Hypothermia and Barbiturates: Individual and Combined Effects on Canine Cerebral Oxygen Consumption

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Following establishment of total spinal anesthesia, the cerebral metabolic effects of progressive hypothermia (37, 28, 18, and 14° C) were studied initially in six awake dogs. The EEG became isoelectric at temperatures below 18° C. At 14° C, CMRO₂ was reduced to 7% of control. Thereafter, 40 mg/kg thiopental, iv, was given and the dogs were rewarmed while an isoelectric EEG was maintained by a continuous thiopental infusion. The CMRO₂ was then compared at the different temperatures with and without thiopental. The CMRO₂ was unaffected by the barbiturate at 14 and 18° C. At 28 and 37° C the CMRO₂ was significantly reduced by the barbiturate (at 37° C to 55% of the 37° C value without thiopental). The change in CMRO₂ with temperature in the absence of EEG activity (due to barbiturates) closely approximated an Arrhenius curve (relating log CMRO₂ to the reciprocal of absolute temperature). In the presence of EEG activity (no barbiturates) such a simple relationship was less apparent. The results support the following conclusions: barbiturates only affect CMRO₂ in the presence of neuronal electrical activity; the combined effect of hypothermia and barbiturates on CMRO₂ cannot be expressed as a simple additive relationship; and in the presence of electrical activity, the relationship between temperature and CMRO₂ cannot be defined by any simple mathematical function. (Key words: Anesthetics, intravenous; thiopental. Brain: metabolism; oxygen consumption. Hypothermia.)

Barbiturates in doses that render the EEG isoelectric approximately halve the cerebral metabolic rate for oxygen (CMRO₂) while additional doses have no further effects.¹ It therefore was suggested that a barbiturate-induced reduction in CMRO₂ is secondary only to reduced electrophysiologic function which is responsible for 50–60% of the total CMRO₂. In contrast, hypothermia would be expected to reduce the rates of all energy-requiring processes in the brain whether subserving electrophysiologic function or the maintenance of cellular integrity.¹ The validity of dividing the energy-consuming processes of the brain into these two components has been disputed.² Alternatively, it has been suggested that barbiturates and hypothermia should affect the metabolism of the brain in the same basic manner.²

In an effort to resolve this controversy, we examined the effect of hypothermia alone on canine CMRO₂ to a level sufficient to abolish EEG activity (18° C) and then compared the effects of further temperature reduction (to 14° C) with that of thiopental on CMRO₂. The dogs then were rewarmed from 14° C to 37° C while the EEG was kept isoelectric by a continuous thiopental infusion. This enabled a comparison of the effects of hypothermia on CMRO₂ in the presence (cooling) and absence (rewarming) of neuronal electrical activity over a large temperature range (37–14° C). This relationship of temperature and CMRO₂ has also been a matter of controversy. Some suggest that CMRO₂ changes as a rectilinear function of the temperature,²⁻⁴ others suggest a logarithmic-linear function,⁵,⁶ approaching an Arrhenius curve where ln CMRO₂ = −k· 1/T where k is a constant and T is the absolute temperature.²

Materials and Methods

Six unmedicated, fasting, adult mongrel dogs, weighing 11.1 ± 1.1 kg, (mean ± SE) were studied. Anesthesia was induced and maintained throughout the surgical procedure with 1% halothane in 60–70% nitrous oxide and oxygen. Succinylcholine, 2 mg/kg, was given intravenously to facilitate endotracheal intubation and thereafter was infused continuously (7.5 mg·kg⁻¹·h⁻¹) to maintain muscle paralysis. Ventilation was controlled with a Harvard® small animal ventilator. Cannulae were inserted in a femoral artery for pressure measurements (MAP) and blood sampling and in a femoral vein for drug and fluid administration. After heparinization (300–400 units/kg intravenously), the sagittal sinus was exposed, isolated, and cannulated as described previously for direct measurements of cerebral blood flow (CBF) from anterior, superior, and lateral portions of both hemispheres (equal to approximately 54% of the total brain weight).²⁸ Flow was recorded continuously with a flow-through electromagnetic flow probe (Carolina Medical Electronics, Inc., King, NC). Cerebral metabolic rate for oxygen (CMRo₂) was calculated as the product of CBF and arterial-sagittal sinus blood oxygen content differences. A four-lead bilateral

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EEG was recorded from electrodes glued to the skull. Body temperature was measured with an esophageal thermistor and brain temperature with a parietal epidural thermistor. Both had been calibrated previously with a mercury thermometer for the temperature range 37–14°C.

To enable partial or complete cardiopulmonary bypass, a small left-sided thoracotomy was performed and a cannula placed in the right atrium for venous drainage to the extracorporeal circuit. The blood circulated through an oxygenator (Temptrol Pediatric Q110®) and through a waterbath for temperature control and was returned via a large bore cannula in a femoral artery. The bypass machine was primed with blood (~1 liter) from a donor dog, and saline (~500 ml) and volume was added (300–600 ml saline) as needed.

Total spinal anesthesia was then established via a lumbar subarachnoid needle with 2 ml of 1% tetracaine HCl and the surgical wound in the head was infiltrated with 1% lidocaine. The eyes were taped closed and the ears plugged with cotton. Halothane was then discontinued and nitrogen was substituted for nitrous oxide for at least 20 min before control cerebral and systemic measurements were obtained at 37°C. Thereafter, the dogs were cooled by cardiopulmonary bypass to brain temperatures of 28, 18, and 14°C, requiring approximately 10 min for each temperature shift, and the measurements were performed at each temperature level during a 5- to 10-min period. Thiopental, 40 mg/kg, then was given intravenously, followed by a continuous infusion of 2 mg·kg⁻¹·min⁻¹. After 10 min, another set of measurements were taken; thereafter, the temperature was increased with new measurements repeated at 18, 28, and 37°C. Total time on cardiopulmonary bypass was less than 2.5 h.

Carbon dioxide was added to the gas mixture to keep $P_{\text{aCO}_2}$ close to 35 mmHg. temperature corrected. For samples taken at 37 and 28°C, blood oxygen contents were calculated from Oxyhemoglobin concentration (IL-282 CO-oximeter®) and $O_2$ tensions measured on IL electrodes, both measured at 37°C. This was not possible for samples taken at 18 and 14°C because of bubble formation and inaccurate measurements when the samples were warmed to 37°C. Blood oxygen contents at 18 and 14°C, therefore, were determined in duplicate by Van Slyke's method.⁹ Previous unpublished results showed good correlation with no systematic difference in oxygen content for the two different methods at normal temperatures.

Measurements taken at each temperature before and after barbiturate infusion were compared by Wilcoxon's Rank test for paired samples; $P < 0.05$ was regarded as significant. For comparing CMRO₂ at 18°C with barbiturate, 18°C without barbiturates and 14°C without barbiturates, a Friedman test was performed.¹⁰ CMRO₂ vs. temperature was tested for a rectilinear and a log-linear relationship both with and without barbiturates by an analysis of variance. If $P < 0.05$, a linear regression line was constructed.

**Results**

The reduction in temperature from 37°C to 14°C was accompanied by a progressive reduction in CMRO₂ (table 1, figs. 1, 2, and 3). Thus, at 14°C the CMRO₂ was decreased to 7% of the control value, while CBF was decreased approximately 50% in this model in which MABP was maintained above 70 mmHg and close to constant (table 1) by cardiopulmonary bypass. By analysis of variance, there was no rectilinear (fig. 1) or log-linear (fig. 2) relationship between CMRO₂ and temperature or the reciprocal of the absolute temperature during cooling. The EEG became isoelectric at approximately 18–17°C in all dogs and stayed isoelectric throughout the rest of the experiment (fig. 4).

During rewarming one dog experienced a severe transfusion reaction to blood from a donor dog and the

| Table 1. Brain temperature, CBF, CMRO₂, MABP, and Temperature-corrected Blood Gases. Values are Means ± SE. One Animal Died during Rewarming and Is Thus Only Reported during the First Four Periods (Cooling). First Four Periods without Barbiturates, Last Four Periods with Barbiturates |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Brain temperature °C | 37.0 ± 0.1 | 28.1 ± 0.2 | 18.0 ± 0.0 | 13.9 ± 0.1 | 13.9 ± 0.2 | 18.2 ± 0.2 | 28.0 ± 0.0 | 36.8 ± 0.1 |
| CBF (ml·100 g⁻¹·min⁻¹) | 6 | 6 | 6 | 6 | 5 | 5 | 5 | 5 |
| CMRO₂ (ml·100 g⁻¹·min⁻¹) | 56 ± 7 | 45 ± 5 | 25 ± 5 | 28 ± 5 | 30 ± 8 | 34 ± 8 | 30 ± 5* | 29 ± 2* |
| MABP (mmHg) | 93 ± 6 | 92 ± 4 | 86 ± 3 | 91 ± 8 | 104 ± 5 | 95 ± 10 | 92 ± 8 | 81 ± 5 |
| $P_{\text{aCO}_2}$ (mmHg) | 150 ± 14 | 184 ± 54 | 122 ± 6 | 117 ± 3 | 112 ± 8† | 125 ± 7 | 118 ± 13† | 168 ± 21 |
| pH | 7.33 ± 0.03 | 7.44 ± 0.03 | 7.35 ± 0.04 | 7.29 ± 0.02 | 7.27 ± 0.02 | 7.28 ± 0.03 | 7.34 ± 0.02 | 7.34 ± 0.03 |
| BB̂ (mEq/l) | 42 ± 2 | 41 ± 1 | 39 ± 1 | 38 ± 1 | 37 ± 1 | 38 ± 1 | 39 ± 1 | 39 ± 1 |

* Significantly different from same temperature without barbiturates (CBF and CMRO₂).
† Significantly different from control, 37°C (MABP and blood gases).
‡ BB = buffer base.
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Fig. 1. CMRO₂ during cooling with spinal anesthesia, and rewarming during deep barbiturate anesthesia. CMRO₂ in per cent of control vs. temperature in °C. Asterisk indicates values significantly different from the CMRO₂ value at the same temperature without thiopental (P < 0.05).

The experiment could not be completed. Data for the rewarming period are thus from five dogs only. The infusion of thiopental had no significant effect upon CMRO₂ or CBF at 14°C, while rewarming during maintained deep barbiturate anesthesia caused a gradual increase in CMRO₂ to approximately 55% of the awake control value at 37°C. With rewarming, in the absence of electrophysiologic function, the relationship of CMRO₂ to temperature closely approximated an Arrhenius curve wherein the log CMRO₂ is near linear with respect to the reciprocal of the absolute temperature (fig. 2). By analysis of variance P < 0.05 for such a relationship, and the equation for the linear regression line was ln O₂ = 31.24 - 8422/1/T with an r of 0.99. There was not a significant rectilinear relationship between CMRO₂ and temperature during rewarming.

By comparing values at each temperature before and after thiopental injection, CMRO₂ was found to be reduced significantly by the barbiturate at 37°C and 28°C, but not at 18°C and 14°C. CMRO₂ at 14°C without barbiturate was significantly lower than at 18°C with and without barbiturate.

Fig. 2. Same data as in figure 1, but plotted as log CMRO₂ (in per cent of control) vs. the reciprocal of the absolute temperature. During rewarming in the absence of EEG activity, the relationship of CMRO₂ to temperature closely approximated a log-linear one. During cooling and with EEG activity, the relationship appears to be more complex.

Fig. 3. CMRO₂ at different temperatures during spinal anesthesia with and without barbiturates. Asterisk indicates significant difference with and without barbiturate at the same temperature.
CMRO₂ by similar mechanisms. He considered it "adventurous" to separate metabolism into one component suberving function and another for preserving cellular integrity. Nevertheless, we must conclude that the effects of barbiturates and hypothermia are not the same. This does not mean necessarily that two different metabolic pathways are affected. We suggest that barbiturates primarily decrease excitability (presumably by a membrane effect) and impulse traffic, which in turn decreases the need for ATP production. Hypothermia also decreases the impulse traffic and with the same overall metabolic effects, but in addition, a decrease in temperature can reduce energy demands and production by slowing other rate-limiting reactions. There are obviously more cell functions requiring ATP than those bound to impulse traffic. Accordingly, in our study CMRO₂ was significantly more decreased when the EEG was rendered isoelectric by hypothermia (to about 10% of control), than when thiopental (at 37°C) was used to induce an isoelectric EEG (to about 50% of control). Furthermore, in the absence of electrical activity, CMRO₂ was decreased further when the temperature was decreased further, whereas additional doses of barbiturates had no effect.

If our hypothesis is correct, the effects of hypothermia and barbiturates on CMRO₂ cannot be simply additive as suggested by Astrup et al.,¹¹ Lafferty et al.,¹² and Hägerdal et al.¹³ for temperatures down to 27°C. This was supported by our experimental data. A decrease in temperature from 37 to 28°C without barbiturates caused a 55% decrease in CMRO₂, while large doses of thiopental at 37°C caused a 45% decrease; both values agree with previous reports.¹,² If additive, the combination should produce a CMRO₂ of near zero, while the actual CMRO₂ at 28°C with thiopental was 28% of control.

Astrup et al.¹¹ reported in dogs a further decrease in CMRO₂ when barbiturates were given at 18°C. Only three dogs were studied at this temperature and all were reported to have maintained an active EEG. In the absence of EEG activity, induced by hypothermia combined with lidocaine, barbiturates had no effect on CMRO₂ in their study. Thus, although the EEG differences at 18°C between our study and theirs are unexplained, their results seem to agree with our hypothesis. Even so, there may have been a methodologic problem in their study. Blood oxygen contents were calculated from measured oxygen tensions and hemoglobin saturations using a Radiometer OSM® O₂ analyzer maintained at 37°C. With samples taken at 18°C this will usually not give accurate measurements due to bubble formation when the sample is warmed up to the instrument's working temperature. To our knowledge, Van

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Discussion

Two aspects of cerebral metabolism were studied. First, the CMRO₂ effects of barbiturates at different temperatures were determined, and second, the temperature dependence of CMRO₂, with and without electrophysiologic function (as reflected by the EEG), was examined.

The results support the hypothesis that barbiturates can alter CMRO₂ only when brain function can be affected. At 37 and 28°C the EEG was normally active and when suppressed to isoelectricity by thiopental, the CMRO₂ was decreased significantly as has been reported previously.¹,² At 18 and 14°C the EEG manifested little or no activity without thiopental, and administration of the drug had no effect upon CMRO₂. Not so with hypothermia which might be expected to decrease CMRO₂ by affecting rate-limiting reactions under all circumstances, regardless of the functional status. Thus, while barbiturates failed to affect CMRO₂ at 18°C, a further decrease in temperature did cause a significant further decrease in CMRO₂.

These observations are contrary to the suggestion of Siesjö² that barbiturates and hypothermia decrease
Slyke's method is the only one that can yield accurate results at these low temperatures.

Lafferty et al. calculated the effects of barbiturates and moderate hypothermia (30°C) on CMRO₂, claiming an additive effect of the two. Their results are difficult to interpret, however, because the control situation was with barbiturate anesthesia. Thus, while Lafferty et al. found a further reduction in CMRO₂ when the two were combined, it is not possible from their data to conclude that the effects are simply additive.

The second question addressed in the present study was the temperature dependence of CMRO₂. The results suggest that this relationship is different with and without an isoelectric EEG induced by barbiturate anesthesia. With brain electrophysiologic function abolished, there appears to be a near linear relationship between log CMRO₂ and the reciprocal of the absolute temperature (1/T), thus approaching an Arrhenius curve (fig. 2). This is in agreement with studies by Bering and Nordström and Rehncrona, and is supportive of the hypothesis that CMRO₂ changes with temperature as a function of the rate constants of rate limiting reactions. Hägerdal et al. reject this and suggest instead that CMRO₂ is simply determined by the energy requirements of the tissue. While the latter may be true, since there is no evidence of tissue hypoxia during extreme hypothermia, this does not preclude the first suggestion. It seems likely, at least in the absence of cerebral electrophysiologic function, that the cerebral energy requirements are determined by certain rate-limiting reactions. If the rate constants of most chemical reactions follow an Arrhenius curve, the same reactions will continue to be rate-limiting at all temperatures and, thus, CMRO₂ should follow an Arrhenius curve.

For an actively functioning brain the situation may be very different. The extremely complex nature of integrated electrical function must be dependent upon many factors, and it seems unlikely that the energy requirements would be controlled primarily by the rates of certain chemical reactions. It is therefore not surprising that we failed to observe a simple CMRO₂-temperature relationship in the presence of neuronal electrical activity which approximated either a log-linear relationship as suggested by Michenfelder and Theye or simply a rectilinear one. The present results indicate something between a rectilinear and log-linear function.

The reasons for these discrepancies in results are not clear. It is perhaps naive to attempt to force any simple mathematical function upon the relationship between the complex function of the brain (and thereby CMRO₂) and temperature. For example, if the linear curve presented by Hägerdal et al. for 37°C to 22°C is extended, CMRO₂ becomes zero at 17°C which is obviously incorrect (no such extrapolation of course was of course suggested by the authors). If their results are correct, the linearity must stop abruptly at 22°C. As only two temperatures above 22°C were examined in the present study, our results do not necessarily exclude such a rectilinear relationship between 37°C and 22°C without barbiturates.

A variable effect of the background anesthetics used by Hägerdal et al. (70% N₂O), Michenfelder and Theye (0.8–0.9% halothane), and Astrup et al. (1–1.5% halothane) cannot be excluded. The solubility of the anesthetic gases increases during hypothermia and if anesthetic depth is a function of anesthetic concentration, anesthetic depth will be greater at the same partial pressure. This might be reflected in the decrease in MAC produced by hypothermia, although it is difficult to separate the effects of hypothermia itself on brain function and CMRO₂ and the effects of hypothermia on the pharmacokinetics of inhalational anesthetics in such studies of MAC. Similarly, although 70% N₂O at 37°C has no effect upon CMRO₂ in rats, an effect of higher concentrations (at lower temperatures) cannot be excluded. To avoid the effect of temperature on anesthetic solubility and thus possibly on anesthetic depth, the present study was performed in the initial phase without the use of general anesthetics, using instead local anesthetic infiltration, sound and sight deprivation, and total spinal anesthesia in an attempt to avoid possible stress-induced changes in CMRO₂. A pronounced increase in CMRO₂ during stress has been reported by Carlsson et al. It appeared to be catecholamine-induced and was completely prevented by adrenalectomy. The sympathectomy obtained during total spinal anesthesia should have the same effect, and the present control values for CMRO₂ at 37°C are well in agreement with previously published values obtained during N₂O anesthesia which is known to have little or no effects upon CMRO₂. While other effects of the spinal anesthesia cannot be excluded, it seems unlikely that these should affect the effects of hypothermia on the brain.

We conclude: 1) Thiopental can affect cerebral metabolism only when it can alter cerebral electrical function. At temperatures below 18°C when electrical function is absent, barbiturates have no effects whereas progressive hypothermia will continue to affect CMRO₂. 2) The CMRO₂ effects of hypothermia and barbiturates are not simply additive but rather are infra-additive depending on the status of cerebral function. 3) In brain where normal electrophysiologic function is abolished by barbiturates the relationship of CMRO₂ to temper-
nature approximates an Arrhenius curve. No such simple relationship can be derived for brain in which electrophysiologic function is present.

References

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