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Body and brain temperature coupling: the critical role of cerebral blood flow

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Abstract

Direct measurements of deep-brain and body-core temperature were performed on rats to determine the influence of cerebral blood flow (CBF) on brain temperature regulation under static and dynamic conditions. Static changes of CBF were achieved using different anesthetics (chloral hydrate, CH; α -chloralose, α CS; and isoflurane, IF) with α CS causing larger decreases in CBF than CH and IF; dynamic changes were achieved by inducing transient hypercapnia (5% CO₂ in 40% O₂ and 55% N₂). Initial deep-brain/body-core temperature differentials were anesthetic-type dependent with the largest differential observed with rats under α CS anesthesia (ca. 2°C). Hypercapnia induction raised rat brain temperature under all three anesthesia regimes, but by different anesthetic-dependent amounts correlated with the initial differentials— α CS anesthesia resulted in the largest brain temperature increase ($0.32 \pm 0.08^\circ\text{C}$), while CH and IF anesthesia lead to smaller increases (0.12 ± 0.03 and $0.16 \pm 0.05^\circ\text{C}$, respectively). The characteristic temperature transition time for the hypercapnia-induced temperature increase was 2–3 min under CH and IF anesthesia and ~4 min under α CS anesthesia. We conclude that both, the deep-brain/body-core temperature differential and the characteristic temperature transition time correlate with CBF: a lower CBF promotes higher deep-brain/body-core temperature differentials and, upon hypercapnia challenge, longer characteristic transition times to increased temperatures.

Keywords

Brain temperature; Temperature regulation; Cerebral blood flow (CBF); Brain metabolism; Hypercapnia; Anesthesia

Introduction

Basic mechanisms responsible for temperature regulation in living animals are well understood. Since no “heat storage” is known to exist in the brain, temperature regulation in the brain can only rely on communication between brain and body as metabolites are delivered

and heat is exchanged through blood flow. In humans, on average 3.75 μmol of oxygen is delivered per 1 g of brain tissue every minute (Siesjo 1978). Given that the oxygen extraction fraction (OEF) under normal physiological conditions is about 40% (Raichle et al. 2001), and most of the oxygen is utilized through chemical reaction with glucose, on average 0.66 J of energy is released every minute per gram of brain tissue. If not removed, this heat generation would lead to 0.16°C/min increase in brain temperature (Yablonskiy et al. 2000). The major heat-removal mechanism is blood flow—blood vessels form a dense network that “collects” excessive heat and delivers it to the body surface. The balance between heat generation and heat removal by blood flow defines brain temperature in humans and other large animals.

One might imagine that if blood flow is reduced, which would lead to less efficient heat removal, the brain temperature would increase. Indeed, this might occur as a transient effect; however, since reduced blood flow would also lead to diminished oxygen delivery, heat production would also be reduced. Even increasing OEF would not affect brain temperature substantially. Indeed, a heat balance equation derived previously (Yablonskiy et al. 2000) predicts that under steady conditions brain temperature T_b can only slightly exceed arterial blood temperature T_a (defined largely by body temperature) by the quantity T_m , which depends on the OEF:

$$T_b = T_a + T_m; \quad T_m = T_m^* \cdot \text{OEF} \quad (1)$$

In this equation T_m^* is the maximum metabolic temperature shift that can be achieved if all oxygen delivered to the brain is consumed ($T_m^* = 0.9^\circ\text{C}$ for typical hematocrit level of 40%). We emphasize that this theoretical conclusion, derived for a brain isolated from the external environment, does not depend directly on the rate of blood flow, although T_a might. Even if oxygen extraction fraction would increase to 100% (hypothetical case), the brain/body temperature differential could not increase more than 0.9°C. Under normal physiological conditions (OEF = 0.4) brain temperature is expected to exceed body temperature only by $T_m = 0.36^\circ\text{C}$. With fixed OEF this differential does not depend on the temperature of arterial blood, however, decreasing blood temperature could change the rate of metabolic reactions leading to decreased OEF (this effect will be addressed in “Discussion”). Hence Eq. 1 predicts that under normal conditions brain temperature is mostly defined by the body temperature (temperature of arterial blood) and is practically independent of metabolic processes in the brain itself. While no systematic studies have been undertaken to test these theoretical predictions, previous theoretical and experimental results corroborate these conclusions. A computer model directed toward selective human brain cooling predicted that the parenchyma brain temperatures should be 0.2–0.3°C above arterial temperatures regardless of surface conditions (Nelson and Nunneley 1998). Studies on human brain temperature during prolonged exercise confirmed that the average brain temperature was at least 0.2°C higher than that of the body core (Nybo 2007; Nybo and Secher 2004). It was also reported that brain ventricle temperature was $0.40 \pm 0.07^\circ\text{C}$ higher than the rectal temperature in neurosurgical patients in various level of consciousness when general anesthesia was not used (Mariak 2002; Mellergard 1995). Corresponding animal studies give findings similar to these. Brain temperature greater than that of either arterial blood or rectal temperature by 0.3–0.4°C was reported in immobilized monkeys (Hayward and Baker 1968). Brain temperatures exceeding body temperature by 0.2–0.5°C were found in horses (Mitchell et al. 2006) and pronghorn antelopes (Lust et al. 2007) exposed to heat. A higher brain temperature than that of carotid blood or of the body core in awake cats was observed (McElligott and Melzack 1967). One group reported that the brain temperature in freely moving rats is about 0.2–0.3°C warmer than that of the incoming arterial blood (Kiyatkin et al. 2002). Even un-anesthetized mice have been found to have 0.4°C higher brain temperature than rectal (Sedunova 1992).

On the other hand, studies of small animals under anesthesia reported an opposite situation to that predicted by Eq. 1. A positive body-core/brain temperature differential (brain temperature less than core temperature) of about 1.8°C was found between rectal and brain temperature in a chloral hydrate anesthetized rat model when the temperature probe was positioned in the cortical area (LaManna et al. 1988). This finding is in agreement with reports from our laboratory where a temperature differential of about 2°C between body-core and brain surface was found in chloral hydrate (CH) and isoflurane (IF) anesthetized rats, while a larger temperature differential of about 4°C was found under α -chloralose (α CS) anesthesia (Zhu et al. 2004). Also a body-core/brain temperature differential as large as 4°C was reported in pentobarbital anesthetized cats (Erickson and Lanier 2003).

Resolution of this apparent contradiction with the predictions of Eq. 1 is to be found in modest dimensions of small animal brains. Here the assumption that deep lying brain regions are isolated from the external environment is not valid and heat exchange with the environment is important. As was demonstrated previously (Sukstanskii and Yablonskiy 2004), blood flow acts as a “shield” against brain temperature changes due to heat exchange with the environment. The effectiveness of this temperature shield is quantified by the characteristic temperature shielding length, Δ , the length over which the ingress of environmental temperature is attenuated by roughly one e-folding. Brain regions deeper than $\sim 3\Delta$ from the brain surface can be considered isolated from the environment. Brain regions less than $\sim 3\Delta$ deep can be considered superficial regions and are affected by the temperature of the external environment. The characteristic temperature shielding length

$$\Delta = \left(\frac{K}{\rho \rho_b c_b \text{CBF}} \right)^{1/2} \quad (2)$$

depends on the cerebral blood flow (CBF). Here, K is the tissue thermal conductivity, c_b is the specific heat of blood, ρ and ρ_b are the densities of tissue and blood, respectively. In human brain, CBF is about 0.6 ml/(g min), leading to $\Delta \sim 2$ mm. Hence only very small superficial fraction of human brain (as well as of the brain of other large animals) defined by Eq. 2 can have temperature lower than the deep brain temperature. However, in small animals (especially when their CBF is suppressed by anesthesia) Δ can be on the order of brain dimensions, which will lead to inhomogeneous temperature distribution throughout the whole brain. Detailed measurements of temperature distribution and blood flow in anesthetized rats (Zhu et al. 2006) quantitatively confirmed Eq. 2. Blood flow in anesthetized animals can become especially low, leading to a rather large characteristic temperature shielding length, reversing the body/brain temperature differential and leading to temperatures even in the deep brain to be lower than the body temperature. This effect is solely due to heat loss to the external environment and, of course, can be present only if ambient temperature is not artificially elevated to the animal's temperature. This issue can have important ramifications as temperature substantially affects the rate of chemical reactions, hence, brain metabolism and other physiological functions. We should also mention that the above considerations can be altered in animals with the carotid rete (Daniel et al. 1953) where blood entering brain is “precooled” through this special mechanism. The contribution of carotid rete to brain temperature variability was demonstrated in the recent publication (Maloney et al. 2007).

Due to known effects of different anesthetics on blood flow regulation, steady state brain temperature and body-core temperature can be investigated among animals under different anesthesia regimes (also referred to as static or baseline condition in this paper). To disturb the heat balance in the brain, a change of CBF can be realized by inducing hypercapnia (higher blood CO₂ partial pressure), which is known to generate a global increase of blood flow in the

mammalian brain with small changes in the cerebral metabolic rate of oxygen utilization (CMRO₂).

In this study, three distinctive anesthesia regimes (chloral hydrate, CH; α -chloralose, α CS; and isoflurane, IF) with different effects on blood flow were chosen to investigate deep-brain and body-core temperatures in the static condition of rats. Thus, the relationship between the body and brain temperatures as well as dependency upon CBF are determined. The brain temperature dependence on dynamic change of CBF was determined through measurements of brain temperature under transient (15 min) hypercapnia (5% CO₂ in 40% O₂ and 55% N₂) after establishing baseline conditions under all three anesthetics. Also, the brain/body temperature differential was determined over a broad range of body temperatures.

Materials and methods

Animal preparation

All experimental protocols were approved by the Washington University Institutional Animal Care and Use Committee. Male Sprague Dawley rats ($n = 18$) weighing 270–360 g each were divided into three groups based on the major anesthetics used: CH (group #1, $n = 6$), α CS (group #2, $n = 6$) and IF (group #3, $n = 6$). After initial induction of anesthesia with a ketamine–xylazine mixture (55.5 mg/kg ketamine plus 11.1 mg/kg xylazine, i.p.), the femoral arteries were catheterized with PE50 tubing for mean arterial blood pressure (MABP) measurement as well as blood sampling. Rats were then endotracheal intubated with a 16 gauge Teflon catheter and artificially ventilated with oxygen/nitrogen mixture (FiO₂ = 40%, N₂ = 60%) at a tidal volume of 7 ml/kg and respiration frequency of 75 min⁻¹. Breathing gas was set at 1 l/min flow rate and was passed through a heat exchanger (equilibrated with room temperature water) before reaching the ventilator to ensure constant inspired gas temperature. Rats were secured in a stereotaxic headframe (David Kopf, Instruments, Tujunga, CA) with body temperature maintained at $37 \pm 0.5^\circ\text{C}$ by water circulating through tubes looped underneath the subject. The temperature of the circulating water was regulated and kept stable by a thermostated water bath (Model DC10-B3; Thermo Haake, Karlsruhe, Germany). A thermocouple wire was inserted 7 cm deep rectally to measure body-core temperature (Miyazawa and Hossmann 1992).

Roughly 30 min after the initial dose of ketamine–xylazine, group #1 rats ($n = 6$) were anesthetized with CH (400 mg/kg, i.p.); group #2 rats ($n = 6$), with α CS (40 mg/kg, i.p.); group #3 rats ($n = 6$), with 2.0% IF in 1 l/min breathing gas. A 2 cm incision was made along the inter-aural line on the top of the subject's head. Minimal retraction of the scalp exposed a small area of skull. A 1 mm diameter burr hole was drilled 2–3 mm anterior to and lateral from the lambda. A super-fine polyvinyl insulated thermocouple probe (36 gauge, T-type; Physitemp Instruments, Inc., Clifton, NJ) was implanted at 6 mm deep into the brain (measured from the surface of the brain). The temperature probes (both brain and body) were fixed to the stereotaxic headframe support and connected to a data acquisition module (Model OMB-DAQ-55; OMEGA, Stamford, CT). Temperatures were monitored and recorded via data acquisition software (Personal DaqView; IOTech, Inc., Cleveland, OH) with a 0.25 s⁻¹ sampling rate. Following surgery, the incision was closed to its pre-surgical position. A layer of 5 mm thick cotton fabric was put on the top and around the incision area to minimize heat loss due to fur skull-patch removal during the surgery.

Throughout all protocols, heart rate and O₂ saturation values were monitored noninvasively with a veterinary pulse oximeter (Model 8500V; Nonin Medical, Inc., Plymouth, MN) attached to each subject's legs. All temperature probes were calibrated before and after each experiment by a factory-calibrated precision mercury thermometer (Fisher Scientific, Pittsburgh, PA) to be within $\pm 0.05^\circ\text{C}$ absolute accuracy.

Induction of hypercapnia

Transient hypercapnia was initiated roughly 50 min after administration of the primary anesthesia regime (CH, α CS, or IF), during which time both rectal and brain temperature were confirmed to have stabilized. The transient hypercapnia condition was imposed by switching the breathing gas to an oxygen/nitrogen mixture (40% O₂, 55% N₂) containing 5% CO₂ at the same flow rate (1 l/min) for 15 min. Blood samples (0.1 ml) were retrieved from the femoral artery of three rats in each group for blood gas analysis (i-STAT PCA; HESKA, Fort Collins, CO) immediately before and at the end of the hypercapnia period.

Induction of hypothermia

Three rats were anesthetized with 1.2% isoflurane and their body core temperature slowly lowered from 38°C, at a rate of ~3°C/h, by cold water circulating through tubes looped underneath the subject. Temperatures were recorded from both deep brain and body-core.

Statistics

Student's *t*-test was used to compare difference between groups. A *P* value of 0.05 was accepted as statistically significant. Unless otherwise noted, measurements are reported as mean $\pm$ standard deviation (SD).

Results

Blood gases as well as MABP results are reported in Table 1. MABP was 120–140 mmHg under ketamine/xylazine pre-anesthesia (data not shown) and dropped to 70–90 mmHg under CH, α CS, or IF anesthesia. Heart rate was typically in the range of 200–250 beats/min. Blood oxygen saturation values were always above 95% throughout the procedures.

Consistent with our previous study (Zhu et al. 2004), rats under different anesthesia regimes had different deep-brain/body-core temperature differentials, with brain temperature consistently lower than body-core. Initial pre-hypercapnia brain/body-core temperature differentials were most significant under α CS anesthesia. Baseline brain/body-core temperature differentials before onset of hypercapnia challenges were found to be: ($-2.09 \pm 0.34^\circ\text{C}$) for α CS, ($-1.08 \pm 0.20^\circ\text{C}$) for CH and ($-1.43 \pm 0.18^\circ\text{C}$) for IF. Statistically significant temperature differences were found when comparing α CS versus CH, and α CS versus IF. The corresponding temperature differences compared between CH and IF were not statistically significant.

A representative time course of the brain/body-core temperature differential during a transient hypercapnia event is shown in Fig. 1. Following initiation of hypercapnia, deep brain temperature gradually increases ~0.3°C (rectal temperature is constant). Upon switching back to baseline breathing gas (absent CO₂) brain temperature starts decreasing immediately tending to pre-hypercapnia levels. Time course data acquired during hypercapnia were analyzed by modeling brain temperature dynamics as a simple exponential:

$$T(t) = T(0) + \Delta T(1 - \exp(-t/t_c)) \quad (3)$$

In this equation $T(t)$ is the brain temperature at time t (min), $T(0)$ is initial brain temperature at the start of the hypercapnia event, ΔT is the maximum change in the brain temperature, and t_c is the characteristic transition time (inverse of the rate constant) governing the time it takes for the brain temperature to reach a new equilibrium value. A similar equation was used for the post-hypercapnia period. One example of the modeling result is presented in Fig. 2.

Figure 3 describes ΔT and t_c under each anesthesia regime. Rats under α CS anesthesia showed the largest ΔT , as well as the longest t_c (both during hypercapnia and after hypercapnia) compared to the rats under the other two anesthesia regimes. The differences in observed ΔT under CH and IF anesthesia are not statistically significant. The ΔT observed under CH and IF anesthesia is ca. half that seen under α CS anesthesia. Although not reaching a statistically significant level, the characteristic transition time, t_c , is consistently longer during post-hypercapnia compared to that during hypercapnia challenge.

The coupling between body and brain temperatures during hypothermia is shown in Fig. 4.

Discussion

Tight coupling between body-core and deep-brain temperatures

This study focused on the temperature differential between body-core and deep-brain. In a steady-state condition these two parameters are coupled tightly to each other. Indeed, even when body-core temperature changes, the temperature difference between body and brain is kept constant. Thus, reporting the temperature differential between body-core and deep-brain provides a reliable direct comparison between groups. We verified the steady-state coupling between body and brain temperatures by creating a slowly evolving hypothermic condition (Fig. 4). The almost linear correlation between brain and body temperature indicates the tightly coupled relationship of the two temperatures in the (pseudo) steady state. Note also interesting clinical correlates to this research when therapeutic brain cooling for brain injury is achieved via arterial blood (Neimark et al. 2008,2007).

Considering the dynamics of rat brain temperature during transient hypercapnia, rats under α CS anesthesia showed the largest brain/body-core temperature differential, the greatest hypercapnia-induced brain temperature change, ΔT , and the longest hypercapnia-induced brain temperature transition time, t_c , as compared to rats under the other two anesthetics examined, CH and IF. These results can be understood when considering the role of blood flow and metabolism in brain temperature regulation (Sukstanskii and Yablonskiy 2004; Sukstanskii and Yablonskiy 2006, 2000; Zhu et al. 2006).

Blood flow as a critical regulator of brain temperature

First, blood flow is one of two key factors regulating brain temperature: both the dense blood vessel network perfusing the brain and the incoming blood temperature affect brain temperature directly and are responsible for maintaining brain temperature within the physiological range, Eq. 1. The second key factor in the case of small animals is heat exchange with the environment, which generally decreases brain temperature. This effect is important in small animals (Eq. 2) because of their high brain-surface-to-volume ratio. Hence, a decrease in blood flow results in impaired heat transfer between body and brain and decreased temperature shielding effect of blood flow (Eq. 2). Thus the difference between brain/body-core temperature differential found among different anesthetics can be explained by different anesthesia-dependent influences of blood flow.

Isoflurane is reported to slightly increase CBF after administration due to its vasodilatation effect (Young et al. 1991). Hence, we expect only small changes in blood flow under influence of IF. Unfortunately, there are no detailed published reports regarding CBF and cerebral metabolic changes upon CH anesthesia. On the other hand, there is substantial evidence that α CS significantly suppresses blood flow. It is reported that α CS causes a significant decrease in blood flow in rats at a dosage of 50–80 mg/kg (Nakao et al. 2001). It also has been found that resting CBF decreases by $47 \pm 12\%$ when changing from halothane- N_2O to α CS anesthesia (Lindauer et al. 1993). Hence, with α CS anesthesia we can expect an additional decrease in

blood flow and consequently in brain temperature (as indeed observed in our study) as compared to IF anesthesia. To demonstrate this effect directly, an experiment was designed in which brain and rectal temperatures were continuously monitored while changing anesthetics from IF to α CS in a given subject. As expected, the predicted additional decrease in blood flow upon switching from IF to α CS anesthesia led to a dramatic drop in brain temperature (decoupling of brain and body core temperature) (Fig. 5).

Second, the characteristic temperature transition time, which defines the temperature dynamic upon switching from a baseline anesthetized state to one with hypercapnia-induced increased CBF, is predicted to be inversely proportional to the CBF (Yablonskiy et al. 2000, Eq. 6). In this study, the characteristic temperature transition time, t_c , was two fold larger under α CS anesthesia as compared to CH and IF during both hypercapnia challenge and post-hypercapnia periods. This finding is also in accordance with the substantial CBF decrease in α CS anesthetized rats (Nakao et al. 2001). In addition, independent of anesthetics used, the post-hypercapnia time constant was consistently found to be longer than during hypercapnia induction, which is also in agreement with an inverse proportionality relationship with CBF (larger CBF during hypercapnia, shorter time constant). Indeed, when CBF values ($1/t_c$) estimated from dynamic brain temperature changes observed during and after hypercapnia are plotted versus brain/body-core temperature differentials under all anesthesia regimes, a strong non-linear correlation can be found (Fig. 6). A comparison of the data with a theoretical prediction (Eq. 2 in Zhu et al. 2006) in the same graph demonstrates that the heat transfer coefficient h in the current experiments is in the range of 0.001–0.005 W/(cm² °C)—a reasonable estimate for a surgically intervened brain.

Metabolic effect of hypercapnia induced brain temperature changes

The vessel dilation effect of hypercapnia is believed to increase global blood flow in animal and human studies with presumably little influence on CMRO₂ (Artru and Michenfelder 1980; Berntman et al. 1979; Greeley et al. 1993; Horvath et al. 1994; Kassell et al. 1981; Kety and Schmidt 1947; Yang and Krasney 1995). While some published studies suggest that hypercapnia might change brain metabolism, the data are not consistent on this point. For example, no changes in oxygen consumption during hypercapnia were reported in normal young men (Kety and Schmidt 1947); decreases in oxygen utilization were detected in anesthetized rhesus monkey (Kliefoth et al. 1979); and increases in the metabolism were registered in awake sheep (Yang and Krasney 1995). One study of rats (Horvath et al. 1994) reported an increase in CMRO₂ of more than 50% following hypercapnia, and another reported that severe hypercapnia increased CMRO₂ by 25% (Berntman et al. 1979). Thus, the exact effect of hypercapnia on CMRO₂ remains uncertain.

Inconsistent findings regarding the relationship between CMRO₂ and hypercapnia may be partially attributable to the changes in brain temperature reported herein. Because temperature substantially affects the rate of chemical reactions, hypercapnia-induced increases in brain temperature may contribute to changes in brain metabolic rates. Different findings observed under various experimental conditions may, thus, be explained (at least partially) by differences in the brain/body-core temperature differentials and rates of CBF. An average Q_{10} coefficient (the temperature coefficient that defines the change of a chemical reaction rate as a consequence of increasing the temperature by 10°C) is on the order of 2.3 in the physiologic temperature range (Michenfelder and Milde 1991; Swan 1974). Therefore, changes in brain temperature can cause changes in brain metabolic rates on the order of 8% per degree centigrade. However, as brain temperature monitoring was not performed in the above-cited reports, predictions cannot be made regarding the possible contribution of temperature changes occurring during hypercapnia to the changes, or lack thereof, in CMRO₂. Nevertheless, it is possible to predict the likely possible magnitude of such effects in different species. The brain/body-core

temperature differential in normal awake humans and large animals is expected to be positive (brain warmer than body core, CBF serves as coolant) and rather small, $\sim 0.3^{\circ}\text{C}$ (Yablonskiy et al. 2000). In this situation hypercapnia is expected to reduce this differential even further. Indeed, using chronically implanted probes, Baker and Hayward (Baker and Hayward 1968) showed that in awake sheep hypercapnia reduces positive brain/body-core temperature differential and that hypocapnia increases this difference. Hence we can expect decreases in CMRO_2 under hypercapnia. On the contrary, in small animals, like rat as reported herein, the brain/body-core temperature differential is negative and its absolute value may be quite large depending on experimental circumstances. In this situation, hypercapnia-induced increase in blood flow will increase brain temperature leading to increased CMRO_2 . These effects would contribute to previous findings from other laboratories regarding hypercapnia-induced CMRO_2 changes (Berntman et al. 1979; Horvath et al. 1994). However, we are not aware of any measurements or estimates of brain/body-core temperature differentials in these studies.

The hypercapnia-induced changes in brain temperature reported herein should also be taken into account in the so-called calibrated fMRI experiments (Davis et al. 1998; Hoge et al. 1999) proposed for the evaluation of functionally induced changes in CMRO_2 . In this scheme, the MR functional signal is calibrated to a baseline CMRO_2 with transient hypercapnia, based on the assumption that hypercapnia leads to an increase in CBF without a significant corresponding increase in CMRO_2 (Davis et al. 1998; Kim et al. 1999). While, as noted about, this maybe a plausible assumption in awake humans, it may well be violated in animal experiments, especially conducted under anesthesia. In any case, temperature effects should be taken into consideration if accurate measurements are required since the BOLD effect (Ogawa et al. 1990; Ogawa et al. 1993) relies upon a complex interaction between the oxygenation of blood hemoglobin, blood flow, and cerebral metabolism—all temperature dependent variables.

Activation induced changes in brain temperature

Among the general effects that may change oxygen consumption and brain metabolism are activation-induced changes in the brain temperature. Decreases in the local brain temperature on the order of 0.2°C were reported in the visual cortex during prolonged visual stimulation of human brain (Yablonskiy et al. 2000). These changes were explained by the overwhelming cooling effect of increased blood flow (in the presence of brain/body-core temperature differential) versus the marginal brain heating from increased metabolic rate. Previous direct measurements of changes in brain temperature during functional activation in animals have given contradictory results. Localized temperature variations under visual, auditory, and somatic stimulations that were variable in duration, sign, magnitude, and form, ranged from 0.01 to 0.2°C in cat brain (McElligott and Melzack 1967; Melzack and Casey 1967). Local decreases in brain temperature on the order of 0.2°C were observed in awake monkeys following amygdala stimulation (Hayward and Baker 1968). The temperature from activated brain regions has been reported to increase slowly by $\sim 0.1^{\circ}\text{C}$ during 2 min forepaw stimulation with α -chloralose anesthetized rats (Trubel et al. 2006). An infrared mapping technique (Gorbach 1993) was used to detect thermal changes on the surface of rat brain and differences in temperature of up to 0.5°C were registered in different cortical areas during the resting state (Shevelev 1998). Short visual stimulation invoked a temperature rise on the order of 0.1°C on the surface of the skull covering the visual cortex as measured with this technique. No temperature changes were detected using MRI measurements in human visual cortex during short visual stimulation (Katz-Brull et al. 2006; Kauppinen et al. 2008). This is most likely because low accuracy of MRI temperature measurements and short stimulated time used when temperature changes are expected to be very small (Yablonskiy et al. 2000). Detail theoretical analysis of temperature changes during functional activation (Sukstanskii and Yablonskiy 2006) demonstrated that the sign and amplitude of temperature changes depend on a number

of parameters, the most important being brain/body-core temperature differential, blood flow and the size and position of activated area (see also (Collins et al. 2004)). Variability in these previous studies of brain temperature changes during functional activation are likely due in large part to differences in the brain/body-core temperature differentials under different experimental conditions.

In conclusion, CBF is the major parameter defining (1) the initial brain/body-core temperature differential in anesthetized rats, (2) the magnitude of changes in the brain temperature during hypercapnia, and (3) the characteristic temperature transition time. Different anesthetic regimes change brain temperature in proportion to the degree to which they suppress CBF. A change in brain temperature in the face of a hypercapnia-induced CBF increase is expected to affect metabolic rates of chemical reactions in the brain, in particular CMRO₂. Variations in hypercapnia-induced brain temperature changes with species, anesthetics, and experimental conditions may explain the often contradictory and inconsistent literature regarding CMRO₂ versus hypercapnia.

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Abbreviations

OEF	Oxygen extraction fraction
CBF	Cerebral blood flow
CH	Chloral hydrate
IF	Isoflurane
α CS	α -Chloralose
MABP	Mean arterial blood pressure
FiO ₂	Fraction of inspired oxygen
CMRO ₂	Cerebral metabolic rate of oxygen

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Fig. 1. A typical time course of brain temperature changes induced by a 15-min period of hypercapnia. Data were obtained from one rat under α CS anesthesia. Hypercapnia was induced at 20 min, and was switched off at 35 min (*shaded bars* indicate hypercapnia period)

Fig. 2.

Graph showing a typical result from exponential modeling (*solid line*) of one of the 15 min hypercapnia induced brain temperature time courses. Data (*dots*) represent measurement duration of those 6 mm deep brain location during first hypercapnia period for a rat under α CS anesthesia

Fig. 3.

Magnitudes of brain temperature changes, ΔT , and characteristic temperature transition times, t_c , during and after hypercapnia events for rats under three different anesthesia regimes. Data represent all rats (α -chloralose, α CS, $n = 6$; chloral hydrate, CH, $n = 6$; isoflurane, IF, $n = 6$). Error bars represent SD. Statistical significance analysis is for CH versus α CS or IF versus α CS (** $P < 0.005$; * $P < 0.05$). Differences for t_c between CH and IF do not reach statistical significance

Fig. 4. Example of temperature correlation between body and 6 mm deep brain location in a rat solely anesthetized by 1.2% isoflurane during a process of slow body cooling from 38 to 33°C in 3 h

Fig. 5.

Graph shows further decoupling of brain temperatures during a 65-min period when IF was substituted with α CS anesthesia. The rat was first anesthetized with 2.0% IF, then further administered with 40 mg/kg α CS i.p. at 10 min. The 2.0% IF anesthesia was removed after the shaded 5-min period. Note that the small decrease of body-core temperature at 10 min is due to temporary rectal temperature drop by cold α CS solution injected

Fig. 6.

Correlation of brain/body-core temperature differential and CBF* under three anesthesia regimes. Here CBF* values are estimated from the characteristic time constant t_c obtained during both hypercapnia challenge (*filled symbols*) and post-hypercapnia (*empty symbols*) periods: $CBF^* = c_{\text{tissue}} / (\rho_b \cdot c_b \cdot t_c)$, in which c_{tissue} represents brain tissue heat capacity, c_b and ρ_b are the same as previously defined in Eq. 2. We use the term CBF* because exact relationship between t_c and CBF in the presence of heat exchange with the environment is not known. “x” and “-” are simulated data based on a previously published brain temperature distribution equation (see (Zhu et al., 2006), Eq. 2) and with heat transfer coefficient h equal to 0.005 and 0.001 (W/(cm² °C))

Table 1

Physiologic Parameters

Anesthetic	Baseline		Hypercapnia			MABP (mmHg)
	pH	PaCO ₂ (mmHg)	PaO ₂ (mmHg)	pH	PaCO ₂ (mmHg)	PaO ₂ (mmHg)
CH (<i>n</i> = 3)	7.40 ± 0.07	43.9 ± 3.8	164.3 ± 14.0	7.26 ± 0.03	66.9 ± 5.1	179.7 ± 5.1
αCS (<i>n</i> = 3)	7.33 ± 0.03	43.2 ± 7.5	149.3 ± 21.6	7.20 ± 0.04	62.9 ± 4.2	164.7 ± 24.6
IF (<i>n</i> = 3)	7.40 ± 0.02	43.9 ± 0.9	153.0 ± 17.4	7.30 ± 0.04	59.1 ± 11.0	180.0 ± 28.3
						82.6 ± 2.3
						69.4 ± 1.3
						87.3 ± 5.0