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Regional Cerebral Blood Flow and Glucose Utilization during Hypocapnia and Adenosine-induced Hypotension in the Rat

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Hypocapnia and induced hypotension have been claimed by some to cause cerebral hypoxia because of insufficient perfusion. Regional cerebral blood flow (rCBF) and regional cerebral glucose utilization ($rCMR_{glc}$) were measured simultaneously in the same animal subjected to hypocapnia or hypocapnia combined with induced arterial hypotension. The $rCMR_{glc}$ was measured with (^3H) deoxyglucose and the rCBF with (^{14}C) iodoantipyrine with the use of tissue biopsy methods and scintillation counting. Nineteen male Wistar rats were anesthetized with halothane and artificially ventilated. Anesthesia was maintained with nitrous oxide/oxygen (70:30) and succinylcholine. Six rats were maintained at normocapnia, six rats were ventilated to a Pa_{CO_2} of 20 mmHg, and seven animals were ventilated to Pa_{CO_2} 20 mmHg combined with arterial hypotension of 50 mmHg (mean blood pressure) induced by infusion of adenosine. Although hypocapnia alone did not cause a statistically significant decrease of rCBF except in hippocampus, hypocapnia combined with hypotension resulted in a significant reduction of rCBF in four of seven regions when compared with hypocapnia alone; $rCMR_{glc}$ values were unchanged during hypocapnia. However, the addition of hypotension induced by adenosine led to a significant decline of glucose utilization in five of seven brain regions. In the present study the authors observed no increase of regional glucose utilization and hence no signs of cerebral ischemia during hypocapnia alone or combined with hypotension induced by adenosine. (Key words: Anesthetic techniques: hypocapnia; hypotension; adenosine. Blood pressure: induced hypotension. Brain: blood flow, regional; metabolism, regional.)

HYPOCAPNIA AND INDUCED HYPOTENSION are often used simultaneously during neurosurgery to improve surgical conditions and reduce blood loss. Profound hypocapnia is believed to produce excessive vasoconstriction and hence tissue ischemia.[1,2] It is controversial, however, as to which level Pa_{CO_2} can be safely reduced. A further concern of many clinicians is that the combination of hypocapnia and hypotension may act together to increase ischemia. Again, this is controversial because the various results reported are not in agreement.[3–6]

Adenosine has recently been advocated as a drug causing easily induced and maintained hypotension without rebound hypertension, tachyphylaxis, or toxicity.[7–9] Although the effect of adenosine-induced hypotension on cerebral blood flow (CBF) and cerebral metabolic rate (CMR) has been examined in some studies,[8–10] the consequences of simultaneous hypocapnia and hypotension are unknown. In the present study we investigated the effects of hypocapnia alone and in combination with adenosine-induced hypotension on regional cerebral blood flow (rCBF) and regional cerebral glucose utilization ($rCMR_{glc}$) in rats during oxygen–nitrous oxide anesthesia.

Materials and Methods

Regional cerebral glucose utilization and rCBF were measured with ^3H-labeled deoxyglucose and ^{14}C-labeled iodoantipyrine with the use of tissue biopsy methods and scintillation counting.[11–14] The 2-deoxyglucose method was used in a form slightly modified from that of Sokoloff *et al.*[12] to allow measurements to be made of the magnitude of the precursor pool of labeled deoxyglucose in brain and of the lumped constant in the hypocapnia groups. The modifications have been explained in the Appendix. In normal rats, distribution volume (0.35) and lumped constant (0.40) were adopted from Gjedde.[13] In the hypocapnic rats, the values were determined experimentally, as listed in table 1 and the Appendix.

Male Wistar rats weighing 300–400 g were fasted overnight. After induction of anesthesia with halothane in a closed jar, a tracheostomy was performed and the animals' lungs were ventilated to normocapnia (Pa_{CO_2} 35–45 mmHg) by a rodent respirator with the use of 1% halothane in nitrous oxide/oxygen (7:3). The rats were paralyzed with succinylcholine (1 $mg \cdot kg^{-1}$). Catheters were inserted into the tail artery and a femoral artery and vein. After insertion of the catheters, halothane was discontinued and anesthesia continued with 70% nitrous oxide in oxygen while relaxation was maintained by intermittant doses of succinylcholine. The experimental design was approved by the Animal Experimental Committee of the Department of Justice, Kingdom of Denmark. Arterial pressure was measured continuously by strain gauge transducer, and arterial blood samples were assayed for *p*H, Pa_{CO_2}, and Pa_{O_2} with appropriate microelectrodes (Radiometer, Copenhagen). The animals were considered to be in the respiratory steady state when Pa_{CO_2} agreed within 10% in samples taken 20 min apart. Rectal temperature of 37° C ± 0.5° C was servocontrolled by an electric lamp.

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TABLE 1. Physiologic Variables in the Three Experimental Groups

	Normocapnia (n = 6)	Hypocapnia (n = 6)	Hypocapnia and Hypotension (n = 7)
Weight (g)	339 ± 10	299 ± 32	341 ± 12
MAP (mmHg)	133 ± 8	120 ± 11	50 ± 1*
Pa_{O_2} (mmHg)	140 ± 13	153 ± 20	120 ± 19
Pa_{CO_2} (mmHg)	39 ± 2	18 ± 1†	22 ± 0.5†
*p*H	7.40 ± 0.02	7.61 ± 0.03†	7.53 ± 0.04*
P-glc (mM)	7.9 ± 1.8	8.2 ± 1.5	8.1 ± 2.9
Hct (%)	48 ± 2	45 ± 4	41 ± 2*
Vg (ml/g)	0.35‡	0.48 ± 0.12 (n = 3)	—

Each value represents the mean ± SD.

MAP = mean arterial pressure; Pa_{O_2} = arterial O_2 tension; Pa_{CO_2} = arterial CO_2 tension; P-glc = plasma glucose concentration; CO = cardiac output; Vg = distribution volume of unphosphorylated deoxyglucose.

* Significantly different from hypocapnia ($P < 0.0253$).

† Significantly different from normocapnia ($P < 0.0253$).

‡ Gjedde 1982.

The animals were divided into three groups in a random fashion. In the first group (control animals, n = 6) normocapnia was continued throughout the study. Forty-five minutes after discontinuation of halothane, 20 μCi 2-deoxy-D-(^{3}H)glucose was injected as a bolus into the femoral vein for determination of $rCMR_{glc}$. Arterial blood was then sampled into a syringe attached to a Harvard® withdrawal pump at a known and constant rate (9 $\mu l \cdot min^{-1}$) from the tail catheter. After 44 min, withdrawal was discontinued and the catheter connected to a second pump. One minute later, withdrawal was resumed and blood sampled in a second syringe (91 $\mu l \cdot min^{-1}$). Ten seconds later an iv bolus of 5 μCi 4-(N-methyl-^{14}C)iodoantipyrine was injected for determination of rCBF; after 20 s of isotope circulation, withdrawal was stopped and the animals decapitated with a rodent guillotine. No blood was replaced during the experiment.

In the second group (n = 6), hypocapnia (Pa_{CO_2} 20 mmHg) was established and maintained throughout the study after discontinuation of halothane. After 45 min of hypocapnia the same procedure was followed as described for rats in the normocapnic group beginning with the bolus injection of 20 μCi 2-deoxy-D-(^{3}H)glucose.

In the third group (n = 7) an additional catheter was inserted into the contralateral femoral vein. Hypocapnia was established and maintained throughout the study after 45 min of discontinuation of halothane. Then the animals were rendered hypotensive by a continuous infusion of 10.8 $mg \cdot ml^{-1}$ adenosine. The average infusion rate was 70 $\mu l \cdot min^{-1}$. Because of the low solubility of adenosine in saline and to minimize the volume load, the adenosine solution was heated before infusion. Mean arterial pressure (MAP) was maintained at a level of 50 mmHg for 45 min. In this group, the bolus injection of 2-deoxy-D-(^{3}H)glucose occurred when steady state at the desired level of hypotension was achieved. Withdrawal of blood samples, bolus injection of 4-(N-methyl-^{14}C)iodoantipyrine, and decapitation were performed as described for rats in the first group.

In all animals, the brain was rapidly removed after decapitation and dissected bilaterally into frontal and parietal cortex, hippocampus, thalamus, mesencephalon, cerebellar hemisphere, and medulla oblongata. The blood and tissue samples were rapidly transferred to preweighed vials containing 1.5 ml of soluene and isopropanol mixture (1:1). The vials and samples were reweighed, blanched with 0.5 ml 30% hydrogen peroxide, and stored overnight at 50° C. The next morning, preparation was completed by addition of 20 ml Instagel® (Packard) and 0.5 N HCl mixture (9:1). The vials were allowed to stabilize for 24 h before counting in a Tri-Carb® 2425 liquid scintillation spectrometer. The radioactivities originating from ^{3}H and ^{14}C were separated by the channels ratio method, after correction for quench by automated external standardization based on laboratory-prepared samples of pure ^{3}H and ^{14}C standards.

In each group the results from corresponding areas of left and right hemispheres were compared with the use of a paired *t* test. Because no difference was found, all results from an area (*i.e.*, left and right side) were combined. Thereafter, differences between Groups 1 and 2 and between Groups 2 and 3 were tested with the use of the nonparametric Mann-Whitney significance test. Because two tests were carried out on the data from each region, a significance level of 0.0253 was used for each test. The physiologic variables were tested in the same way.

Results

Hypotension was easily induced and maintained by adenosine at the desired MAP with no tachyphylaxis. A hypotensive steady state was achieved within an average of 6 min. The adenosine concentration was increased in a step-wise fashion until the desired MAP was obtained. The average dose of adenosine required to maintain MAP at 50 mmHg was 2.3 $mg \cdot kg^{-1} \cdot min^{-1}$.

The physiologic variables of the animals are given in table 1. The groups did not differ with respect to Pa_{O_2} and plasma glucose concentration. A significant decrease in hematocrit was seen in the group having combined hypocapnia and hypotension. In the hypocapnic group, *p*H in blood increased significantly. This increase was reduced significantly when hypotension was added. Mean ± SD of lumped constant measurements during hypocapnia was 0.61 ± 10. The regional values are given in the

TABLE 2. Regional Cerebral Blood Flow (rCBF)* and Regional Cerebral Glucose Utilization ($rCMR_{glc}$)†

Region	Normocapnia (n = 6)		Hypocapnia (n = 6)		Hypocapnia and Hypotension (n = 7)	
	rCMRglc	rCBF	rCMRglc	rCBF	rCMRglc	rCBF
Frontal lobe	57 ± 8	170 ± 38	60 ± 18	127 ± 33	37 ± 12	77 ± 18‡
Parietal lobe	56 ± 10	177 ± 40	58 ± 19	143 ± 35	36 ± 12	92 ± 17‡
Hippocampus	40 ± 10	102 ± 19	39 ± 12	72 ± 17§	23 ± 7‡	58 ± 9
Thalamus	53 ± 14	154 ± 47	51 ± 16	110 ± 18	33 ± 10‡	80 ± 13‡
Mesencephalon	46 ± 8	146 ± 33	50 ± 18	111 ± 25	28 ± 10‡	74 ± 7‡
Cerebellum	36 ± 6	125 ± 28	38 ± 12	90 ± 29	23 ± 7‡	63 ± 6
Medulla oblongata	36 ± 6	128 ± 27	38 ± 12	92 ± 28	22 ± 8‡	60 ± 4

Each value represents the mean ± SD.
* $ml \cdot 100\ g^{-1} \cdot min^{-1}$.
† $\mu mol \cdot 100\ g^{-1} \cdot min^{-1}$.
‡ Significantly different from hypocapnia ($P < 0.0253$).
§ Significantly different from normocapnia ($P < 0.0253$).

Appendix. The distribution volume (V_g) measured was 0.48 ± 0.12 (mean ± SD) (table 1). Hypocapnia alone caused a significant reduction of rCBF only in hippocampus (table 2). Hypocapnia combined with induced hypotension caused a significant reduction of rCBF in four of seven regions when compared with hypocapnia alone. The $rCMR_{glc}$ values were identical in Groups 1 and 2. However, hypotension induced by adenosine led to a significant decline of $rCMR_{glc}$ in five of seven regions examined. The ratio between rCBF and $rCMR_{glc}$ averaged 3:1 in Group 1, and during hypocapnia the ratio declined to 1:7 because of reduced rCBF. When $rCMR_{glc}$ declined during combined hypocapnia and hypotension, the ratio was 2.4, thus tending toward a "resetting" of the couple between rCBF and $rCMR_{glc}$.

Discussion

HYPOCAPNIA

Hypoxia of brain (and other) tissue induces the Pasteur Effect, which may elevate the CMR_{glc} level up to sevenfold.[14] The absence of an increase of CMR_{glc} effectively rules out the presence of hypoxia. Therefore, the study showed conclusively that hypocapnia to Pa_{CO_2} 20 mmHg is associated with no hypoxia of the brain tissue and, further, that adenosine-induced hypotension corrects the flow metabolism imbalance associated with hypocapnia. Hypocapnia reduces CBF by increasing the cerebral vascular resistance and shifts the oxyhemoglobin dissociation curve to the left.[15] Reduced brain oxygen tension and altered brain metabolism have been measured under these circumstances.[16] However, evidence of permanent cell damage has not been documented. Mueller *et al.*[17] reported parallel decreases in five brain regions in dogs at Pa_{CO_2} 25 mmHg. In cats, Grote *et al.*[18] reported parallel decreases of rCBF in corresponding areas of the right and left hemispheres at Pa_{CO_2} 20 mmHg. In the present study, rCBF decreased statistically significant only in hippocampus during hypocapnia. This probably results from the relatively small number of animals in each group together with a significant regional variability in CBF values.

Significant changes of global cerebral metabolism indicative of hypoxia have been reported only during extreme hypocapnia (Pa_{CO_2} about 10 mmHg).[1,19,20] The regional CMR_{glc} has not previously been determined during hypocapnia. Compared with control animals, our finding of almost identical values of $rCMR_{glc}$ in 14 regions indicates that rCBF is sufficient to maintain normal oxidative metabolism during hypocapnia. Alexander *et al.*[19] and Wollman *et al.*[21] found no significant changes of glucose or oxygen metabolism at Pa_{CO_2} 18–19 mmHg. Weyne *et al.*,[22] Plum and Posner,[23] and Grothe *et al.*[18] all found increases of lactate concentrations of CBF and brain tissue at 20 mmHg Pa_{CO_2}. However, there is no general agreement about the cause of this increase, which may result from the alkalosis stimulation of glycolytic metabolic pathway.[1]

HYPOCAPNIA AND HYPOTENSION

An average total of 3.5 ml adenosine in saline was infused at a mean rate of 70 $\mu l \cdot min^{-1}$ in order to obtain the desired MAP of 50 mmHg. Although hemodilution may influence the measurements of blood flow to the brain both by increasing the blood flow and by influencing the partition coefficient of the blood flow tracer, the total infusion was not deemed sufficient to affect the measurements appreciably because of the decrease in hematocrit (table 1).

During adenosine infusion, MAP was reduced by 60%. Compared with animals subjected to hypocapnia, rCBF was significantly reduced in four of seven areas examined (table 2). Kassel *et al.*[8] also found a reduction of rCBF in

dogs exposed to adenosine-induced hypotension of 40 mmHg for 60 min at 40 mmHg Pa_{CO_2}. Newberg *et al.*[10] reported a decrease in CBF of 55–65% in dogs subjected to adenosine-induced hypotension of 50 mmHg for 60 min at Pa_{CO_2} 35 mmHg. This was the result of a 50% decrease of MAP and an increase in intracranial pressure, resulting in a profound decrease of the perfusion pressure. Artru investigated the cerebral effects of combined hypocapnia/hypotension in dogs.[5,6] He reported that CBF was not significantly reduced when hypotension of 50 mmHg was induced by isoflurane during hypocapnia of 20 mmHg.

Autoregulation of CBF during alterations of perfusion pressure is well established.[24] During hypocapnia the low pressure limit of autoregulation is lower than during normocapnia.[25] However, Mueller *et al.* reported heterogeneous autoregulation in different structures of the brain.[17] The reduction of rCBF in some areas in the present study suggests that the lower limit of autoregulation was exceeded, even though the animals were subjected to hypocapnia. Yet, there is a considerable margin of safety of CBF and MAP between the lower limit of autoregulation and the ischemic thresholds for EEG silence and failure of the cell membranes.[26]

An additional factor that may have added to the reduction of rCBF is the coupling between flow and metabolism. This mechanism adjusts blood flow to metabolism when metabolism (and the functional state) changes. The adjustment of blood flow to function and metabolism in the brain is well established.[27,28]

The decrease in $rCMR_{glc}$ in the present study may be the result of inhibition of synaptic transmission by intravenously administered adenosine. However, endogenously released adenosine may have added to the decrease in $rCMR_{glc}$. Adenosine depresses the firing of central neurons. This action has been postulated to occur at a presynaptic receptor site associated with inhibition of transmitter release.[29] This is consistent with our finding of an average reduction of 35% of $rCMR_{glc}$ during the 45 min of adenosine-induced hypotension. This reduction ranged from 29 to 40% in the different brain regions. Winn *et al.* elicited hypotension in rats by hemorrhage and demonstrated a nearly sixfold increase in brain levels of adenosine when MAP decreased from 135 to 45 mmHg.[30] Rubio *et al.*[31] hyperventilated rats by increasing ventilation from 60 min^{-1} to 100 min^{-1} (Pa_{CO_2} was not determined). Brain adenosine level increased from 6.7 ± 1.0 to 11.8 ± 1.4 nmol/g, explained as the result of reduced oxygen supply.[31] However, two other investigations have disclosed no reduction in the CMR for oxygen during adenosine-induced hypotension in dogs during normocapnia.[8,10] The difference may be caused by species or methodologic differences.

In conclusion, hypocapnia alone caused no change in $rCMR_{glc}$. During hypocapnia combined with adenosine-induced hypotension, $rCMR_{glc}$ declined significantly in five of seven brain regions. We observed no increase of $rCMR_{glc}$ and hence saw no signs of cerebral ischemia.

Appendix

Theory

The ^{3}H-labeled deoxyglucose and ^{14}C-labeled iodoantipyrine method measures the clearance of the tracers. The clearance is the ratio between the amount of tracer accumulated in the organ and the amount of tracer supplied and equals the ratio between the radioactivity in the organ and the radioactivity integral of the tracer in arterial blood. If the permeability of the tracer is very high and the observation period very short, the clearance equals the blood flow because all the delivered tracer accumulates in the organ and none has time to leave the organ again. Iodoantipyrine has a sufficiently high permeability to qualify for blood flow measurements.[11]

Cerebral glucose metabolism was measured with ^{3}H-labeled 2-deoxyglucose.[12] The tracer undergoes phosphorylation by brain hexokinase but is not metabolized further and not dephosphorylated and therefore remains in brain cells. In this case, the clearance reflects the rate of phosphorylation of 2-deoxyglucose that is a fraction (usually half) of the rate of phosphorylation of glucose. This fraction, the lumped constant, must be known in advance. In brief, the glucose metabolism equals the clearance of deoxyglucose, divided by the lumped constant and multiplied by the plasma glucose concentration.

The net rate of irreversible trapping of labeled deoxyglucose metabolites, K, equals:

$$K = \frac{M_m(T)}{\int_0^T C_a(t)dt - \frac{M_e(T)}{K_1}} \quad (1)$$

where M_m (T) is the accumulated metabolic product, M_e (T) the remaining unmetabolized tracer in brain, exchangeable with blood plasma, C_a (t) the tracer concentration in arterial plasma as a function of time, and K_1 a rate constant representing the unidirectional tracer flux from the arterial plasma to the brain tissue. The M_e (T)/K_1 term is a correction term for the delay of tracer equilibration between blood plasma and brain water.

In the near steady state (*e.g.*, at 45 min), the equation can be simplified by exclusion of entities that cannot be measured directly (M_m and M_e) as follows:

$$K = \frac{M(T) - V_g C_a(T)}{\int_0^T C_a(t)dt} \quad (2)$$

where M (T) is the total concentration of label in the tissue and V_g is the apparent distribution volume of unphosphorylated deoxyglucose that must be known to calculate K from the accumulated radioactivity in the tissue.[32,33]

In hypocapnic animals both V_g and the lumped constant of

deoxyglucose may change. For this reason, during hypocapnia we determined the magnitude of V_g i 3 separate experiments in which brain tissue was sampled at different times. In these experiments V_g was the ordinate intercept of the rectilinear relationship between the M (T)/C_a (T) ratio and the normalized time-integral of C_a (t) derived from equation (2):

$$\frac{M(T)}{C_a(T)} = K \frac{\int_0^T C_a(t)dt}{C_a(T)} + V_g \quad (3)$$

The glucose consumption rate was calculated from the following formula:

$$CMR_{glc} = \frac{KC_{glc}}{LC} \quad (4)$$

where CMR_{glc} is the glucose phosphorylation rate, C_{glc} the native glucose concentration in arterial plasma, and LC the lumped constant. The lumped constant is actually the ratio between the net rates of deoxyglucose and glucose metabolism in the steady state. It can be shown to be a function of the relative amounts of glucose and deoxyglucose (excluding metabolites) in the brain in the steady state, multiplied by the ratio between the affinities for the hexokinase reaction (P_r):

$$LC = P_r \frac{M(\infty)/C_a(\infty)}{M_{glc}/C_{glc}} \quad (5)$$

where M_{glc} is the brain glucose content, M (∞) the steady-state radioactive deoxyglucose content in the brain, C_a (∞) the steady-state radioactive deoxyglucose concentration in arterial plasma, and C_{glc} the arterial plasma glucose concentration. In the equation, both the relative content of unphosphorylated deoxyglucose in brain and the brain content of free glucose can be estimated with the aid of radioactive methylglucose, which is a nonmetabolized glucose analogue. Native glucose influences the steady-state distributions of both tracer deoxyglucose and tracer methylglucose in a manner that can be used to estimate the value of the lumped constant.

In hypocapnic rats, in four separate experiments, the lumped constant was determined from the steady-state distribution of radioactive 3-0-methylglucose between blood and brain by the following equation:

$$LC = \frac{P_r}{1 - \frac{K_t}{C_{glc}}\left[\frac{V_d}{V_e} - 1\right]} \quad (6)$$

where V_d is the water volume of the rat brain, V_e the steady-state methylglucose distribution, and K_t the Michaelis constant of glucose transport between blood and brain. The values used for the constants were V_d 0.77 ml g^{-1}, P_r 0.3, and K_t 7 mM.[32]

The regional values of the lumped constant measured during hypocapnia were as follows (each value represents the mean, n = 4): frontal lobe 0.55, parietal lobe 0.55, hippocampus 0.57, thalamus 0.65, mesencephalon 0.70, cerebellar hemisphere 0.51, and medulla oblongata 0.78.

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