Anesthesiology
70:787–792, 1989

Different 1.2 MAC Combinations of Nitrous Oxide–Enflurane Cause Unique Cerebral and Spinal Cord Metabolic Responses in the Rat

Daniel J. Cole, M.D., Harvey M. Shapiro, M.D.†*

The effect of three different 1.2 MAC combinations of nitrous oxide (N_2O) and enflurane upon glucose metabolism in the central nervous system was evaluated in male rats (n = 30). Anesthesia was induced with enflurane and N_2O prior to tracheal intubation and mechanical ventilation. Physiologic variables (temperature, blood pressure, *p*H, Pa_{O_2}, Pa_{CO_2}, serum glucose, and hematocrit) were maintained within normal limits. Each rat was randomly assigned one of the following 1.2 MAC anesthetic regimens: 1) control—0% N_2O/2.76% enflurane, 2) treatment I—30% N_2O/2.26% enflurane, or 3) treatment II—60% N_2O/2.12% enflurane. Following anesthetic equilibration, an autoradiographic evaluation of local cerebral and spinal cord glucose utilization was performed. There were no differences in the physiologic data. As enflurane was partially replaced by an equivalent MAC fraction of N_2O (0–30%), a heterogeneous activation of cerebral metabolism was observed in selected sensory input structures, and in components of the limbic system. The values tended to return to control when N_2O was increased to 60% (and the enflurane was appropriately reduced). At all spinal cord levels, a homogeneous increase in metabolism was observed in both white and grey matter when enflurane was replaced by the 0–30% N_2O change, with a return to control when the N_2O was further increased from 30–60%. Thus, in rats, increasing the N_2O concentration (while concurrently decreasing enflurane) produced a biphasic metabolic response. Metabolism was activated when N_2O was increased from 0–30%, with a relative depression in metabolism when N_2O was further increased from 30–60%. These results may have implications in elucidating an anatomical site(s) of action for either N_2O or enflurane; and in the selection of an optimal anesthetic when metabolic suppression of the central nervous system is considered. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, volatile: enflurane. Brain, metabolism: glucose utilization. Spinal cord: metabolism.)

NITROUS OXIDE (N_2O) is a common component of many clinical anesthetic regimens, often in combination with a volatile anesthetic agent such as enflurane. Despite the ability of concurrent doses of N_2O and enflurane to additively contribute to anesthetic depth, previous studies have demonstrated marked differences in the neurophysiological properties of N_2O and enflurane. One such property that has shown differences is the affect of N_2O and enflurane upon central nervous system metabolism.[1–9] Metabolic differences may be of interest to anesthetic practice for many reasons, two of which include: 1) the metabolic properties of an anesthetic may provide evidence regarding a potential mechanism of anesthetic action, and 2) the metabolic state may influence neuronal outcome following a central nervous system insult.

As a surgical plane of anesthesia can be obtained with enflurane, it is possible to evaluate the dose-dependent effect of enflurane upon specific neurophysiological properties, such as metabolism. Previous studies have demonstrated that enflurane has a dose-dependent excitatory and depressant effect upon cerebral metabolism.[10,11] However, as a surgical plane of anesthesia cannot be obtained with N_2O (without the use of a hyperbaric chamber), it is impossible to evaluate the effect of N_2O upon central nervous system metabolism over a similar dosage range. The metabolic properties of N_2O have therefore been evaluated either during a N_2O anesthetic administered at sub-MAC levels to previously awake, restrained animals, or during the addition of N_2O to a previously established surgical plane of anesthesia.[12–21]

In this study, we evaluated the effect of three different 1.2 MAC combinations of N_2O and enflurane on cerebral and spinal cord glucose utilization. We did this to identify possible central nervous system interactive effects of N_2O and enflurane.

Methods

Following approval by the Institutional Animal Research Committee, male, Sprague-Dawley rats (n = 30) of similar ages and weights were administered one of three 1.2 MAC anesthetic regimens (N_2O/enflurane) based on N_2O concentrations of 0, 30, or 60%. An 1.0 MAC value for each N_2O/enflurane combination was determined in previous studies in our laboratory, and the remaining 0.2 MAC of anesthesia was delivered as an enflurane MAC fraction.[9] (Enflurane MAC at the three different N_2O concentrations was: 0% N_2O–enflurane = 2.30%, 30% N_2O–enflurane = 1.85%, and 60% N_2O–enflurane = 1.75%. An additional 0.46% of enflurane was added

* Assistant Professor of Anesthesiology, Loma Linda University. Work performed as a neuroanesthesia research fellow at the University of California at San Diego.

† Professor and Chairman, Department of Anesthesiology; and Professor of Neurosurgery, University of California at San Diego.

Received from the Departments of Anesthesiology, Veteran's Administration Medical Center, San Diego, California; University of California at San Diego, La Jolla, California; and the Department of Anesthesiology, Loma Linda University, Loma Linda, California. Accepted for publication December 26, 1988.

Address reprint requests to Dr. Shapiro: Department of Anesthesiology, T-001, University of California at San Diego, La Jolla, California 92093.

TABLE 1. Physiologic and Pharmacologic Conditions at the Time of the Metabolic Study (Mean ± SD). The Anesthetic Levels are Presented as End-tidal Concentrations

	Control	30% N2O	60% N2O
Age (days)	83 ± 5	84 ± 5	86 ± 5
Weight (g)	314 ± 8	316 ± 12	314 ± 12
*p*H (units)	7.41 ± 0.04	7.42 ± 0.02	7.42 ± 0.03
Pa_{O_2} (mmHg)	120.3 ± 28.9	117.9 ± 15.9	108.7 ± 19.4
Pa_{CO_2} (mmHg)	37.9 ± 1.4	37.1 ± 1.1	37.3 ± 0.8
Hematocrit (%)	41 ± 2	41 ± 2	42 ± 3
Mean arterial pressure (mmHg)	78 ± 4	78 ± 5	81 ± 8
Serum glucose (mg/dl)	170 ± 31	172 ± 23	178 ± 26
Nitrous oxide (%)	0.00	30.8 ± 0.7	61.2 ± 0.9
Enflurane (%)	2.76 ± 0.04	2.26 ± 0.08	2.12 ± 0.10

to each of the enflurane concentrations for an additive 1.2 MAC.)

All studies were performed between 0700–1500 h. Anesthesia was induced in a 2.5-liter plexiglass box with a fresh gas flow of 1.5 liters/minute (consisting of a 50: 50 ratio of oxygen and N_2O with 3.0% enflurane). The trachea of each anesthetized rat was then intubated using the otoscope method and the lungs were mechanically ventilated with a Harvard® Rodent ventilator adjusted to maintain physiologic arterial blood gas parameters. Each rat was then randomly assigned one of the following anesthetic protocols for a 120-min anesthetic stabilization period: control—N_2O-0%/enflurane-2.76%; treatment I—N_2O-30%/enflurane-2.28%; treatment II—N_2O-60%/enflurane-2.12%. An air/oxygen mixture at a total fresh gas flow of 1.0 liter/minute was delivered, with a FI_{O_2} of 40%.

The first 30 min of the stabilization period consisted of a preparatory period during which the femoral vessels were cannulated. Arterial and venous catheters were inserted in the right groin for continuous blood pressure monitoring, and drug and isotope administration. A low dead space (6 μl) arterial to venous shunt with a sampling side-arm was placed in the left groin for rapid blood collection. Following the surgical period, 90 min was allowed during which the rat was left undisturbed. No local anesthetic was used at the incision site. Using microsample technique (<100 μl), arterial blood gas analysis was performed by a Radiometer® blood gas analyzer. Rectal temperature (Yellow Springs Instruments®) was servo-controlled at 37° C with a heat lamp.

The endotracheal tube was constructed of PE-240 tubing (14-gauge) and was attached to inspiratory and expiratory circuits with a Y-connector. A Cordis® catheter introducer system was permanently placed at the bifurcation of the Y-connector, and was modified to allow the passage of a 20-gauge blunt needle through a leak-free orifice. End-tidal gases (enflurane, N_2O, oxygen, and carbon dioxide) were sampled with a Perkin-Elmer® mass spectrometer with a sampling rate of 60 ml/minute. Sampling was achieved by passing a lubricated 20-gauge blunt needle through the Cordis® catheter port site to the tip of the endotracheal tube. During the sampling period (1 min) the respiratory frequency was decreased to 40 breaths/minute and the tidal volume was increased by 33%. This technique allowed for optimal differentiation of the respiratory phases with neglible disturbance of ventilation (as indicated by stable arterial blood gas measurements during mass spectrometry sampling). A more rapid ventilation rate during the sampling period did not allow for mass spectrometry differentiation of the expiratory and inspiratory respiratory phases. The tidal volume was increased to compensate for the decrease in minute ventilation caused by the decrease in respiratory rate.

Anesthetic equilibration of the desired anesthetic regimen was verified at the conclusion of the 120-min anesthetic stabilization period, and was defined as end-tidal samples of anesthetic gas(es) at 5-min intervals that differed by less than 5% over a 20-min time span.

The following physiologic variables were monitored and maintained within normal ranges (*p*H, Pa_{CO_2}, Pa_{O_2}, mean arterial pressure, serum glucose, and hematocrit). At the conclusion of the anesthetic stabilization period, 100 μCi/kg of ^{14}C-2-deoxyglucose was administered and a quantitative evaluation of local cerebral and spinal cord glucose utilization was performed.[22] Timed collection of 14 arterial blood samples (50–100 μl) occurred over a 45-min period for determination of plasma glucose levels, and arterial ^{14}C-2-deoxyglucose activity. At the end of the study period the rat was decapitated and the brain and spinal cord were rapidly removed and frozen in 2-methyl-butane cooled to −35° C with freon. The brain and spinal cord were cut in 20-micron sections using a cryostat at −20° C. Each section was rapidly dried on a hot plate (60° C) and subsequently exposed with six ^{14}C-methylmethacrylate calibrated standards to single-emulsion x-ray film (Kodak SB-5®) for 21 days. Following film development, optical densities were determined on 41 brain and 18 spinal cord structures by an auto-scanning densitometer (Optronics®, P-1000, International, Inc.) with an aperature of 200 μm. All data were collected online with a Prime® computer for calculation of local cerebral and spinal cord utilization of glucose.[22] A lumped constant of 0.48 was used.

The physiologic and metabolic data were analyzed by Dunnett's *t* test comparing treatment groups (30% and 60% N_2O) to control (0% N_2O).[23] A *P* value of less than 0.05 was considered significant.

Results

The physiologic and pharmacologic data at the time of the metabolic study are presented in table 1. There were no differences between the treatment groups (30

TABLE 2. Local Cerebral Metabolism of Glucose ($\mu mol \cdot 100\ g^{-1} \cdot min^{-1}$ [mean ± SD])

	Abbreviation	Control	30% N2O	60% N2O
Auditory system				
Cortex	AC	77 ± 8	79 ± 9	80 ± 7
Medial geniculate	MG	55 ± 7	63 ± 10*	59 ± 7
Inferior colliculus	IC	73 ± 9	85 ± 8*	73 ± 8
Olivary body	OB	81 ± 12	100 ± 10*	84 ± 13
Cochlear nucleus	CN	171 ± 21	157 ± 24	145 ± 26*
Lateral lemniscus	LL	71 ± 12	80 ± 12	81 ± 9
Visual system				
Cortex	VC	67 ± 12	74 ± 10	65 ± 6
Lateral geniculate	LG	40 ± 11	48 ± 15	46 ± 17
Superior colliculus	SC	63 ± 11	74 ± 9*	71 ± 9
Sensorimotor system				
Cortex	SM	80 ± 13	78 ± 11	76 ± 11
Thalamus:ventral	VT	59 ± 11	73 ± 10*	67 ± 12
Thalamus:dorsomedial	DT	59 ± 9	73 ± 9*	68 ± 9
Periventricular grey	PG	71 ± 10	71 ± 5	71 ± 7
Cerebellar grey	CG	86 ± 13	86 ± 9	83 ± 20
Extrapyramidal				
Caudate-putamen	CP	78 ± 8	83 ± 9	83 ± 14
Globus pallidus	GP	78 ± 14	72 ± 11	74 ± 12
Substantia nigra	SU	77 ± 24	75 ± 17	86 ± 21
Red nucleus	RN	91 ± 16	103 ± 14	103 ± 17
Limbic system				
Cingulate gyrus	CI	50 ± 6	61 ± 15	63 ± 14*
Entorhinal cortex	EC	61 ± 7	70 ± 12*	67 ± 8
Claustrum	CL	59 ± 8	64 ± 9	65 ± 10
Nucleus accumbens	AN	57 ± 9	60 ± 11	63 ± 5
Septal nucleus	SN	49 ± 10	55 ± 10	52 ± 6
Piriform cortex	PC	65 ± 6	72 ± 9	86 ± 20*
Amygdala	AM	58 ± 8	64 ± 9	60 ± 8
Hypothalamus	HT	62 ± 10	62 ± 10	61 ± 7
Hippocampus	HH	63 ± 9	73 ± 9*	71 ± 8*
Dentate gyrus	DH	90 ± 22	103 ± 15	90 ± 15
Ammons horn	AH	67 ± 7	71 ± 13	75 ± 12
Ventral hippocampus (CA1 + CA3)	VH	63 ± 12	74 ± 15	67 ± 10
Interpeduncular nucleus	IN	56 ± 7	64 ± 14	62 ± 8
Mammillary bodies	MB	86 ± 14	90 ± 15	92 ± 16
Habenula	HA	97 ± 8	100 ± 13	100 ± 27
Pineal body	PB	119 ± 22	109 ± 40	112 ± 29
Myelinated fiber tract				
Corpus callosum	CC	54 ± 6	56 ± 9	55 ± 6
Internal capsule	IW	54 ± 11	57 ± 8	58 ± 11
Cerebellar white	CW	64 ± 8	72 ± 7*	72 ± 16*
Medial lemniscus	ML	54 ± 12	59 ± 8	61 ± 11
Cerebral association areas				
Frontal cortex	FC	76 ± 12	71 ± 6	69 ± 9
Reticular formation	RF	56 ± 8	65 ± 8*	65 ± 8*
Midbrain				
Pons	PO	90 ± 15	99 ± 27	84 ± 13

* Difference from control at $P < 0.05$.

and 60% N_2O) and the control group (0% N_2O) in age, weight, pH, Pa_{CO_2}, Pa_{O_2}, hematocrit, temperature, or mean arterial pressure.

The cerebral metabolic values are listed in table 2, and the relative changes are summarized in figure 1. As the enflurane contribution to MAC was replaced by an equal MAC fraction of 30% N_2O, an activation of cerebral metabolism occurred in selected sensory input structures, and in components of limbic system. As the MAC fraction of N_2O was further increased from 30–60% there was a tendency for local metabolism to return to control; however, this was not evident in all cerebral structures in which a metabolic change had occurred for the 0–30% N_2O incremental change. Of particular note is the preferential activation of sub-cortical auditory system structures. The spinal cord metabolic values are listed in table 3, and summarized in figure 2. As N_2O was increased from 0–30% (with enflurane concurrently reduced), there was an observed homogeneous activation of spinal cord metabolism in both white and gray matter structures at all spinal cord levels. When the N_2O was further increased from 30–60%, the metabolic values returned to control.

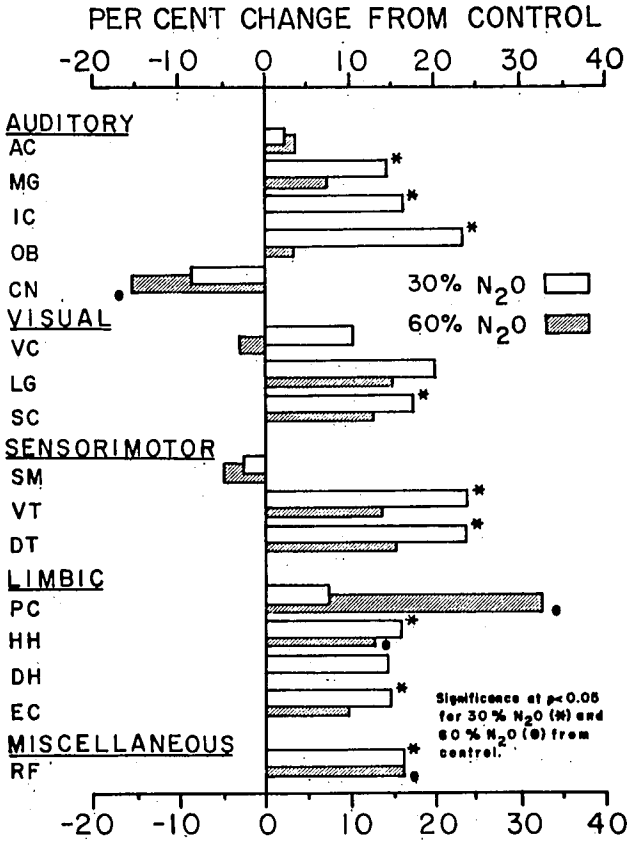

FIG. 1. Summary of differences as a percent change in the local cerebral metabolism of glucose for the 30% and 60% N_2O groups from 0% N_2O control values. The (*) represents a difference from control for the 30% N_2O group, and the (●) represents a difference from control for the 60% N_2O group ($P < 0.05$). Abbreviations for brain structures are given in table 3.

Discussion

Evaluated in the methodological context of the present study, the above results suggest that 1.2 MAC combinations of N_2O and enflurane produce a biphasic metabolic response in the central nervous system. If the 0% N_2O metabolic values are considered baseline, addition of 30% N_2O resulted in an activation of cerebral and spinal cord metabolism. When the 60% N_2O group is compared to the 0% N_2O group, few differences exist in the brain, and no differences are evident in the spinal cord. This finding has not previously been described, and may be due to the manner in which N_2O was utilized in this study.

In the present study, N_2O was administered by substituting a MAC fraction of a volatile anesthetic with an equal MAC fraction of N_2O, resulting in three iso-MAC groups. Despite the advantages of equal anesthetic planes, a drawback involves the use of two concurrent drug manipulations (increase in N_2O while enflurane was decreased).

In previous experimental protocols, N_2O has been administered and evaluated in one of two ways. The first involves administering N_2O (without any other anesthetic) to awake, restrained (and possibly physiologically stressed) animals. With this method, N_2O results in either a negligible effect or an increase in the cerebral metabolism, as compared to awake, restrained controls.[12-17] As the MAC value for N_2O in the rat has been reported to be 136%,[24] little more than a one-half MAC level of anesthesia can readily be achieved with N_2O in the rat. One could argue with a reasonable degree of certainty that such a level of anesthesia is rarely acceptable as appropriate anesthetic practice. While the results from this type of N_2O administration are important to the overall understanding of the metabolic properties of N_2O, the deviation from accepted anesthetic levels limits the applications of such studies.

In the second type of N_2O metabolic evaluation, a surgical plane of anesthesia is established with a baseline anesthetic (commonly halothane or a barbiturate). Nitrous oxide is then added to this previously established anesthetic, and its effect upon cerebral metabolism is determined. With this type of protocol, more extensive increases in cerebral metabolism have been attributed to N_2O.[18-21] This situation may be more comparable to the clinical use of N_2O, with one exception. In this type of protocol, N_2O is added to an appropriate surgical plane

TABLE 3. Local Spinal Cord Metabolism of Glucose ($\mu mol \cdot 100\ g^{-1} \cdot min^{-1}$ [mean ± SD])

	Cervical			Thoracic			Lumbar		
	0% N_2O	30% N_2O	60% N_2O	0% N_2O	30% N_2O	60% N_2O	0% N_2O	30% N_2O	60% N_2O
Gray matter									
Subgelat	59 ± 5	68 ± 5*	55 ± 6	53 ± 5	64 ± 5*	50 ± 7	63 ± 6	72 ± 5*	61 ± 6
Dorsal horn	64 ± 5	75 ± 6*	63 ± 6	55 ± 5	69 ± 6*	57 ± 5	70 ± 6	80 ± 5*	72 ± 6
Ventral horn	63 ± 5	74 ± 6*	62 ± 5	57 ± 5	69 ± 6*	57 ± 5	68 ± 6	81 ± 6*	73 ± 6
White matter									
Dorsal	39 ± 4	51 ± 5*	38 ± 6	38 ± 5	48 ± 6*	38 ± 5	43 ± 6	56 ± 6*	42 ± 5
Lateral	43 ± 4	56 ± 6*	42 ± 5	37 ± 5	50 ± 6*	37 ± 5	53 ± 5	65 ± 6*	54 ± 6
Ventral	41 ± 4	52 ± 5*	38 ± 4	40 ± 6	51 ± 5*	39 ± 5	51 ± 6	62 ± 5*	52 ± 6

* Difference from control ($P < 0.05$).

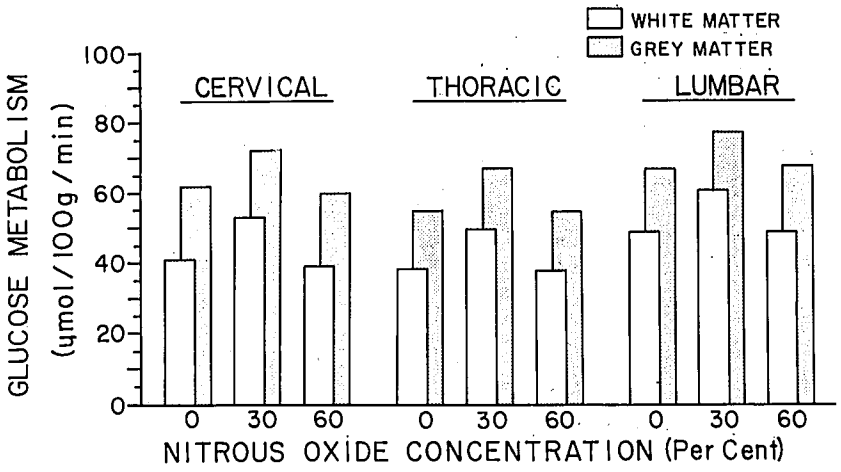

FIG. 2. Summary of metabolic changes in the spinal white and grey matter for the 0%, 30%, and 60% N_2O groups. There was an increase in the local spinal cord metabolism of glucose for both white and grey matter as the N_2O concentration was increased from 0 to 30%, and a return to control values as the N_2O concentration was further increased from 30 to 60% ($P < 0.05$).

of anesthesia in a superfluous manner. As a result, the metabolic properties attributed to N_2O are measured at anesthetic depth ranges beyond the conventional use of N_2O. Thus, any conclusions may quantitatively and qualitatively differ from measurements made if N_2O were used at conventional anesthetic depths.

All of the abovementioned methodologies are important to the overall understanding of the metabolic properties of N_2O in the central nervous system.[12–21] However, when evaluating the metabolic properties of N_2O, the anesthesiologist should note the methodology of the protocol and potential weaknesses. In past protocols, while a single drug manipulation was made, the metabolic properties of N_2O were determined at dissimilar and unconventional anesthetic levels. In the present study, although the anesthetic levels were similar and within conventional ranges, two concurrent drug manipulations were made. Thus, it is not possible to ascribe metabolic changes to either drug, but rather to the metabolic interrelationship between enflurane and N_2O as used in this protocol. When evaluated collectively, the metabolic evaluations of N_2O suggest that N_2O has the potential to alter the metabolic state of the central nervous system in a manner that may not be as predictable as other anesthetic agents.

One of our concerns involved the possibility that the additive MAC values previously determined in our lab were in error. If the MAC values were erroneous, we may have been measuring metabolism at unequal levels of anesthesia (not three iso-MAC groups). To evaluate this possibility, we repeated our MAC determinations in a blinded fashion and found the results identical to our previous determinations.[9] In addition, if the differences found in the present study were due to unequal MAC levels of anesthesia, one would have expected to see a more homogeneous difference in the brain metabolic data between N_2O groups. Thus, we feel confident that we were indeed measuring the central nervous system metabolic response to three different 1.2 MAC combinations of N_2O and enflurane.

An observation of interest concerns the heterogeneous change that occurred in the brain when N_2O was increased (and enflurane decreased), while at all levels of the spinal cord a strict homogeneous change in both white and gray matter was observed. This observation leads to speculation concerning an anatomical center(s) where N_2O and/or enflurane preferentially act to activate and/or inhibit glucose utilization in more distal neural pathway sites. Again, as two drugs were concurrently manipulated, the possible combinations of anatomical sites of interaction either through activation or inhibition by N_2O and/or enflurane are multiple, and further study would be necessary to elucidate the specific sites of action unique to N_2O and/or enflurane. In addition, as the mechanism of anesthetic action and potential metabolic interactions are poorly understood, consideration of an anatomical site of action for either of these two drugs remains highly speculative.

A relationship between neuronal function and metabolic activity has been described.[25] However, a correlation between the MAC level of anesthesia and local central nervous system metabolism may be tenuous at best. The results of the present study indicate that different combinations of iso-MAC anesthesia may result in marked differences in central nervous system metabolism. In view of the fact that MAC is simply a clinical determination of the ability of an anesthetic dose to produce insensibility to pain, it is not surprising that different iso-MAC anesthetics produce different metabolic patterns. If different iso-MAC anesthetic combinations were to produce similar metabolic patterns, identical actions at specific neuroanatomic sites would be required. As enflurane and N_2O have dissimilar neurophysiologic properties,[2,6,10] it should

be expected that different iso-MAC combinations correlate only with the perceptibility of noxious stimuli, and not necessarily with central nervous system function.

In conclusion, studied in the context of comparing iso-MAC combinations of anesthetic agents, we observed a homogeneous biphasic response in the metabolic interaction between N_2O and enflurane in the spinal cord, and a heterogeneous response in the brain. These findings require further evaluation as to the possible existence of a central nervous system anatomical site(s) of action for either N_2O and/or enflurane; and to the possibility that there may be combinations of N_2O and volatile anesthetics that have unique effects upon central nervous system metabolism.

References

1. Mori K, Winters WD: Neural background of sleep and anesthesia. Int Anesthesiol Clin 13:67–108, 1975
2. Mori K, Winters WD, Spooner CE: Comparison of reticular and cochlear multiple unit activity with auditory responses during various states induced by anesthetic agents: II. Electroencephalogr Clin Neurophysiol 24:242–248, 1968
3. Clark DL, Hosick EL, Rosner BS: Neurophysiological effects of different anesthetic in unconscious man. J Appl Physiol 31:884–891, 1971
4. Julien RM, Kavan EM: Electroencephalographic studies of a new anesthetic: enflurane (Ethrane). J Pharmacol Exp Ther 183: 393–403, 1972
5. Miyata R: The effects of anesthetics on the pinprick evoked responses in the central nervous system. Masui 17:1219–1222, 1968
6. Stevens JE, Oshima E, Mori K: Effects of nitrous oxide on the epileptogenic property of enflurane in cats. Br J Anaesth 55: 145–153, 1983
7. Torri G, Damia G, Fabiani ML: Effect of nitrous oxide on the anesthetic requirement of enflurane. Br J Anaesth 46:468–472, 1974
8. Gion H, Saidman LJ: The minimum alveolar concentration of enflurane in man. ANESTHESIOLOGY 35:361–364, 1971
9. Cole DJ, Kalichman MW, Shapiro HM: Non-linear additive anesthetic effects of nitrous oxide-enflurane combinations. ANESTHESIOLOGY 65:A329, 1986
10. Myers RR, Shapiro HM: Local cerebral metabolism during enflurane anesthesia: Identification of epileptogenic foci. Electroencephalogr Clin Neurophysiol 47:153–162, 1979
11. Nakakimura K, Sakabe T, Funatsu N, Maekawa T, Takeshita H: Metabolic activation of intercortical and corticothalamic pathways during enflurane anesthesia in rats. ANESTHESIOLOGY 68: 777–782, 1988
12. Crosby G, Crane AM, Sokoloff L: A comparison of local rates of glucose utilization in spinal cord and brain in conscious and nitrous oxide- or pentobarbital-treated rats. ANESTHESIOLOGY 61:434–438, 1984
13. Kennedy C, Sakurada O, Shinohara M, Jehle J, Sokoloff L: Local cerebral glucose utilization in the normal conscious macaque monkey. Ann Neurol 4:293–301, 1978
14. Ingvar M, Abdul-Rahman A, Siesjo B: Local cerebral glucose consumption in the artificially ventilated rat: Influence of nitrous oxide analgesia and of pheriobarbital anesthesia. Acta Physiol Scand 109:177–185, 1980
15. Tommesino C, Shapiro HM: Effect of nitrous oxide analgesia on local cerebral glucose utilization during immobilization stress. J Cereb Blood Flow Metab 3(Suppl 1):S572–573, 1983
16. Ingvar M, Siesjo BK: Effect of nitrous oxide on local cerebral glucose utilization in rats. J Cereb Blood Flow Metab 2:481–486, 1982
17. Pelligrino DA, Miletich DJ, Hoffman WE: Nitrous oxide markedly increases cerebral cortical metabolic rate and blood flow in the goat. ANESTHESIOLOGY 60:405–412, 1984
18. Theye RA, Michenfelder JD: The effect of nitrous oxide on canine cerebral metabolism. ANESTHESIOLOGY 29:1119–1124, 1968
19. Sakabe T, Kuramoto T, Inoue S, Takeshita H: Cerebral effects of nitrous oxide in the dog. ANESTHESIOLOGY 48:195–200, 1978
20. Sakabe T, Tsutsui T, Maekawa T, Ishikawa T, Takeshita H: Local cerebral glucose utilization during nitrous oxide and pentobarbital anesthesia in rats. ANESTHESIOLOGY 63:262–266, 1985
21. Oshita S, Ishikawa T, Tokutsu Y, Takeshita H: Cerebral circulatory and metabolic stimulation with nitrous oxide in the dog. Acta Anaesthesiol Scand 23:177–181, 1979
22. Sokoloff L, Reivich M, Kennedy C, Des Rosiers MH, Patlak CS, Pettigrew KD, Sakurada O, Shinohara M: The [14C]-deoxyglucose method for the measurement of local cerebral glucose utilization: Theory, procedure, and normal values in the conscious and anesthetized rat. J Neurochem 28:897–916, 1977
23. Zar JH: Biostatistical Analysis. Englewood Cliffs, Prentice-Hall, 1984, pp 185–205
24. Difazio CA, Brown RE, Ball CG, Heckel CG, Kennedy SS: Additive effects of anesthetics and theories of anesthesia. ANESTHESIOLOGY 36:57–63, 1972
25. Sokoloff L: Relation between physiological function and energy metabolism in the central nervous system. J Neurochem 29:13–26, 1977