricle allowing drainage of the venous blood to a Rygg-Kyvsgaard bubble-oxygenator (Venoterm®5000) primed with 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 $CaCl_2$) and 300 ml Ringer's solution to

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TABLE 1. Physiological Variables on Bypass Circulation Prior to Measurements of Cerebral Metabolism

	Brain Temperature (°C)	BP (torr)	Pa_{CO_2} (torr)	Pa_{O_2} (torr)	BE (mEq/l)	pH	Hb (mM)	Glucose (mM)
Normothermia (n = 22)								
MEAN	37.1	69	25.3	170	−4.1	7.474	4.4	7.11
SD	0.1	12	4.1	56	3.7	0.070	2.1	1.06
Hypothermia (n = 8)								
MEAN	28.1	70	16.5*	206	−6.1	7.569*	4.4	6.84
SD	0.2	17	4.3	112	5.1	0.083	0.7	1.24
(n = 7)								
MEAN	18.0	66	11.1*	230	−9.0	7.636*	3.8	6.94
SD	0.2	14	2.3	108	3.5	0.078	0.7	1.42

* $P < 0.01$, Student t test.

obtain hemodilution. The oxygenated blood was pumped by a roller-pump into the animal via the cannula in the left femoral artery. Heparinization was induced by 3 mg/kg heparin and maintained by 1 $mg \cdot kg^{-1} \cdot h^{-1}$. Cardioplegia was obtained by flushing the coronary circulation using potassium chloride 1 M after clamping the ascending aorta. The cardiopulmonary bypass circulation was maintained at a flow rate of 100 $ml \cdot kg^{-1} \cdot min^{-1}$, and BP controlled within 50–100 torr by occasional injection of 0.5–1 mg methoxamine or 1–2 mg chlorpromazine. Brain temperature was controlled by adjusting the water temperature in the heat exchanger of the oxygenator.

Cerebral blood flow was measured according to the method of Rapela *et al.*[2] using the modification described by Michenfelder *et al.*[3] The bone flap over the superior sagittal sinus was isolated except for the very thin part forming the floor in the frontal sinuses. Bleeding from the diploic veins in the skull was controlled with bone wax. The ethmoidal veins were ligated to prevent escape of part of the venous outflow from the brain by that route. The occipital part of the superior sagittal sinus was cannulated using a metal cannula (ID = 2 mm). The sinus was occluded distal to the cannula by compression and ligation. Two dural incisions were placed parallel to the sinus to allow collapse of the sinus. After these precautions, the sinus outflow was little affected by changes in outflow resistance (catheter level was 10 cm above or below sinus level). These precautions were considered necessary to ensure venous outflow from a constant part of the brain.[3] Three animals were lost because of occlusion of the sinus outflow cannula. Cerebral blood flow (CBF) was measured as venous outflow. The cerebral metabolic rates of oxygen (CMR_{O_2}) and glucose (CMR_{gluc}) were calculated from blood flow and arteriovenous differences of oxygen (AVD_{O_2}) and glucose (AVD_{gluc}). Oxygen content of the blood was calculated from measurements of hemoglobin concentration and oxygen saturation (Radiometer OSM_{O_2} equipment) adding the dissolved amount of oxygen calculated from the oxygen tensions by using solubility constants of 0.022 (37°C), 0.026 (28°C), and 0.030 (18°C) ml $O_2 \cdot 760\ torr^{-1} \cdot ml\ blood^{-1}$. At hypothermia the dissolved amount of oxygen contributes significantly to the AVD_{O_2}. Whole blood glucose concentration was measured in triplicate using a refined standard technique.[4]

The EEG was monitored by placing chlorinated silver wires on the dural surface over the parietal part of the right hemisphere. Brain temperature was measured by a thermister inserted into the left hemisphere.

EXPERIMENTAL PROCEDURES

Flow was measured and arterial and venous blood sampled every five min for analysis of hemoglobin, saturation, gas tensions, acid-base status, and glucose. The following subgroups were studied:

Lidocaine, 160 mg/kg. To avoid seizures and metabolic stimulation, lidocaine was given as a bolus in the pump reservoir. By this procedure, the EEG became flat within seconds. Six studies were performed at 37°C, 4 at 28°C, and 2 at 18°C. The lidocaine effect was studied only at one temperature level in each animal.

Pentobarbital, 40 mg/kg. Pentobarbital was given by infusion at a constant rate over a 13–32 min interval (mean = 19 min). Onset of flat EEG was noted as absence of bursts for more than one min. Six studies were performed at 37°C, 3 at 28°C, and 3 at 18°C.

Lidocaine, 160 mg/kg, subsequent to pentobarbital, 40 mg/kg. Ten min after the pentobarbital infusion (Group 2), lidocaine was infused at constant rate over a 20–37 min period (mean = 28 min). EEG remained flat.

Pentobarbital, 40 mg/kg, subsequent to lidocaine, 160 mg/kg. Pentobarbital was given either as a bolus (n = 3) or as constant rate infusion (n = 3) over a 11–15 min interval, 25–45 min after lidocaine (Group 1). Three studies were performed at 37°C, 2 at 28°C, and 1 at 18°C. EEG was flat.

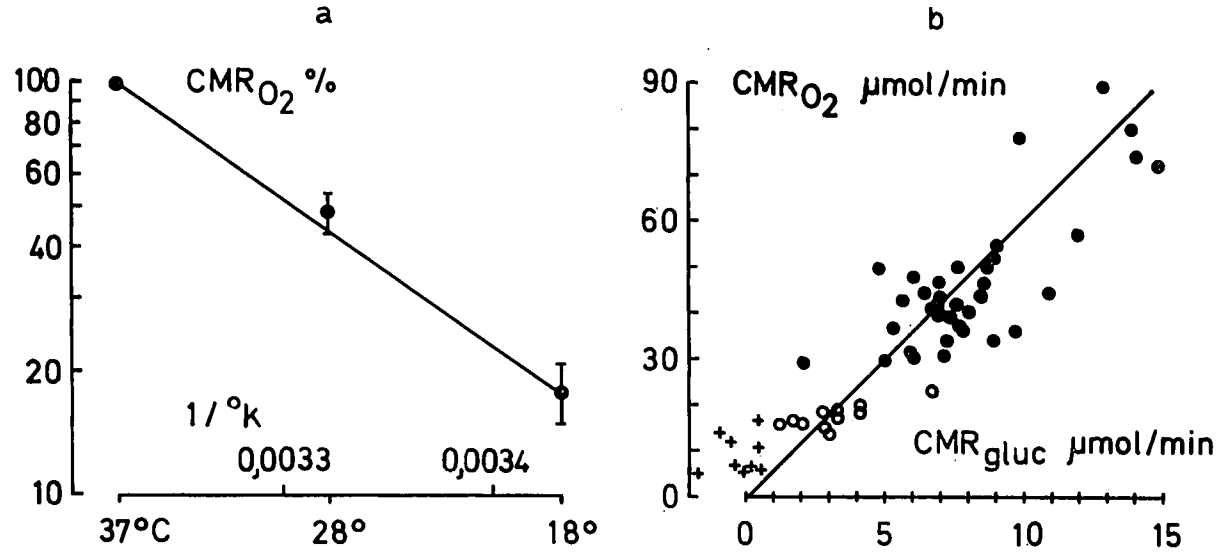

FIG. 1*A*. Correlation between cerebral oxygen consumption and temperature (Arrhenius plot, log CMR_{O_2} per cent = 0.0392 × °C − 0.529, r = 0.956, Q_{10} = antilog 0.392 = 2.47). The means ± SEM are shown.

FIG. 1*B*. Correlation between the cerebral oxygen and glucose consumption at 37°C, 28°C, and 18°C. No drugs were given. The line indicates the 6.0 molar ratio.

The effect of hypothermia alone was also studied as part of the above described procedures. Eight paired measurements were obtained at 37°–28°C, and 7 at 37°–18°C.

Student's *t* test was used to calculate level of significance. Six animals in each group allowed the use of the simple "sign-test" according to which a change in the same direction in all animals is significant at the $P < 0.05$ level.

Results

Physiological Variables

Table 1 summarizes the physiological variables on cardiopulmonary bypass circulation. These data represent the first set of measurements, and the metabolic acidosis was corrected prior to the experimental procedures. Because of a constant gas flow through the oxygenator, Pa_{CO_2} fell during cooling. This was reflected by a progressive alkalosis.

Brain Temperature

Figure 1*A* shows the interrelation between temperature and CMR_{O_2} displayed as an Arrhenius plot. The linear correlation (log CMR_{O_2} per cent = 0.0392 × C° = 0.529, r = 0.956, Q_{10} = antilog 0.392 = 2.47) is almost identical to the data obtained by Michenfelder and Theye[4] at 38°–28°C. The correlation between CMR_{O_2} and CMR_{gluc} is shown in figure 1*B*. The CMR_{O_2}/CMR_{gluc} molar ratio at 37°C was 5.8 ± 0.23 (mean ± SEM, n = 34). This result is not significantly different from the 6.0 ratio indicated in figure 1*B*. At 18°C the AVD_{gluc} values become extremely small, and the frequently negative values are accounted for by the limited resolving power of the glucose method. Hypothermia slowed EEC activity, but signs of activity persisted at 18°C.

Lidocaine and Pentobarbital

Tested one by one, lidocaine and pentobarbital had similar effects on cerebral function and metabolism. Synaptic transmission was abolished and metabolism inhibited. Pentobarbital was given by infusion, and it was observed that the metabolic inhibition reached a maximum when the EEG became flat. This effect corresponds to the effect of thiopental as described by Michenfelder.[5] The overall effects of lidocaine and pentobarbital on the halothane-anesthetized brain were not significantly different (table 2, section 1). However, the subsequent experiments showed that the effect of pentobarbital is related to suppression of the EEG activity, while the effect of lidocaine has two causes. One is related to suppression of EEG activity (a "barbiturate-like" effect), the other to an additional effect on the brain in which the EEG activity had been suppressed. This latter effect was evidenced by the additional metabolic inhibition of 15–20 per cent by lidocaine acting on the pentobarbital suppressed brain with flat EEG (table 2, section 2). Pentobarbital, however, had no

TABLE 2. Effect of Pentobarbital and Lidocaine on Cerebral Oxygen and Glucose Consumption. The Separate Effects of the Drugs are Shown in Section 1, and the Combined Effects in Section 2 and Section 3. Values are Means ± SEM

	Section 1				
	CMR_{O_2} Per Cent			CMR_{gluc} Per Cent	
	37°C	28°C	18°C	37°C	28°C
Halothane 1–1.5 Per cent Control	100	100	100	100	100
Pentobarbital (40 mg/kg)					
MEAN	69.4	69.6	74.7	74.2	87.2
SEM	5.5	—	—	6.1	—
n	6	3	3	6	3
Lidocaine (160 mg/kg)					
MEAN	65.1	71.0	58.0	61.2	73.2
SEM	4.7	—	—	5.1	—
n	6	4	2	6	2
	Section 2				
Pentobarbital (40 mg/kg)	100	100	100	100	100
Lidocaine (160 mg/kg)					
MEAN	84.8	84.7	87.7	81.0	72.0
SEM	3.4	—	—	5.3	—
n	6	3	3	6	3
	Section 3				
Lidocaine (160 mg/kg)	100	100	100	100	100
Pentobarbital (40 mg/kg)					
MEAN	95.8	104.5	105	101.3	115
SEM	—	—	—	—	—
n	3	2	1	3	2

effect on metabolism when acting on the lidocaine suppressed brain with flat EEG (table 2, section 3). These effects of lidocaine and pentobarbital were demonstrated at brain temperatures of 37°C and 28°C, and could be detected even at 18°C. At 18°C the EEG showed persisting but markedly slowed synaptic activity. The CMR_{gluc} values obtained at 18°C were inaccurate due to very small AVD_{gluc} values, and are omitted from table 2. Plasma concentrations of pentobarbital and of lidocaine reached 58 ± 2.3 mg/l^{-1} and 108 ± 16 mg/l^{-1} (mean ± SEM, n =4), respectively, at the end of infusion. Figure 2 shows the CMR_{O_2}-CMR_{gluc} correlation obtained during the lidocaine and pentobarbital experiments. This figure, like table 2, shows, that both drugs caused a near equal reduction in oxygen and glucose consumption. Table 3 summarizes the effects of lidocaine and pentobarbital on physiological variables. Lidocaine caused an increase in cerebrovascular resistance (CVR) (BP = CVR × CBF). This effect "overshoots" the expected metabolic flow regulation as indicated by the increase in oxygen extraction (lower venous P_{O_2}, increasing AVD_{O_2}). This points towards a specific vasoconstrictory effect of lidocaine. The calculated CMR_{O_2} values are included in table 3. Lidocaine caused additional metabolic inhibition in all the pentobarbital suppressed brains ($P < 0.05$).

Discussion

The venous outflow technique in the dog measures flow and metabolism in the drained part of the brain, assuming no extracerebral contamination. The portion of the brain drained must be constant. If it varies with experimental procedures, proportional variations in oxygen and glucose consumption will occur. We found that the venous outflow to some extent varied with outflow resistance, indicating that blood from the drained portion of the brain may seek other routes. However, the satisfactory temperature–CMR relation[6–8] supports method reliability. It indicates that experimental procedures which cause changes in cerebral metabolism and hemodynamics within the range of the changes induced by hypothermia are safe for study with this method. Method reliability was further confirmed by the observation of a flat EEG in

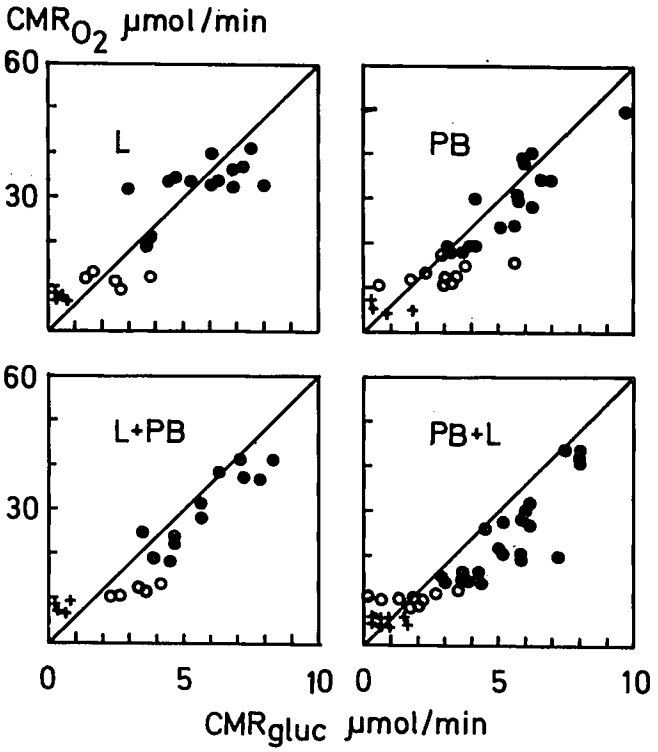

FIG. 2. CMR_{O_2} – CMR_{gluc} correlation during the lidocaine (L) and pentobarbital (PB) experiments. The drugs caused an equimolar reduction in cerebral oxygen and glucose consumption. The lines indicate the 6.0 molar ratio. ● = 37°C, ○ = 28°C, and + = 18°C.

TABLE 3. Effect of 160 mg/kg Lidocaine on Physiological Variables. Lidocaine Was Given Either as the Only Drug, or After 40 mg/kg Pentobarbital at 37°C

	BP (torr)	CBF (ml/min)	CVR (torr/ml·min^{-1})	Pa_{CO_2} (torr)	pH	Pa_{O_2} Sagital Vein (torr)	AVD_{O_2} (μmol/ml)	Hb (mM)	CMR_{O_2} (μmol/min)
Halothane 1–1.5 Per cent (n = 6)									
MEAN	66.0	19.4	3.6	27.1	7.473	36.1	2.56	5.6	49.6
SEM	3.3	2.1	0.4	2.0	0.019	1.5	0.12	0.4	3.4
Lidocaine (n = 6)									
MEAN	54.7*	8.2*	8.1*	28.3	7.406*	30.7*	3.84*	6.1	31.5*
SEM	4.5	0.9	1.9	2.6	0.021	0.9	0.12	0.3	2.6
Halothane 1–1.5 Per cent (n = 6)									
MEAN	66.2	19.7	3.5	23.4	7.449	35.5	2.20	4.6	43.4
SEM	3.9	1.4	0.3	2.4	0.037	2.4	0.25	0.4	6.2
Pentobarbital (n = 6)									
MEAN	45.2*	12.6*	3.7	23.9	7.454	30.8*	2.48*	4.2	31.2*
SEM	4.3	1.3	0.3	2.5	0.039	1.9	0.21	0.5	4.1
Lidocaine (n = 6)									
MEAN	48.0	9.6*	5.1	23.6	7.378*	30.2	2.71*	4.2	26.0*
SEM	2.9	0.2	0.4	1.9	0.036	2.3	0.29	0.5	4.0

* $P < 0.05$, sign test.

three animals with unintended occlusion of the sinus outflow cannula. If outflow by alternative routes had allowed sufficient drainage, EEG activity would have persisted. This observation indicates that capacity of the alternative outflow routes is small, and certainly less than the flow threshold of electrical failure, *i.e.*, less than 15–18 ml·100 g^{-1}·min^{-1}.[9]

The aim of this study was to examine the effect of lidocaine on cerebral metabolism. Lidocaine has a complex action on brain function and metabolism. As examined by Sakabe *et al.*,[10] small dosages of lidocaine suppress electrical function and reduce metabolism, while higher dosages (25–30 mg/kg) elicit seizures and cause metabolic stimulation. In analogy to its local anesthetic action, lidocaine may have effects on excitable membranes in the brain. As a local anesthetic lidocaine blocks excitation by blocking the sodium channels in the nerve membranes.[11] It was therefore assumed that the sodium permeability of membranes in the brain might be, at least partly, blocked by lidocaine. Such an action will not only abolish electrical function, but will also reduce ion leak fluxes. The study was designed to show both actions. When tested alone, lidocaine abolished synaptic transmission and inhibited metabolism. This is the function-metabolism coupled action of lidocaine. It resembles the effect of barbiturates. The other action was evidenced by the effect of lidocaine on the functionally arrested brain. In these brains, lidocaine further reduced metabolism by 15–20 per cent. We conclude that lidocaine, in analogy to its local anesthetic action, acts on the membranes in the central nervous system by blocking, at least partly, the sodium channels. This restricts ion leak fluxes and reduces associated ion pumping and related energy consumption. In the ischemic brain this membrane effect of lidocaine appears as a delayed potassium efflux.[1] In the nonischemic brain it appears as metabolic inhibition. A quantitative comparison of these effects provides further support for their interrelation. At 37°C, lidocaine reduced the rate of potassium efflux in the ischemic brain by 33 per cent, from 0.9 to 0.6 mM/min. These rates were calculated from the initial 10 mV change in potassium electrode potential (from 3.0 to 4.8 mM in extracellular potassium concentration.[1] Accordingly, the metabolic saving on the ion transport is of this order of magnitude, but when measured in relation to the total energy consumption, including all residual energy consuming processes and not just the ion transport, it appears as a smaller fraction of 15–20 per cent. Thus, the lidocaine effect on potassium efflux rate compares reasonably well to the effect on metabolism.

Can we be certain that the additional metabolic inhibition by lidocaine is a specific membrane effect and not merely a nonspecific toxic effect on the mitochondrion inhibiting oxidative metabolism? Such a toxic effect has been observed with large doses of halothane and is associated with very low oxygen and glucose consumption in combination with energy failure, *i.e*, very low levels of ATP and PCr, and lactic acid accumulation.[12] Metabolically, this condition resembles the condition of severe incomplete ischemia. A toxic effect of lidocaine on oxidative metabolism cannot be ruled out, but not to the extent of energy failure. This can be concluded since $(K^+)_s$ remains normal during the pentobarbital–lidocaine combination.[1] This indicates sufficient ATP production for ion pumping. Energy failure, ion pump failure, and efflux of potassium are associated phe-

nomenons, as demonstrated by studies of severe incomplete ischemia.[13]

Pentobarbital was without effect on metabolism in the brains with flat EEG. This observation confirms the view advanced by Michenfelder[5] that once synaptic transmission is abolished, barbiturates have no further effect on metabolism.

In accordance with studies of Lafferty *et al.*[14] and Nordström and Rehncrona[15] it was found that metabolic inhibition by barbiturate is additive to the metabolic inhibition by hypothermia suggesting different mechanisms of action. Lidocaine had a similar additive action. Even at 18°C the drug-induced metabolic inhibition could be ascribed to inhibition of synaptic activity. This degree of hypothermia is generally considered the borderline of EEG flattening, but consistent with other studies[16,7] we found that some EEG activity persists at this temperature. We may assume that the metabolic inhibition of barbiturates and of lidocaine related to EEG suppression approximates zero at progressive brain cooling and EEG flattening. The specific membrane effect of lidocaine could also be detected at 27°C and 18°C. Since this effect appears unrelated to synaptic activity, it may well persist at even lower brain temperatures.

Does the specific "membrane-stabilizing" effect of lidocaine as described in this and the preceding study[1] have relevance to the problem of protection of the ischemic brain? This remains controversial, but the effect of lidocaine is interesting: additional metabolic inhibition in spite of flat EEG, and a delay of the ischemic potassium efflux. These effects resemble those of hypothermia. Furthermore, the effects of lidocaine and hypothermia are additive. These results encourage experimental testing of lidocaine or related drugs as adjuvants to the hypothermic protection of the ischemic brain. As discussed in the preceding study[1] this task seems particularly relevant to the problem of brain protection during the often prolonged periods of complete circulatory arrest in open heart surgery in infancy.

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