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Modification of Cerebral Metabolic and Circulatory Response to Nitrous Oxide by Diazepam, Morphine or Hypocapnia in Dogs

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Abstract Modification of cerebral metabolic and circulatory response to nitrous oxide by prior administration of diazepam, morphine or induction of hypocapnia was studied in 24 dogs. Nitrous oxide (60 per cent end-tidal) increased cerebral oxygen consumption by 20 per cent and increased cerebral blood flow by 150 per cent initially and then cerebral blood flow declined to 50 per cent above the control during a 60-min period. Cerebrospinal fluid pressure significantly increased. Diazepam, 0.5 mg/kg, significantly attenuated cerebral metabolic and circulatory stimulation with nitrous oxide for 30 min. Morphine, 1 mg/kg, blocked the cerebral stimulation with nitrous oxide throughout the period. Increase in cerebrospinal fluid pressure was significantly attenuated by both drugs for the early period. Induced hypocapnia transiently but significantly attenuated the increases in cerebral blood flow and cerebrospinal fluid pressure with nitrous oxide, while cerebral oxygen consumption was unaffected. These results indicated that cerebral metabolic and circulatory response to nitrous oxide is attenuated or blocked by diazepam, morphine or induced hypocapnia in dogs.

Key words: cerebral metabolism and circulation, nitrous oxide, diazepam, morphine, hypocapnia

Introduction

Nitrous oxide, in combination with other intravenous or inhalational anesthetics has been widely used in clinical anesthesia, and its effects on cerebral oxygen consumption ($CMRo_2$) and blood flow (CBF) have been studied by several investigators. Carlsson et al[1]. showed a synergistic decrease in $CMRo_2$ with the combined use of diazepam and nitrous oxide in rats. Jobes et al[2]. reported that nitrous oxide-morphine anesthesia did

not affect $CMRo_2$ and CBF in humans, indicating no effect with either drug. In our laboratory we found that nitrous oxide increased $CMRo_2$ and CBF in dogs and these effects were blocked by thiamylal, a cerebral vasoconstrictor[3]. From this study, it had been anticipated that diazepam[4], morphine[5] and induced hypocapnia, also known to increase cerebrovascular resistance, may attenuate or block cerebral stimulation with nitrous oxide in dogs. This consideration led us to examine the interaction of nitrous oxide with diazepam, morphine or induced hypocapnia in dogs, and we found that they modified cerebral metabolic and circulatory responses to nitrous oxide in a way different from previous studies[1,2].

Materials and Methods

Twenty-four unpremedicated dogs, weighing 8–19 kg were anesthetized with halothane (1 to 2 per cent inspired) in oxygen, 40 per cent, and nitrogen. Succinylcholine, 2 mg/kg, was given intramuscularly to facilitate tracheal intubation and thereafter administered 8–10 mg/kg/h to maintain muscular paralysis. Ventilation was controlled with a Harvard pump through a cuffed endotracheal tube. In the supine position, both femoral arteries were cannulated for blood sampling and pressure monitoring, both femoral veins for infusion of drugs and lactated Ringer's solution, and the left external jugular vein for returning drained blood from the brain. Thereafter, dogs were placed in the prone position and then the surgical preparation for the measurement of CBF was made by the method originally described by Michenfelder et al[6]. Briefly, the skin of the head was incised and the parietal and temporal muscles were reflected. The sagittal sinus was exposed and isolated from extracerebral communications. After the dogs were heparinized by an initial dose of 2 mg/kg (1 mg/kg/h, subsequently), cannulation of the sagittal sinus was performed. The drained blood was returned to the external jugular vein. A suitably sized electromagnetic flowmeter probe (Nihon Kohden MF-46 with a lumen diameter of 3mm was placed around the cannula 1 cm away from draining portion of the sinus. To ensure exact measurements, the electromagnetic flowmeter (Nihon Kohden MFV-1100) incorporated a nonocclusive zero and a 1.0-sec time constant, and was frequently calibrated by direct timed measurement of sagittal sinus blood flow. After completion of surgery, the inspired halothane concentration was decreased to 0.2 per cent and at least one hour allowed to elapse before the start of the experiment. To minimize the noxious stimuli, lidocaine, 5 mg/kg, 0.5 per cent solution, was injected into the skin and muscle of the head and at the area where the cannulas were placed at the end of surgery. Additional lidocaine (half of the initial dose) was administered hourly.

Blood Po_2, Pco_2 and pH were measured with appropriate electrodes at 37°C (IL 313 electrodes). Pao_2 was maintained at 178±5 mmHg (mean± SEM) (23.7±0.7 kPa) by adjusting the inspired concentration of oxygen. $Paco_2$ was maintained at 37±1 mmHg (4.9±0.1 kPa) except for the case of dogs subjected to examination of the interaction of nitrous oxide with induced hypocapnia. The oxygen content of arterial and sagittal sinus blood was calculated from the measurements of oxyhemoglobin (IL 182 CO-oximeter) and oxygen tension. The EEG was recorded throughout the study, using parietal bipolar silver-silver chloride electrodes. The end-tidal concentrations of halothane and nitrous oxide were measured by gas chromatography. $CMRo_2$ was calculated as the product of CBF and the arterial-sagittal sinus blood oxygen content difference. Cerebrospinal fluid pressure (CSFP) was measured continuously through a 20-gauge needle inserted into the cisterna magna. Cerebral perfusion pressure (CPP) was calculated as the mean arterial pressure (MAP) minus CSFP. Cerebral vascular resistance (CVR) was calculated as the ratio of CPP to CBF.

Dogs were divided into four groups. In each group, control values were obtained before the administration of drugs or induced hypocapnia over a 20-min period, and the mean value of $CMRo_2$ was calculated from six to eight consecutive determinations of CBF and the arterial-sagittal sinus blood oxygen content difference. To examine the effects of nitrous oxide, MAP, CBF and arterial-sagittal sinus blood oxygen content difference were determined over a 120-min period divided into two intervals, an addition period and a withdrawal period, each lasting 60 min. At the beginning of the addition period, nitrous oxide was abruptly substituted for nitrogen in the inspired

gases. Sixty minutes later, nitrogen was again abruptly substitued for nitrous oxide. Measurements were made 3, 5, 7, 10, 15, 30, 45 and 60 min after the start of each period. In nitrous oxide (alone) group, 6 dogs, the effects of nitrous oxide, 60 per cent end-tidal, were examined during administration of halothane, 0.2 per cent. In diazepam group, 6 dogs, after the control measurement, diazepam, 0.5 mg/kg, was given intravenously over a 10-sec period. Following the measurement of CBF and $CMRo_2$ 5 min after the administration of diazepam, the effect of nitrous oxide was examined as in nitrous oxide group. In morphine group, 6 dogs, after the control measurement, morphine, 1.0 mg/kg, diluted in 20 ml of saline was infused over 20 min. At the end of morphine infusion, three consecutive determinations of CBF and $CMRo_2$ were made over a 6-min period and the mean values were calculated, and then the effects of nitrous oxide were examined, as in nitrous oxide group. In hypocapnia group, 6 dogs, after the control measurement, hypocapnia was induced to decrease $Paco_2$ from 39 ± 1 (5.2 ± 0.1 kPa) to 26 ± 1 mmHg (3.5 ± 0.1 kPa) by changing the inspired carbon dioxide concentration. Fifteen minutes were allowed to elapse for stabilization and six consecutive determinations of CBF and $CMRo_2$ were made over a 12-min period, mean values were calculated, and then the effects of nitrous oxide were examined, as in nitrous oxide group. Nasopharygeal temperature was monitored and maintained at 37.5 ± 0.1°C with the aid of an electric heating pad. Hemoglobin levels were maintained at 14 ± 0.2 g/dl. The percentage of the total brain weight drained from the sagittal sinus was determined by injecting colored vinyl acetate at the completion of each experiment and was used to convert units of flow ml/min to ml/100g/min. Results were tested for statistical significance by two-way analysis of variance with critical difference. $P<0.05$ was considered significant.

Results

Results of each experimental group are summarized in Tables 1, 2, 3 and 4. Changes in $CMRo_2$ and CBF in each group are shown as the per cent of control values in Fig. 1 and 2, respectively. Sixty per cent nitrous oxide, when added to halothane, 0.2 per cent, produced a significant increase in $CMRo_2$ by about 20 per cent from 5 to 60 min (Table 1). The mean CBF increased by 100 to 150 per cent from 5 to 30 min, and then gradually declined to a level of about 50 per cent above the control at 60 min, while no significant change in CPP was observed. The increase in CBF was accompanied by a significant decrease in CVR and by a significant increase in sagittal sinus blood Po_2 ($Psso_2$). The mean CSFP significantly increased by 45 to 80 per cent at 3 to 15 min. Predominant EEG frequencies shifted from 12–14 Hz to 6–8 Hz with the addition of nitrous oxide as shown in Fig. 3. These cerebral metabolic, circulatory and EEG changes became insignificant 5 min after the withdrawal of nitrous oxide. Diazepam produced a significant decrease in $CMRo_2$ by 12 per cent at 5 min with the parallel decrease in CBF. The changes in EEG were variable, showing either slow wave in some and fast wave in others with addition of nitrous oxide but no apparent relationship between EEG and $CMRo_2$ was observed. With the addition of nitrous oxide ,the mean $CMRo_2$ and CBF did not increase significantly as compared to the control values, although there was a decrease in CVR and tendency toward an increase in CBF 30 min after the addition of nitrous oxide. When these changes were compared to the results of nitrous oxide group, the response was significantly attenuated for 30 min. There was no significant increase in CSFP with the addition of nitrous oxide for the first 15 min, but at 30 min, CSFP increased significantly. With morphine, the decrease in $CMRo_2$ 16 per cent was accompanied by a decrease in CBF of the same magnitude, though it was statistically insignificant. The decrease in $CMRo_2$ and CBF was accompanied by EEG slowing (Fig. 4). With the addition of nitrous oxide, no significant increases in $CMRo_2$ and CBF from the control were observed. The mean CSFP did not increase with the addition of nitrous oxide

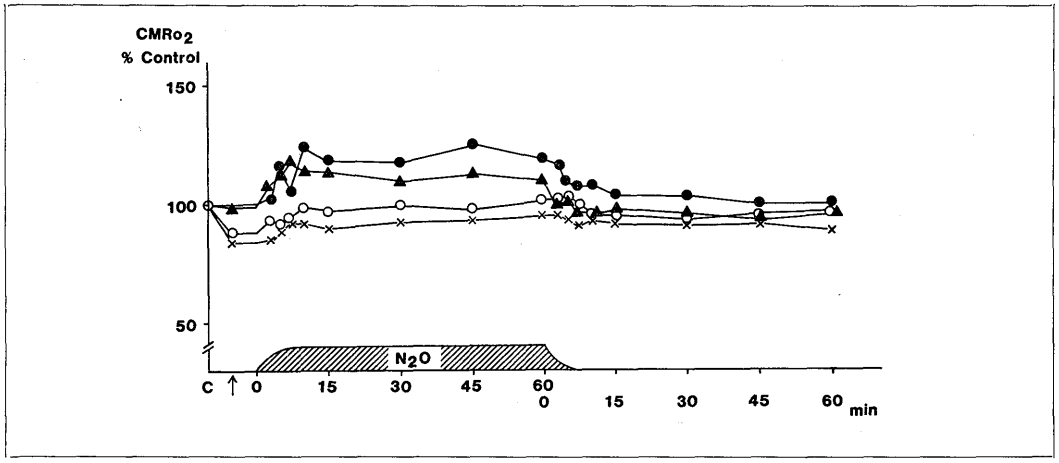

Fig. 1 Effects of nitrous oxide, 60 per cent end-tidal, on $CMRo_2$. ●; nitrous oxide alone group, ○; diazepam (0.5 mg/kg) group, ×; morphine (1.0 mg/kg) group, ▲; hypocapnia ($Paco_2$, 26±1 mmHg) group. C indicates the control values. Arrow indicates the values after the administration of drugs or induced hypocapnia.

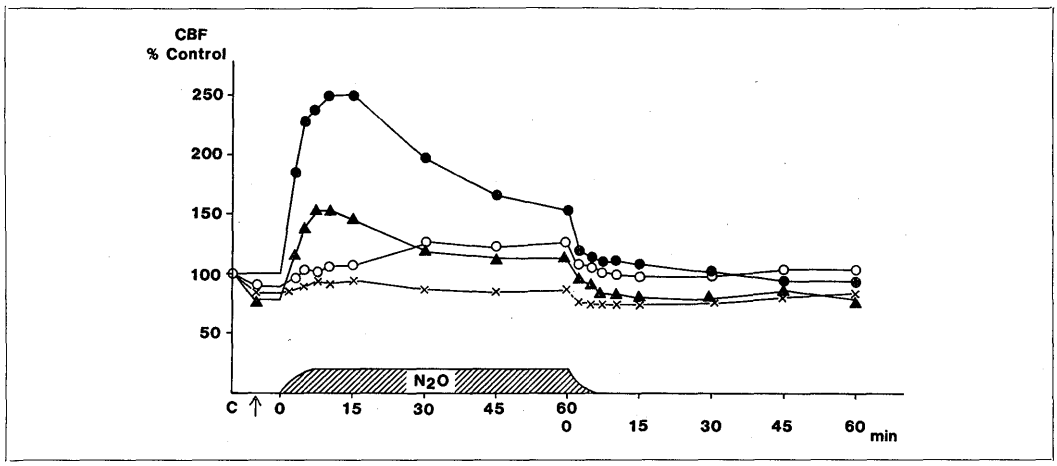

Fig. 2 Effects of nitrous oxide, 60 per cent end-tidal, on CBF. Symbols and abbreviations are similar to those of Fig. 1.

until 30 min and, thereafter, slight increase was observed. After the withdrawal, the mean $CMRo_2$ and CBF remained decreased and slow wave activity continued. With hypocapnia, $Paco_2$ 26±1 mmHg (3.5±0.1 kPa), 15 min after stabilization, the mean $CMRo_2$ did not change significantly, but the mean CBF decreased by 18 per cent as compared to the control. The decrease in CBF was accompanied by significant decrease in $Psso_2$. With the addition of nitrous oxide, $CMRo_2$ and CBF increased by a maximum of 14 and 52 per cent of the control, respectively, but the increases were signifi-

Table 1 The Effects of 60 per cent Nitrous Oxide on Cerebral Metabolism and Circulation

	Time (min)	$CMRo_2$ ($ml \cdot 100g^{-1} \cdot min^{-1}$)	CBF ($ml \cdot 100g^{-1} \cdot min^{-1}$)	CVR ($mmHg \cdot ml^{-1} \cdot 100g \cdot min$)	CPP (mmHg)	CSFP (mmHg)	$Psso_2$ (kPa)
Control	—	6.71±0.12	59±6	1.90±0.22	107±5	11±2	4.4±0.3
N_2O addition	5	7.62±0.30*	135±32*	0.95±0.15*	105±6	20±3*	6.5±0.4*
	10	8.25±0.26*	148±30*	0.85±0.14*	107±8	19±3*	6.7±0.5*
	30	7.88±0.16*	116±20*	1.12±0.19*	112±5	11±2	5.8±0.4*
	60	7.91±0.45*	90±14*	1.33±0.16*	110±4	11±2	5.1±0.3*
withdrawal	5	7.30±0.24	66± 9	1.83±0.23	112±5	9±1	4.3±0.3
	10	7.18±0.25	65±11	1.86±0.27	109±6	10±1	4.1±0.3
	30	6.83±0.36	59± 5	1.76±0.17	100±5	11±2	4.0±0.3
	60	6.57±0.38	56± 5	1.96±0.26	105±6	12±2	4.3±0.4

The values are mean±SE.
* Significantly different from control ($P<0.05$).

Table 2 Interaction of 60 per cent Nitrous Oxide with Diazepam in Cerebral Metabolism and Circulation

	Time (min)	$CMRo_2$ ($ml.\ 100g^{-1} \cdot min^{-1}$)	CBF ($ml.\ 100g^{-1} \cdot min^{-1}$)	CVR ($mmHg \cdot ml^{-1} \cdot 100g \cdot min$)	CPP (mmHg)	CSFP (mmHg)	$Psso_2$ (kPa)
Control	—	6.67±0.32	58±2	2.07±0.09	120±5	9±1	4.8±0.4
Diazepam 0.5mg/kg	5	5.89±0.31*	,51±3	2.15±0.13	110±5	10±1	4.4±0.3
N_2O addition	5	6.06±0.26#	59±3#	1.86±0.12#	109±7	12±1#	4.9±0.3#
	10	6.55±0.31#	62±4#	1.83±0.14#	111±8	12±1#	4.5±0.3#
	30	6.60±0.21#	72±6#	1.60±0.13*#	112±8	15±2*	5.3±0.3*
	60	6.75±0.07#	73±4	1.59±0.10*	115±6	12±1	5.1±0.4
withdrawal	5	6.86±0.26	62±3	1.82±0.10	113±8	12±1	4.5±0.3
	10	6.39±0.31#	58±2	1.98±0.10	114±6	11±1	4.4±0.3
	30	6.20±0.27	57±3	1.97±0.10	111±7	12±1	4.1±0.3
	60	6.47±0.32	60±3	1.86±0.17	111±8	12±2	4.4±0.4

The values are mean±SE.
* Significantly different from control ($P<0.05$).
# Significantly different from the values in group anesthetized with nitrous oxide alone at corresponding time ($P<0.05$).

Table 3 Interaction of 60 per cent Nitrous Oxide with Morphine in Cerebral Metabolism and Circulation

	Time (min)	$CMRO_2$ ($ml \cdot 100g^{-1} \cdot min^{-1}$)	CBF ($ml \cdot 100g^{-1} \cdot min^{-1}$)	CVR ($mmHg \cdot ml^{-1} \cdot 100g \cdot min$)	CPP (mmHg)	CSFP (mmHg)	$Psso_2$ (kPa)
Control	—	6.23±0.15	61±4	1.91±0.11	114±5	8±1	5.1±0.3
Morphine 1 mg/kg	20	5.24±0.21*	51±2	1.96±0.18	97±5	10±1	5.3±0.3
N_2O addition	5	5.51±0.27*#	54±3#	1.81±0.17#	96±5	11±1#	5.3±0.4#
	10	5.66±0.26#	56±4#	1.91±0.21#	104±5	11±1#	5.3±0.3#
	30	5.73±0.27#	53±2#	1.90±0.13#	99±4	12±1*	5.2±0.4
	60	5.91±0.17#	53±2#	1.94±0.12#	101±4	12±1*	4.9±0.5
withdrawal	5	5.78±0.17#	46±2	2.15±0.14	98±4*	11±1	4.5±0.4
	10	5.74±0.15#	46±2	2.18±0.17	98±5*	11±1	4.5±0.3
	30	5.68±0.15#	48±2	1.87±0.13	88±4*	13±1*	4.7±0.3
	60	5.46±0.09*#	50±2	1.87±0.11	92±4*	13±1*	4.7±0.1

The values are mean±SE.
* Significantly different from control ($P<0.05$).
# Significantly different from the values in group anesthetized with nitrous oxide alone at corresponding time ($P<0.05$).

Table 4 Interaction of Hypocapnia with 60 per cent Nitrous Oxide in Cerebral Metabolism and Circulation

	Time (min)	$CMRO_2$ ($ml \cdot 100g^{-1} \cdot min^{-1}$)	CBF ($ml \cdot 100g^{-1} \cdot min^{-1}$)	CVR ($mmHg \cdot ml^{-1} \cdot 100g \cdot min$)	CPP (mmHg)	CSFP (mmHg)	$Psso_2$ (kPa)
Control	—	6.95±0.35	71±5	1.62±0.22	111±1	12±1	4.4±0.1
Hypocapnia	15	6.90±0.46	58±4	1.91±0.22	109±11	10±1	3.5±0.1*
N_2O addition	5	7.88±0.58*	99±14*#	1.36±0.21#	125±11#	15±1*#	4.4±0.4#
	10	7.92±0.55*	108±13*#	1.07±0.16*	115±12	17±1*	4.7±0.4#
	30	7.57±0.55	86±11#	1.40±0.15	111±7	14±2	4.3±0.3#
	60	7.61±0.48	80±5	1.37±0.15	107±9	15±2#	4.1±0.4#
withdrawal	5	7.06±0.55	64±6	1.81±0.23	112±5	14±3#	3.5±0.3*#
	10	6.66±0.54	59±6	1.97±0.25*	112±4	13±1	3.3±0.1*#
	30	6.59±0.45	56±6	1.91±0.31	103±8	12±2	3.3±0.1*
	60	6.75±0.34	57±6	2.01±0.33*	110±9	12±1	3.3±0.1*#

The values are mean±SE.
* Signifiaantly different from control ($P<0.05$).
# Significantly different from the values in group anesthetized with nitrous oxide alone at corresponding time ($P<0.05$).

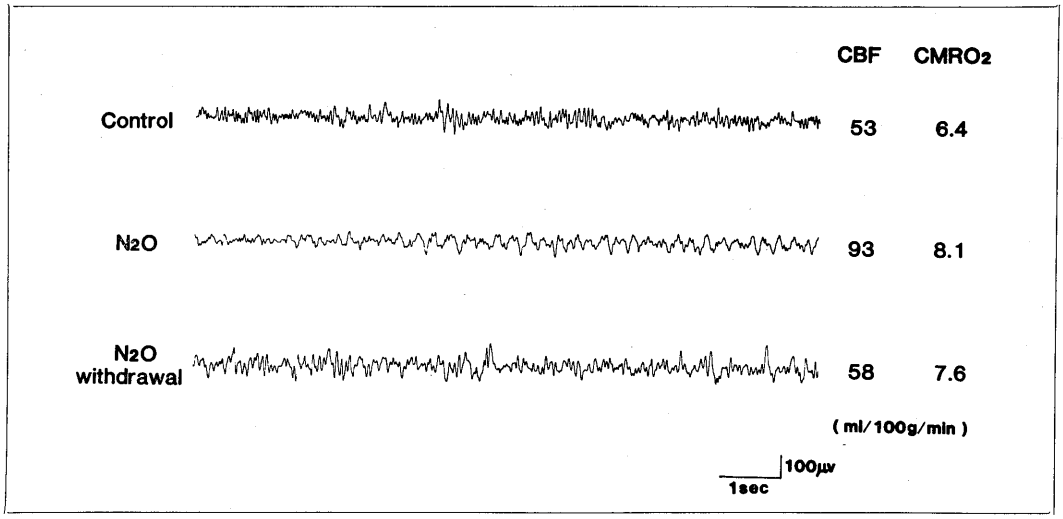

Fig. 3 Representative EEG pattens with corresponding values of $CMRo_2$ and CBF. Recordings of N_2O and N_2O withdrawal were taken at 10 min after the addition of nitrous oxide and after the withdrawal, respectively.

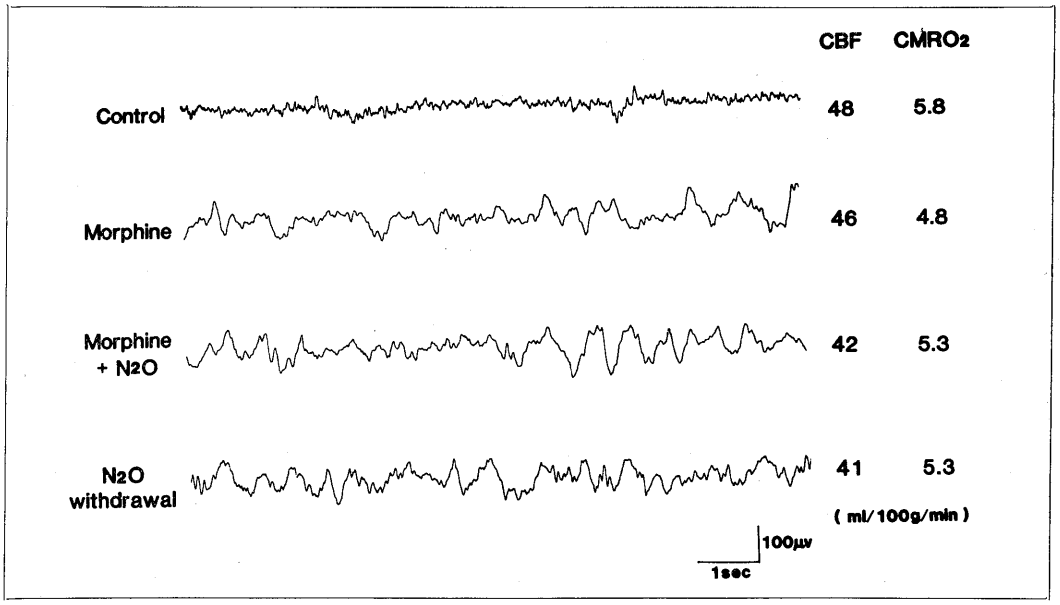

Fig. 4 Representative EEG patterns with corresponding values ef $CMRo_2$ and CBF. Morphine recording was taken at 20 min after the administratien. Morphine + N_2O and N_2O withdrawal recordings were taken at 10 min after the addition of nitrous oxide and after the withdrawal, respectively.

cantly less than those of nitrous oxide group .These cerebral metabolic and circulatory changes were accompanied by EEG slowing with the addition of nitrous oxide. EEG returned to the control pattern upon withdrawal. The mean CSFP increased for the early addition period (5 to 7 min), but the increase was significantly less than that of nitrous oxide group. The mean CSFP for the later period was higher than that of nitrous oxide group, despites continued hypocapnia.

Discussion

The present study, using the venous outflow method[6], reconfirms the cerebral metabolic and circulatory stimulation of nitrous oxide in dogs, and demonstrates that the effects of nitrous oxide are modified by the combined use of diazepam, morphine or by induced hypocapnia. The effects of nitrous oxide on cerebral metabolism and flow are conflicting. The studies in dogs, including the present study, revealed increases in $CMRo_2$ and CBF with nitrous oxide[3,7,8] On the other hand, in rats, Carlsson et al[9], using the modified Kety-Schmidt technique, found no significant difference in $CMRo_2$ and CBF between animals ventilated on nitrous oxide, 70 per cent, and those on nitrogen, 70 per cent. Three subsequent studies[10,11,12] from the same laboratory, using autoradiographic technique, suggested that immobilization with neuromuscular blockade and artificial ventilation in addition to nitrous oxide may increase cerebral blood flow and cerebral glucose utilization which is generally assumed to parallel with cerebral oxygen consumption. Pelligrino et al[13], however recently demonstrated that in freely ventilating, nonstressed goats, nitrous oxide, 70 per cent, increased CBF and $CMRo_2$, particularly in the cortical areas and they postulated that these changes can be attributed to a direct effect of nitrous oxide on the cerebral metabolism and blood flow, and not to factors related to the basic experimental preparation .This is in good agreement, at least qualitatively, with the present study. In humans, the variable effects of nitrous oxide on $CMRo_2$ and CBF have been reported from one laboratory (see review article by Smith and Wollman[14]), but their most recent report[2] showed no significant effect of nitrous oxide on $CMRo_2$ and CBF. We have no satisfactory explanation for this difference among rats, dogs, goats and humans at the present time except difference in species and/or methodology. Diazepam given before nitrous oxide inhalation blocked the cerebral metabolic and circulatory stimulation with nitrous oxide and then $CMRo_2$ and CBF tended to increase with time, suggesting that the action of diazepam has subsided. However, Carlsson et al[1] found a synergistic depression of $CMRo_2$ and CBF, to about 60 per cent of control in the paralized and artificially ventilated rats. The effects of the combined use of nitrous oxide with diazepam on $CMRo_2$ and CBF in rats with immobilization may be different from those in freely ventilating rats since it appears that in rats immobilization modifies drug's effect on $CMRo_2$ and CBF. Whatever the explanation, our results demonstrate that diazepam prevents cerebral metabolic and circulatory response to nitrous oxide.

Our present observation shows that CBF and $CMRo_2$ do not significantly change with combination of morphine and nitrous oxide. As described above, Jobes et al[2]. reported that in human volunteers, nitrous oxide combined with morphine did not affect $CMRo_2$ and CBF. Their results are seemingly similar to ours. They indicated, however, that neither nitrous oxide or morphine altered $CMRo_2$ and CBF. In contrast, we found that increases in CBF and $CMRo_2$ with nitrous oxide were completely blocked by morphine, suggesting a competitive interaction between morphine and nitrous oxide, and that predominant slow wave activity was

accompanied by seemingly unchanged $CMRo_2$. This discrepancy may be explained at least in part by the difference in methodology. In the present study, hemispheric, particularly cortical flow, was measured, while Jobes et al[2]. measured the blood flow of the whole brain.

Our previous study demonstrated that thiamylal completely blocked the stimulating effect of nitrous oxide[3]. The possible involvement of the metabolic depressive effect in blocking an increase in CBF with nitrous oxide must be discussed since barbiturates, diazepam and morphine have been known to decrease $CMRo_2$. If there is tight coupling between metabolism and blood flow, the blocking effect of these drugs on the cerebral circulatory response to nitrous oxide may be a secondary manifestation of the metabolic depressive action of these drugs. This may be supported by $Psso_2$ unchanged from the control in both the diazepam and morphine groups. With induced hypocapnia, however, the increase in CBF is significantly attenuated while the increase in $CMRo_2$ remains essentially unaffected. This result suggests that vasoconstriction produced by hypocapnia counteracts the cerebral vasodilating effect of nitrous oxide through the mechanism which may be unrelated to metabolic control.

It has been believed that the qualitative effect of drugs on CSFP can be predicted from the effect of drugs on CBF and CVR. In patients, who has a decreased intracranial compliance, nitrous oxide-induced increases in intracranial pressure (ICP) have been reported[15]. Tateishi et al[16]. reported that a clinical dose of diazepam caused a minimal decrease in ICP in humans. The decreasing effect of ICP with diazepam and thiopental during nitrous oxide inhalation in a case with intracranial disorder was reported by Phirbin and Shapiro[17]. The present results prove that pretreatment with diazepam or morphine prevented significant increases in CBF and CSFP with nitrous oxide. Both diazepam and morphine block the increase in CSFP, perhaps by preventing the increase in intracranial blood volume when they are used before inhalation of nitrous oxide. Our finding in diazepam group that CSFP increased after 30 min following inhalation of nitrous oxide with a parallel increase in CBF, suggests that the opposing effect of diazepam to the nitrous oxide-induced increase in CBF and CSFP have subsided at this time. These results may account for the findings by Henriksen and Jorgensen[15] that diazepam premedication (10 mg) administered an hour prior to anesthesia in a series of neurosurgical patients did not prevent an increase in ICP due to subsequent exposure to nitrous oxide. The increase in CSFP in the later stages of the addition period and the withdrawal period from the control in the morphine group cannot be readily explained by the present results, suggesting the need for further study which includes the consideration of cerebrospinal fluid formation and absorption.

It has been known that induced hypocapnia prevents the increase in CSFP produced by the administration of inhalational anesthetics which have cerebral vasodilative effect. Misfeldt et al[18]. reported that nitrous oxide caused only a minor increase in ICP in patients with increased ICP when hypocapnia had been induced before nitrous oxide. In the present study, the decreasing effect of CSFP with hypocapnia was temporary and the greater value of CSFP was observed 60 min following the nitrous oxide inhalation. This effect may result from prolonged hypocapnia, about 100 min in this study, since it has been reported that decreased CSFP or CBF gradually returns to or overshoots prehypocapnia level during continued hyperventilation[19,20].

In summary the present study reveals that, increases in canine $CMRo_2$, CBF and CSFP with nitrous oxide can be prevented,

totally or partially, by prior administration of diazepam or morphine or by hypocapnia.

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