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Cerebral Blood Flow and Oxygen Consumption in the Rat Brain during Extreme Hypercarbia

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The effects of hypercapnia (Pa_{CO_2} 80, 160 and 300 torr) on cerebral metabolic rate for oxygen (CMR_{O_2}) and blood flow (CBF) were evaluated in paralyzed, mechanically ventilated rats by use of a ^{133}Xe modification of the Kety–Schmidt inert-gas technique. Hypercapnic rats (Pa_{CO_2} 80 torr) maintained on N_2O, 70 per cent, had a sixfold increase in CBF and a 25 per cent increase in CMR_{O_2}, which were not prevented by adrenalectomy or decreases in tissue O_2 tensions to near-normal values. Further increases in arterial blood CO_2 tensions were associated with decreases in CMR_{O_2} to normal (Pa_{CO_2} 160 torr) or subnormal values (Pa_{CO_2} 300 torr). In the last situation there was only a threefold increase in CBF. In rats with Pa_{CO_2} about 80 torr that were given propranolol, 2.5 $mg \cdot kg^{-1}$, during N_2O anesthesia, there was only a threefold increase in CBF, while CMR_{O_2} decreased to below normocapnic control values. Rats with Pa_{CO_2} 80 torr given sedative or anesthetic doses of diazepam (ventilated with O_2, 30 per cent, in N_2) also had decreased CMR_{O_2} values and had a twofold increase in CBF. It is concluded that hypercapnia activates catecholaminergic neurons in the brain, and that this activation increases oxygen consumption. The increase in flow that occurs with hypercapnia is markedly influenced by activity in catecholaminergic neurons. (Key words: Brain: blood flow; carbon dioxide tension; oxygen consumption. Carbon dioxide: hypercarbia. Hypnotics, benzodiazepines: diazepam. Sympathetic nervous system: sympatholytic agents, propranolol.

RESULTS from this laboratory have demonstrated that the cerebral metabolic rate for oxygen (CMR_{O_2}) increases in two conditions that involve activation of the sympathoadrenal system. First, when the nitrous oxide supply is discontinued in paralyzed, artificially ventilated rats, CMR_{O_2} increases to more than 180 per cent of control, with a comparable increase in cerebral blood flow (CBF).[1,2] These increases are prevented by adrenalectomy or by administration of propranolol. Second, recent data demonstrate that, under certain circumstances, a similar increase in CMR_{O_2} occurs with hypoxia, induced by decreasing arterial blood P_{O_2} to 25–30 torr in rats during anesthesia with N_2O, 70 per cent.[3] Although this increase was curtailed by adrenalectomy, all rats maintained on N_2O, 70 per cent, whether or not the adrenal glands had been removed, had 20–30 per cent increases in CMR_{O_2}. Since these increases were blocked by sedative or anesthetic doses of diazepam, they might have been triggered by activation of cerebral catecholaminergic neurons.

Previous studies in man have shown that increases in arterial blood P_{CO_2} to 50–60 torr are accompanied by increases in CBF at an unchanged CMR_{O_2}.[4,5] In the rat, increases in Pa_{CO_2} to 70–80 torr have been found to cause a fourfold increase in CBF with no significant change in CMR_{O_2}.[6] To our knowledge, the effects of even higher CO_2 tensions have not been studied. Since hypercapnia is known to cause sympathoadrenal activation,[7–9] we decided to reinvestigate the effects of hypercapnia (Pa_{CO_2} 70–80 torr) on CMR_{O_2} and CBF. Our approach differed from previous ones in several important respects. First, we used a CBF technique that facilitates measurements at very high flow rates.[3] Second, moderate hypercarbia (70–80 torr) was also induced in animals from which the adrenal glands had been removed, in those given propranolol or diazepam, and in those in which tissue oxygen tensions were prevented from increasing. Third, very high CO_2 tensions, as induced by administration of CO_2, 20 and 40 per cent, were also studied.

Methods

Male Wistar rats, each weighing 320–400 g, were allowed free access to pellet food and water until the day of operation. Anesthesia was induced with halothane, 2–3 per cent. Following tracheotomy, the animals were immobilized with *d*-tubocurarine chloride, 0.5 $mg \cdot kg^{-1}$, iv, and their lungs artificially ventilated. Most animals were maintained on N_2O, 70 per cent, and O_2, 30 per cent, until hypercapnia was induced. In a few animals, diazepam was given in sedative (2.25 $mg \cdot kg^{-1}$) or anesthetic (7.5 $mg \cdot kg^{-1}$) doses, iv, as described previously,[10] and ventilation was continued with N_2, 70 per cent, and O_2, 30 per cent. In some animals maintained on N_2O, 70 per cent, and O_2, 30 per cent, propranolol, 2.5 $mg \cdot kg^{-1}$, was given iv. In one group of animals inspired O_2 concentration was decreased to give Pa_{O_2} 50–60 torr. In all animals ventilation was adjusted to give arterial blood CO_2 tensions of 35–40 torr. Body temperature, measured in the rectum, was maintained close to 37 C by external heating.

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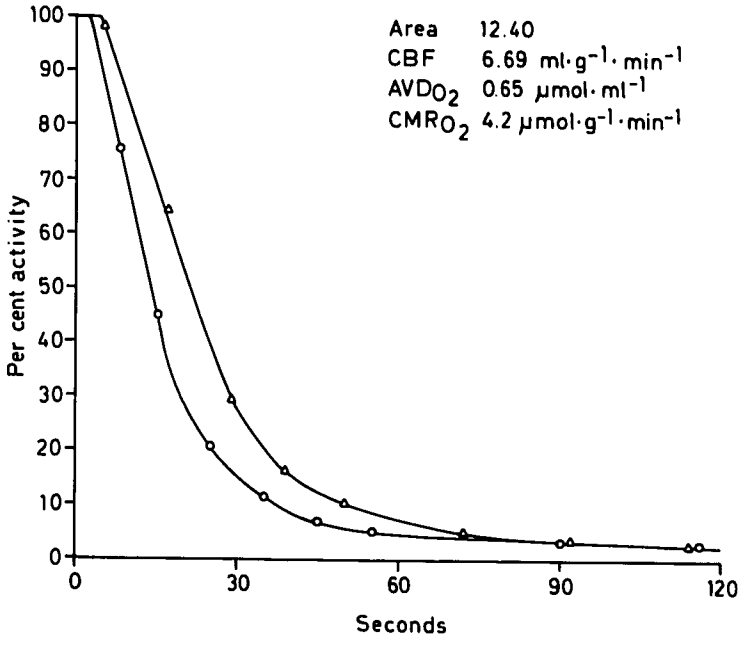

FIG. 1. Example of a ^{133}Xe-desaturation curve where cerebral blood flow exceeds 5 ml·g^{-1}·min^{-1}. O denotes arterial samples and Δ, samples from the superior sagittal sinus. All ^{133}Xe activities are given as percentages of the venous values measured at the end of the saturation period.

Preparations for CBF measurements included cannulation of both femoral arteries (for blood pressure recording and sampling of arterial blood) and one femoral vein (for iv injections and infusions of donor blood), as well as exposure of the caudad portion of the superior sagittal sinus.

A few rats were used for clinical evaluation of the effect of hypercapnia combined with propranolol or diazepam. These animals were anesthetized with halothane, 2–3 per cent, and catheters were inserted into a tail artery and vein for blood sampling and infusions. The animals were allowed to recover for at least an hour in an airtight plastic box, which could be perfused with any desired gas mixture. The animals were then given either propranolol, 2 5 mg·kg^{-1}, iv, and exposed to CO_2, 7 per cent, and O_2, 30 per cent, in N_2O, or diazepam, 2.25 mg·kg^{-1}, and were exposed to CO_2, 7 per cent, and O_2, 30 per cent, in N_2. They were observed for wakefulness, motor activity, reactions to pain and sensory stimulation, and reflexes, and were compared with unmedicated rats in the same box.

TABLE 1. Body Temperatures, Mean Arterial Blood Pressures (MABP), and Arterial Blood Gas and *p*H Values in Rats Exposed to CO_2, 7, 20, and 40 Per Cent, in the Insufflated Gas Mixture (Means ± SEM)

		Hypercapnia		
	Control Normocapnia	CO_2 7 Per Cent	CO_2 20 Per Cent	CO_2 40 Per Cent
Number of rats	15	6	6	6
Temperature (C)	37.0 ± 0.1	36.9 ± 0.3	37.0 ± 0.3	36.5 ± 0.3
MABP (torr)	140 ± 3	138 ± 4	147 ± 2	127* ± 3
P_{CO_2} (torr)	38.8 ± 0.5	81* ± 3	156* ± 3	296* ± 10
P_{O_2} (torr)	125 ± 5	120 ± 6	113 ± 7	144 ± 13
*p*H	7.38 ± 0.01	7.12* ± 0.01	6.92* ± 0.02	6.61* ± 0.04

* Significant difference from control value, $P < 0.05$.

Hypercapnia was induced by adding CO_2 to the insufflated gas mixture for 30 min in amounts sufficient to increase arterial blood CO_2 tensions to 80, 160, or 300 torr, with corresponding decreases in N_2O concentration. Preliminary experiments with unanesthetized, spontaneously breathing rats showed that Pa_{CO_2} 300 torr induced unconsciousness and abolished reaction to pain. For this reason, the nitrous oxide supply was withdrawn a few minutes after induction of hypercapnia. In order to prevent an excessive increase in arterial pressure (> 200 torr), and the development of cardiovascular failure, a 3–5-ml volume of blood was slowly withdrawn, and the CO_2 tension was gradually increased over 3–5 min. The hypercapnia was then maintained for 30 min.

Cerebral blood flow was measured using a ^{133}Xe modification of the Kety–Schmidt technique.[6,11,12] In general principle, the brains were saturated with ^{133}Xe over 20 min by connecting a rubber bag containing a gas mixture with ^{133}Xe to the inlet of the respirator, and arterial and cerebral venous blood samples were taken for measurements of ^{133}Xe activity and oxygen content (C_{O_2}) at the end of saturation. Desaturation was started by disconnecting the rubber bag, and additional arterial and cerebral venous blood samples were collected during the desaturation period. CBF was

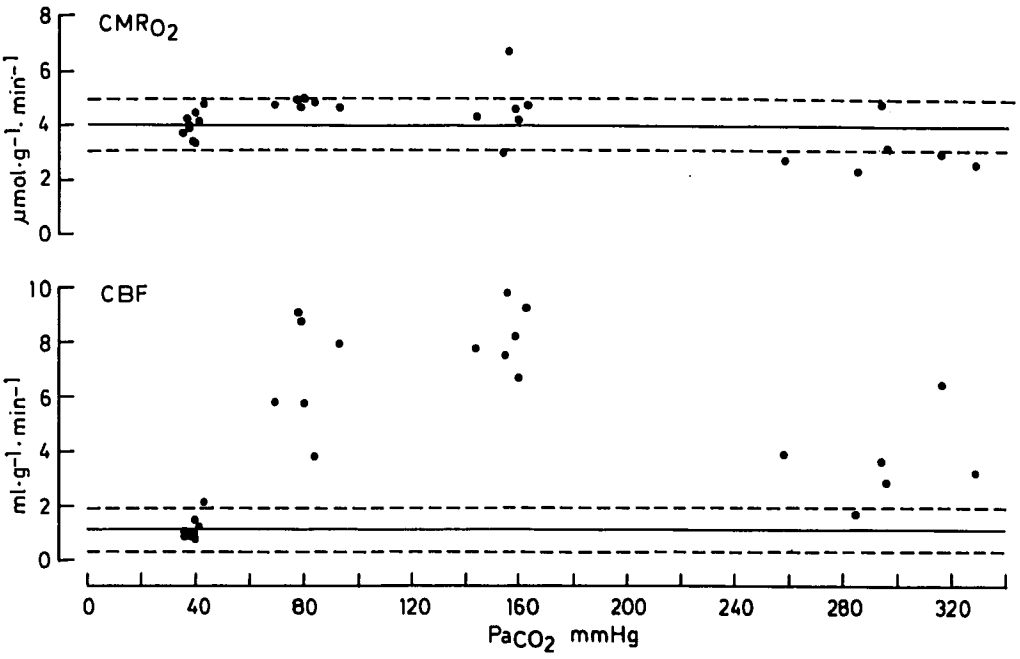

FIG. 2. Individual CBF and CMR_{O_2} values plotted against arterial blood P_{CO_2}. The horizontal uninterrupted lines represent the mean values and the interrupted lines the 95 per cent confidence intervals for CMR_{O_2} and CBF, respectively, for the control group (Pa_{CO_2} 40 torr).

then calculated from the arterial and cerebral venous blood values for ^{133}Xe activity, using the trapezoid rule. CMR_{O_2} was derived by multiplying the CBF value by the mean of the values for arteriovenous oxygen difference [$C(a\text{-}v)_{O_2}$]. Recently, the method has been technically modified so as to allow accurate estimation of CBF even at very high flow rates.[3] These modifications were used in the present experiments, and in addition, mean $C(a\text{-}v)_{O_2}$ was calculated from at least two values, obtained just before and during the first minute of desaturation. When only two $C(a\text{-}v)_{O_2}$ values were obtained, and these differed by more than 10 per cent, the experiment was discarded.

Arterial blood P_{CO_2} and *p*H values were measured using microelectrodes‡ with appropriate corrections for any deviation in body temperature from 37 C. To allow measurements of P_{CO_2} in animals exposed to 40 per cent CO_2, the P_{CO_2} electrode was calibrated with gas mixtures of comparable P_{CO_2}, and samples were analyzed within 2–3 min following withdrawal.[13] Arterial and cerebral venous blood C_{O_2} values were measured in 25-μl samples using the polarographic method of Fabel and Lübbers.[14,15] ^{133}Xe activity in blood was analyzed in a gamma counter as described elsewhere.[12]

Statistical differences were calculated using the Student *t* test for unpaired data. A *P* value of 0.05 was regarded as significant.

Results

In rats that had intact adrenal glands, increases in Pa_{CO_2} to about 80 torr decreased plasma *p*H to about 7.1 (table 1). Arterial blood pressure was similar to that measured in normocapnic animals maintained on N_2O, 70 per cent. Pa_{O_2} exceeded 95 torr in every animal. Arterial *p*H decreased further as Pa_{CO_2} was increased. At the highest Pa_{CO_2} value, blood pressure decreased but still exceeded 120 torr in every animal.

Results for CBF and CMR_{O_2} obtained at flow rates exceeding 3–4 $ml \cdot g^{-1} \cdot min^{-1}$ are critically dependent on the CBF technique. Even when CBF exceeded 5 $ml \cdot g^{-1} \cdot min^{-1}$, it was possible accurately to assess the area between the desaturation curves for arterial and cerebrovenous blood (fig. 1). At these flow rates, the difference between venous and arterial blood ^{133}Xe activities decreased to zero within 90 sec following the

TABLE 2. Values of Arterial Oxygen Content (Ca_{O_2}), Arteriovenous Difference for Oxygen ($C(a-v)_{O_2}$), Cerebral Blood Flow (CBF) and Cerebral Metabolic Rate for Oxygen Corrected to 37 C ($CMR_{O_{2_{37}}}$)[31] in Rats Exposed to CO_2, 7, 20, and 40 Per Cent, in the Insufflated Gas Mixture (Means ± SEM)

	Control Normocapnia	Hypercapnia		
		CO_2 7 Per Cent	CO_2 20 Per Cent	CO_2 40 Per Cent
Number of rats	15	6	6	6
Ca_{O_2} ($\mu mol \cdot ml^{-1}$)	9.83 ± 0.14	8.46* ± 0.33	7.57* ± 0.35	8.47* ± 0.33
$C(a-v)_{O_2}$ ($\mu mol \cdot ml^{-1}$)	3.76 ± 0.17	0.78* ± 0.11	0.55* ± 0.04	0.95* ± 0.15
CBF ($ml \cdot g^{-1} \cdot min^{-1}$)	1.11 ± 0.09	6.84* ± 0.85	8.21* ± 0.47	3.60* ± 0.64
$CMR_{O_{2_{37}}}$ ($\mu mol \cdot g^{-1} \cdot min^{-1}$)	4.00 ± 0.13	4.88* ± 0.09	4.59 ± 0.55	3.14* ± 0.38

* Significant difference from control value, $P < 0.05$.

‡ Eschweiler and Company, Kiel, and Radiometer, Copenhagen, Denmark.

TABLE 3. Values of Mean Arterial Blood Pressure (MABP), Arterial Blood Gas and *p*H, Venous Oxygen Tension in the Superior Sagittal Sinus (Pv_{O_2}), Arteriovenous Differences for Oxygen ($C(a-v)_{O_2}$), Cerebral Blood Flow (CBF), and Cerebral Metabolic Rate for Oxygen Corrected to 37 C ($CMR_{O_{2,37}}$) in Normoxic and Moderately Hypoxic Rats Exposed to CO_2, 7 Per Cent, in the Insufflated Gas Mixture (Means ± SEM)

	CO_2 7 Per Cent Normoxia	CO_2 7 Per Cent Hypoxia
Number of rats	6	6
Temperature (C)	36.9 ± 0.3	37.2 ± 0.2
MABP (torr)	138 ± 4	140 ± 5
Pa_{CO_2} (torr)	81 ± 3	85 ± 3
Pa_{O_2} (torr)	120 ± 6	56 ± 4*
Pv_{O_2} (torr)	70 ± 4†	51 ± 5*
*p*H	7.12 ± 0.01	7.06 ± 0.004*
$C(a-v)_{O_2}$ (μmol·ml^{-1})	0.78 ± 0.11	0.79 ± 0.07
CBF (ml·g^{-1}·min^{-1})	6.84 ± 0.85	7.06 ± 0.68
$CMR_{O_{2,37}}$ (μmol·g^{-1}·min^{-1})	4.88 ± 0.09	5.29 ± 0.31

* Significant difference from normoxic value, $P < 0.05$.
† From Eklöf *et al.*[32]

start of desaturation. Increases in Pa_{CO_2} to 80 torr caused a sixfold increase in CBF and a moderate increase in CMR_{O_2} (fig. 2, table 2). There was a considerable scatter in CBF, less so in CMR_{O_2} values. Figure 2 illustrates data obtained in nine control rats, collected before the present study was performed. During the course of the study six more animals were studied. Since the results were identical the data from the two groups were pooled (table 2). At Pa_{CO_2} 156 torr, mean CBF had increased seven- to eightfold, and CMR_{O_2} was not different from control. One animal had an unusually high CMR_{O_2} value. When results from this animal are excluded, mean CMR_{O_2} was identical to the control value. At Pa_{CO_2} 296 torr, there were statistically significant decreases in CMR_{O_2} and CBF as compared with those measured at Pa_{CO_2} 80–160 torr. For rats having Pa_{CO_2} values close to 80 torr, the mean value for CBF was somewhat lower than that obtained at Pa_{CO_2} 160 torr. However, since the latter animals had an average blood pressure that was 10 torr higher, the cerebrovascular resistances should have been about equal. In other words, maximal vasodilatation probably existed when Pa_{CO_2} was increased to about 80 torr.

In the six animals whose adrenal glands had been removed, mean Pa_{CO_2} was 85 torr (± 3 torr, SEM). In this group, CMR_{O_2} was 5.60 ± 0.32 μmol·g^{-1}·min^{-1}, and CBF was 5.24 ± 0.55 ml·g^{-1}·min^{-1}. Thus, CMR_{O_2} was significantly increased above the normocapnic control value while CBF was five times normal. Obviously, adrenalectomy failed to lower CMR_{O_2} to normal or subnormal values, and had no influence on the CBF response.

It has been speculated that there may be a direct relationship between tissue P_{O_2} and oxygen utilization.[16,17] Since the increase in CBF during hypercapnia increases tissue oxygen concentration, separate animals were exposed to hypercapnia at decreased arterial blood P_{O_2}. However, decreases in arterial and cerebrovenous (and hence tissue) P_{O_2} values did not influence the CMR_{O_2} derived (table 3).

Since it could be suspected that the increase in CMR_{O_2} was related to increased activity in cerebral catecholaminergic neurons (see discussion), hypercapnia was induced in animals given propranolol or diazepam (table 4). To exclude the possibility of a variable response to hypercapnia, four additional animals were studied at N_2O, 70 per cent, and O_2, 30 per cent. Since the CBF and CMR_{O_2} values obtained (6.72 ± 1.10 ml·g^{-1}·min^{-1} and 4.41 ± 0.42 μmol·g^{-1}·min^{-1}, respectively) did not deviate significantly from those given in table 2, the hypercapnic control values were pooled. The results show that administration of propranolol or diazepam had prenounced effects on CBF and CMR_{O_2} (table 5). Thus, during hypercapnia propranolol decreased CBF and CMR_{O_2}, the latter decreasing to values below those measured in normocapnic controls (Table 2). In animals given diazepam, the results were similar but CBF was even further reduced.

All unventilated animals made hypercapnic had arterial blood gas and *p*H values comparable to those observed during artificial ventilation. The rats given propranolol showed moderate sedation when made hypercapnic (Pa_{CO_2} 80 torr), which was more pronounced than that of control rats exposed to the N_2O-

TABLE 4. Values of Body Temperature, Mean Arterial Blood Pressure (MABP), and Arterial Blood P_{CO_2}, P_{O_2} and *p*H in Hypercapnic Rats with and without Administration of Propranolol or Diazepam (Means ± SEM)

	Hypercapnia (7 Per Cent CO_2)			
	"Control" (Hypercapnia)	Propranolol 2.5 mg·kg^{-1}, iv	Diazepam	
			Sedative	Anesthetic
Number of rats	10	4	5	6
Temperature (C)	36.9 ± 0.2	36.9 ± 0.2	37.2 ± 0.1	36.6 ± 0.4
MABP (torr)	147 ± 4	164 ± 6*	148 ± 6	146 ± 12
P_{CO_2} (torr)	80 ± 2	79 ± 1	79 ± 1	80 ± 3
P_{O_2} (torr)	120 ± 4	105 ± 10	108 ± 6	104 ± 10
*p*H	7.01 ± 0.01	7.10* ± 0.02	7.04 ± 0.04	7.01 ± 0.03

All animals' lungs were ventilated with CO_2, 7 per cent, and O_2, 30 per cent. Those serving as controls or given propranolol also received N_2O, 63 per cent, while the diazepam-injected rats were given N_2, 63 per cent.
* Significant difference from control value, $P < 0.05$.

containing gas mixture. Propranolol-injected animals lay in a prone position and had slow reactions to sound and pain and a slow righting reflex.

Diazepam with hypercapnia (Pa_{CO_2} 80 torr) caused excellent sedation. The animals lay in a lateral position and had no reaction to sound, a weak reaction to pain, and no righting reflex. Thus, the combination of hypercapnia and a sedative dose of diazepam clinically resembled the effect of an anesthetic dose of diazepam,[10] and this synergistic effect disappeared when the rats were allowed to breathe room air again.

Discussion

The technique described by Kety and Schmidt[11] forms the basis of most of our knowledge of cerebral blood flow and oxygen utilization, and has been used in a large number of clinical and experimental studies. Since the method is based on the law of conservation of matter (Fick principle) it should give a quantitative measure of CBF and CMR_{O_2}. However, there are some assumptions involved. Most importantly, it is necessary that 1) CBF remain constant during the course of the measurement, 2) no arteriovenous shunt exist, 3) contamination of venous blood from extracerebral tissues be slight, and 4) the tissue not contain slowly perfused masses. It should be emphasized that even when these requirements are fulfilled one obtains a measure of oxygen utilization but not necessarily of energy production. Thus, when there is uncoupling of oxidative phosphorylation there is no strict parallelism between oxygen consumption and rate of energy flux (see below).

There is presently no evidence that arteriovenous shunts normally exist in the brain or that they may be formed with hypercapnia. Since repeated measurements of $C(a\text{-}v)_{O_2}$ can establish that CBF is constant, our main concerns are assumptions 3 and 4. As discussed elsewhere,[12,18] there is evidence that slowly perfused areas do not exist in the rat brain, and that any extracerebral contamination of venous blood is small. Thus, the main problem is to assess CBF accurately at the high flow rates obtained with hypercapnia. Results obtained with the modified and improved ^{133}Xe technique have made it necessary to revise two of our previous findings. First, under control conditions (N_2O, 70–75 per cent, Pa_{CO_2} 35–40 torr), CMR_{O_2} in the rat is close to 4.0 $\mu mol \cdot g^{-1} \cdot min^{-1}$, i.e., about 10 per cent less than previously reported.[6] Values around 4 $\mu mol \cdot g^{-1} \cdot min^{-1}$ have been repeatedly obtained before, at the time, and after the present series of experiments were performed. It seems clear that the difference is due to the fact that with the modified technique the area between the arterial and cerebrovenous curves for ^{133}Xe activity is more accurately assessed during the initial period of desaturation. Second, there is a moderate but significant increase in CMR_{O_2} at Pa_{CO_2} values around 80 torr. In view of the facts that similar results were obtained in four separate groups of animals (two groups of intact rats on different occasions, one group in which the adrenal glands were removed, and one group with moderate hypoxia), and that the clearance curves could be regularly resolved as shown in figure 1, we conclude that the present data more accurately describe the relationship between P_{CO_2} and CMR_{O_2}.

The present results thus differ from those previously reported for man.[4,5] Part of this discrepancy could be due to the fact that the increase in P_{CO_2} in our study (about 40 torr) was considerably greater than those in the studies in man (9–13 torr). However, differences in technique and in anesthesia could have contributed. In one study[4] CBF was calculated without extrapolation of arteriovenous differences in inert gas concentration to infinity. There is evidence that such a calculation overestimates CBF and CMR_{O_2} at normocapnia, but less so at hypercapnia.[19–21] In other words, had extrapolation been performed, the ratio of the CMR_{O_2} values in hypercapnia and normocapnia should have increased (see figure 1 in reference 4). In the other study,[5] CMR_{O_2} during hypercapnia did not change significantly, but the mean value was about 15 per cent lower than control. It cannot be excluded that the anesthesia used (halothane, 1.2 per cent) influenced the results, which are not different from those obtained in our animals given diazepam or

TABLE 5. Values of Arterial Oxygen Content (Ca_{O_2}), Arteriovenous Oxygen Difference ($C(a-v)_{O_2}$), Cerebral Blood Flow (CBF) and Cerebral Metabolic Rate for Oxygen (CMR_{O_2}) in Hypercapnic Rats with and without Administration of Propranolol or Diazepam (Means ± SEM)

	Hypercapnia (7 Per Cent CO_2)			
	"Control" (Hypercapnia)	Propranolol 2.5 $mg \cdot kg^{-1}$, iv	Diazepam	
			Sedative	Anesthetic
Number of rats	10	4	5	6
Ca_{O_2} ($\mu mol \cdot ml^{-1}$)	8.97 ± 0.30	8.62 ± 0.28	8.31 ± 0.30	7.58* ± 0.55
$C(a-v)_{O_2}$ ($\mu mol \cdot ml^{-1}$)	0.74 ± 0.07	0.86 ± 0.05	1.76* ± 0.20	1.36* ± 0.20
CBF ($ml \cdot g^{-1} \cdot min^{-1}$)	6.79 ± 0.63	3.87* ± 0.35	2.04* ± 0.23	2.44* ± 0.59
CMR_{O_2} ($\mu mol \cdot g^{-1} \cdot min^{-1}$)	4.69 ± 0.19	3.33* ± 0.23	3.35* ± 0.17	2.91* ± 0.18

All animals' lungs were ventilated with CO_2, 7 per cent, and O_2, 30 per cent. Those serving as controls or given propranolol also received N_2O, 63 per cent, while the diazepam-injected rats were given N_2, 63 per cent.

* Significant difference from control value, $P < 0.05$.

propranolol. Thus, results obtained in man are not necessarily inconsistent with the present results.

There appears to have been no previous report of CMR_{O_2} or CBF values at CO_2 tensions higher than about 80 torr. Extensive data demonstrate that such hypercapnia gives rise to pronounced changes in function. Thus, whereas excitability (measured as threshold to electroshock seizures) is decreased at CO_2 concentrations below 25 per cent, concentrations of about 30 per cent may elicit spontaneous seizures, and those exceeding 40 per cent are accompanied by anesthesia.[22] The present results show that when Pa_{CO_2} is increased in steps above 80 torr there are gradual decreases in CMR_{O_2} and CBF. However, rats exposed to Pa_{CO_2} 300 torr had CMR_{O_2} values that were decreased by only 20–25 per cent below normocapnic control values. These results may reflect the fact that, whatever the level of consciousness, high CO_2 tensions tend to increase CMR_{O_2}.

Since the peripheral effects of hypercapnia include activation of the sympathoadrenal system with resultant release of adrenal catecholamines,[7–9,23] it seemed possible that such activation could contribute to the increase in CMR_{O_2}. However, since removal of the adrenal glands did not affect CMR_{O_2} or CBF, it appeared more likely that the mechanisms were intrinsic. In parallel studies, we could show that hypercapnia leads to an increase in the rate of hydroxylation of tyrosine to DOPA in the brain, and that this effect is not blocked by a decrease in Pa_{O_2}.[24] In contrast, such a decrease in P_{O_2} prevented the increase in hydroxylation of tryptophane that occurs with hypercapnia at normal P_{O_2} values. Working on the assumptions that hypercapnia increased catecholamine turnover in the brain, and that catecholamines induce increases in CMR_{O_2} and CBF,[25–27] the effects of propranolol and those of diazepam were tested. Propranolol has previously been shown to prevent increases in CMR_{O_2} and CBF due to catecholamines.[25–27] There are reasons to believe that diazepam should act similarly, although the mechanisms may be different. Thus, the drug has been reported to prevent an increase in cerebral norepinephrine turnover in stressful situations, probably via an effect on locus coeruleus neurons.[28,29]

The present results show that, during hypercapnia, both propranolol and diazepam decreased CMR_{O_2} to subnormal values and curtailed the increases in CBF. Previous results from the laboratory had shown that when propranolol, 2.5 $mg \cdot kg^{-1}$, is given to rats maintained on N_2O, 70 per cent, and O_2, 30 per cent, or when diazepam in sedative or anesthetic doses (2.25 or 7.5 $mg \cdot kg^{-1}$, iv, followed by infusion of 4.5 or 15 $mg \cdot kg \cdot h^{-1}$, respectively) is administered to animals ventilated with N_2, 70 per cent, and O_2, 30 per cent, there is no significant change in CMR_{O_2}, but a decrease in CBF following diazepam administration.[10,30] It may seem paradoxical that the drugs should decrease CMR_{O_2} in hypercapnic but not in normocapnic situations. However, the results may be explained if it is assumed that one basic effect of increased CO_2 tensions is to depress oxygen uptake of cortical cells, that this effect is masked by activation of catecholaminergic neurons whose activity secondarily increases CMR_{O_2}, and that propranolol and diazepam, by preventing this activation, unmask the inhibitory effects of hypercapnia on cortical cells.

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