Anesthesiology
V 39, No 2, Aug 1973

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Anesthetic Effects on Cerebral Metabolism

B. Raymond Fink, M.D.,* and Richard H. Haschke, Ph.D.†

A DISCUSSION of the effects of anesthetics on cerebral metabolism presupposes a reasonably adequate knowledge of the normal state of metabolism of the organ. Unhappily, although considerable advances have been made in the last ten years, our knowledge of normal cerebral metabolism is still small, and understanding of the effects of anesthetics on this metabolism is correspondingly fragmentary. This review begins with human and animal data of greatest interest to the clinician, followed by an account of cellular-level developments. A more complete survey of the latter, to the end of 1968, is available.[1] Aspects of cerebral metabolism relevant to changes in cerebral blood flow were recently the subject of an excellent review by Smith and Wollman.[2]

Early biochemical studies related to anesthesia were designed to test the hypothesis that interference with energy metabolism was the fundamental cause of insensibility. This idea doubtless arose from the incontrovertible fact that the maintenance of normal mental function does depend on a sufficient supply of oxygen and glucose to the brain. For normal function the waking brain requires[3] approximately 3.5 ml of oxygen (156 micromoles)/100 g/min, or a total of about 50 ml/min, extracted from an average normal cerebral blood flow of 57/ml/100 g/min. The importance of oxygen to the normal function of neurons is well illustrated by the effects consequent on temporary retinal ischemia. In the experiment of Carlisle *et al.*,[4] where pressure was applied to the eyeball, vision was lost within 4 seconds when the oxygen was at ambient atmospheric pressure but persisted for as long as a minute when the oxygen was at a pressure of 4 atm. But, as Duffy *et al.*[5] point out, there is a difficulty to this reasoning, because during anoxia brain function fails before there is any significant decrease in ATP or any great change in phosphocreatine. For them the depression is not the result of a power failure, but represents a protective reaction to conserve the slender stores of energy. To the reviewers this seems farfetched, for the protective value of coma has yet to be demonstrated.

Present understanding may be summarized as follows:

1) When the internal jugular venous P_{O_2} is reduced to 28–25 torr there is sufficient underoxygenation of the cerebral tissue to elicit compensatory reactions such as dilatation of cerebral vessels ("reaction threshold").

2) At a P_{O_2} of 20–18 torr in internal jugular venous blood the oxygen deficiency is sufficient to lower the rate of oxidative phosphorylation, and consciousness is lost ("critical threshold"). However, the critical intracellular P_{O_2} is probably quite different. Experiments *in vivo* and *in vitro* have demonstrated that a P_{O_2} of 1–2 torr or less is sufficient to allow maximal phosphorylation in brain mitochondria.[6,7]

Hess[8] estimated that the average human cortical neuron with its processes utilizes 122×10^{-6} μl of oxygen per hour, or 16–50 times as much as the average neuroglial cell. Rose[9] concluded that there was little difference between the metabolic rates of neurons and glia, but the most recent data of Ruscak and Ruscakova[10] agree in general with Hess. Metabolic fluxes in single neurons during anesthesia have recently been discussed by Passonneau and Lowry.[11]

Effects of Anesthetics on CMR_{O_2}

Most general anesthetics and cerebral depressants have been shown to reduce the oxygen consumption of the brain under conditions of clinical anesthesia (table 1). Unfortu-

* Professor, Department of Anesthesiology.
† Assistant Professor, Department of Anesthesiology.

Received from the Anesthesia Research Center and Department of Anesthesiology, University of Washington School of Medicine, Seattle, Washington 98195. Supported by USPHS Research Center Grant GM 15991.

TABLE 1. Effects of Anesthetics on Oxygen Uptake of the Human Brain

Induction with Thiopental	Anesthetic	CMR_{O_2}		Reference
		ml/100 g/min	Per Cent Change	
	Thiopental		−36	12
	Thiopental, 0.5–1.6 g		−36	128
	Thiopental, 0.6–1.5 g	2.2	−39	129
	Thiopental, 1–1.5 g		−66	130
	Thiopental	1.5	−55	13
	Ether		−40	30
	Alcohol, 320 mg/100 ml blood	2.2	−31	131
	Alcohol, 68 mg/100 ml blood	2.8	0	131
No	Halothane, 1 per cent, + air	2.2	−27	132
Yes	Halothane, 1 per cent, + N_2O, 50 per cent		−27	133
No	Halothane, 1.2 per cent	2.8	−15	15
Yes	N_2O (60–80 per cent) with:			36
	Halothane, 0.5 per cent		−16	
	Chloroform, 0.5 or 1 per cent		−10	
	Methoxyflurane, 0.5 per cent		−13	
Yes	N_2O (70 per cent) with:			134
	Halothane, 0.5 per cent		−14	
	Halothane, 2 per cent		−33	
No	C_2H_6, 5 per cent		−30	20
No	Ketamine	2.82	0	135

nately, few of the studies can be normalized, as they lack data on blood levels of anesthetic. For example, Himwich [12] observed that during thiopental anesthesia the oxygen consumption of the human brain diminished, on the average, by 36 per cent. Pierce *et al.*,[13] in 1962, made measurements in human subjects anesthetized with sodium thiopental and *d*-tubocurarine, the total doses ranging from 10 to 55 mg/kg and from 0.7 to 1.3 mg/kg, respectively, while P_{CO_2} was maintained at an average of 44 torr. In the presence of clinical and electroencephalographic indications of profound anesthesia, the oxygen consumption rate of the brain represented a reduction of approximately 55 per cent below the rate in conscious normal eucapnic subjects. The cerebral respiratory quotient was unchanged, suggesting that cerebral metabolism was not qualitatively altered.

Concerning trichloroethylene, McDowall *et al.*[14] found that the cerebral oxygen uptake was reduced by 20 per cent in a localized area of the cerebral cortex in dogs. There is general agreement that halothane does reduce oxygen consumption by the brain. Cohen *et al.*[15] observed that in man 1.2 per cent halothane caused a decrease of approximately 15 per cent in cerebral oxygen consumption in the presence of a 1 C fall in body temperature, although for the most part the depression could be accounted for by this fall in temperature. In dogs, Theye and Michenfelder [16] found a 17 per cent reduction in the rate of oxygen consumption by the brain in dogs inhaling 1 per cent halothane in 70 per cent nitrous oxide and oxygen. A comparable depression was recently demonstrated with methoxyflurane [17] a 23 per cent decrease in CMR_{O_2} with 0.44 per cent end-expired methoxyflurane (about twice the minimum alveolar anesthetic concentration). These authors [18] also showed that nitrous oxide by itself increased rather than decreased the cerebral demand for oxy-

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gen. However, Wollman and colleagues [19] concluded that in man 70 per cent nitrous oxide depresses CMR_{O_2} about 15 per cent.

That the effect of nitrous oxide is not a simple stimulation is suggested by the observation of McDowall and Harper [20] that nitrous oxide and halothane are synergistic in their effect on cerebral oxygen uptake. Cyclopropane also appears to have a complex effect, characterized as biphasic by Alexander *et al.*[21] However, the reduction in oxygen uptake with thiopental probably does not occur uniformly throughout the brain. Autoradiographic studies with ^{131}I-labeled trifluoroiodomethane [22] have shown that blood flow through different areas of gray matter is remarkably non-uniform in conscious cats, but that during light anesthesia with thiopental the differences in flow between the various cortical areas become much smaller. Similar data were obtained more recently by Cassano.[23] Perfusion through the regions of highest flow slows down almost to the rate through the more slowly perfused parts. Also pertinent in this connection is Roth's [24] demonstration that the concentrations of labeled thiopental in different areas of the brain vary directly with the local rates of blood flow at the time of injection. If cerebral blood flow is autoregulated by metabolic demand, the observations by Landau [22] seem to indicate that thiopental reduces oxygen uptake most in those areas where oxygen uptake is highest in the conscious state.

In general, significant cerebral metabolic depression occurs during anesthesia with barbiturates [13, 25] and narcotics,[26] but not with ketamine: Takeshita and colleagues [27] report no change in patients; in the dog an increase has been observed.[28, 29] However, preanesthetic medication with hypnotics and narcotics produces only insignificant effects on total-body oxygen consumption rate. In dogs, pentobarbital, 2 mg/kg, or meperidine, 2 mg/kg, administered during halothane anesthesia depressed CMR_{O_2} an additional 7 and 13 per cent, respectively.[30] The neuroleptic, droperidol, 0.3 mg/kg, does not alter CMR_{O_2} in dogs,[26] but fentanyl, 0.006 mg/kg, decreases it by 18 per cent. In combination as Innovar, the two together reduce it 23 per cent. Morphine [31] produces depression of as much as 15 per cent; the effect reaches a plateau at a cumulative dose of 1.2 mg/kg in the dog and is reversed by nalorphine, 0.3 mg/kg. As regards gaseous anesthetics, no general rule can be invoked (fig. 1). Kety [32] has stated that a 40 per cent decrease in CMR_{O_2} occurs with ether anesthesia in man. Cerebral oxygen consumption in man is reduced to approximately 70 per cent of normal during the inhalation of 5 per cent cyclopropane,[33] and remains at this level during the inhalation of 13 and 37 per cent cyclopropane, but returns to nearly normal values with the inhalation of 20 per cent. The observation of a large increase in cerebral blood flow with 20 per cent and 37 per cent cyclopropane in the face of a 42 per cent decline with 5 per cent cyclopropane underscores the complexity of the response. Clearly, there is no simple proportionality between the functional and metabolic depression of the nervous system induced by this anesthetic. Such nonproportionality also appears to hold for diethyl ether. It seems that 1.2 times the so-called minimum alveolar concentration (MAC) of ether depresses the CMR_{O_2} to 65 per cent of normal, whereas 2.3 MAC is associated with a CMR_{O_2} of about 88 per cent of normal.[1]

Alexander *et al.*[33] suggested that the peculiar biphasic actions of cyclopropane and ether on cerebral blood flow and cerebral metabolic rate for oxygen were due to the property of the agents of enhancing sympathoadrenal activity with increasing concentrations. Support for such a mechanism was adduced by Michenfelder and Theye [34] in dogs. Increasing cyclopropane from 5 to 30 per cent in their dogs resulted in no significant change in CMR_{O_2}. They treated one group of dogs with reserpine because reserpine is known to deplete the stores of norepinephrine throughout the body. In the reserpinized dogs the biphasic effect of cyclopropane disappeared, since 13 per cent cyclopropane reduced CMR_{O_2} to 89 per cent of control, and this reduction was maintained as cyclopropane was further increased to 20 and 30 per cent. In other dogs, spinal anesthesia was used as an alternative to reserpine for the purpose of suppressing sympathoadrenal stimulation by cyclopropane. The responses to cyclopropane were the same as in the reserpinized dogs. For good measure, they tested the effects of epi-

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nephrine and norepinephrine in a dog in the presence of cyclopropane and spinal anesthesia. Both epinephrine and norepinephrine produced large increases in CMR_{O_2} and cerebral blood flow, which were rapidly reversed upon cessation of the catecholamine infusion.

In man, cyclopropane is known to produce a progressive increase in the level of circulating norepinephrine,[35] but in the dog the major increase is in the epinephrine fraction.[36] By analogy with the dog, it would seem that a dose-related cerebral response to norepinephrine may account for the biphasic effect of increasing cyclopropane concentrations on CBF and CMR_{O_2} in man: at low concentrations the direct cerebral depressant effects of cyclopropane predominate, whereas at higher concentrations sufficient norepinephrine is released to cause increases in both CMR_{O_2} and CBF. At still higher concentrations of cyclopropane this effect is exhausted or outweighed by the direct depressant effect of the anesthetic. Enflurane (Ethrane) is a potent depressor of CMR_{O_2} in man.[37] A 50 per cent reduction develops with 3 per cent enflurane. Methoxyflurane, chloroform, and trichloroethylene, tested in dogs only, depress CMR_{O_2} 10–20 per cent.[38]

In sum, the effect of anesthetic depression on oxygen utilization by the brain as a whole is variable and not directly related to the degree of electrophysiologic depression, although there does appear to be a direct correlation between the anesthetic depression produced by barbiturates and the depression of oxygen uptake.[39] Altenburg and Michenfelder[25] believe that the effectiveness of thiopental in decreasing CMR_{O_2} is lessened by pretreatment with thiopental as little as two hours previously. The basis for this acute tolerance has not been established. Regional differences probably exist,[40,41] but these may be partly due to nonuniformity of blood flow.

Anesthetics and Tolerance to Ischemia

Just how well can brain cells withstand anoxia? The anesthesiologist is interested in the problem and will further ask: Does anesthesia as such protect the patient's neurons against anoxia at all?

To begin with the first question, the widely held view that permanent loss of function follows 3 or 4 minutes of circulatory arrest to the brain is probably erroneous. If the oxygenation of the heart is maintained during the period of cerebral ischemia, the brain can tolerate an appreciably longer period of total circulatory arrest.[42]

The significance of maintenance of blood pressure above the critical level is patent in the experiments of Hirsch *et al.*[43] in rabbits. Complete ischemia of the brain, produced by inflating a blood pressure cuff around the neck to 300 torr, was tolerated for about 4 minutes at 37 C without neurologic or histologic damage. When the experiments were done with artificial respiration, the revival time was doubled. Studies of electroencephalographic (EEG) recovery in cats subjected to cerebral anoxia but with systemic blood pressure maintained by means of extracorporeal circulation point the same way.[44] If after cardiac arrest the revival time is so short, this is the result of cardiac failure during recovery and not the short revival time of the brain itself. It is therefore crucial to maintain the blood pressure above the critical level during recovery by means of cardiac massage and infusion of norepinephrine.

Experiments by Webster and Ames[45] with the rabbit retina *in vitro* interestingly corroborate the animal data. Electron microscopic examination of retinas deprived of oxygen and glucose for only 3 minutes shows generalized swelling of mitochondria and loss of synaptic vesicles. All these changes are completely reversible when the deprivation lasts as long as 20 minutes, but become irreversible by 30 minutes. It is interesting that simple glucose withdrawal produces only minor changes. This may denote the presence of a sizeable intracellular reserve of glycogen, or metabolism of substitute substrates derived from amino acids or fatty acids.

The second question may now be considered: Is the prospect of cerebral recovery improved if the anoxic or ischemic insult takes place in the presence of general anesthesia? At stake is the crucial point whether the reduced cerebral metabolism induced by certain anesthetics can increase the tolerance of the brain for anoxia during neurosurgical interventions on the cerebral vascular system.

Important insights have been gained from studies under controlled conditions *in vitro.*

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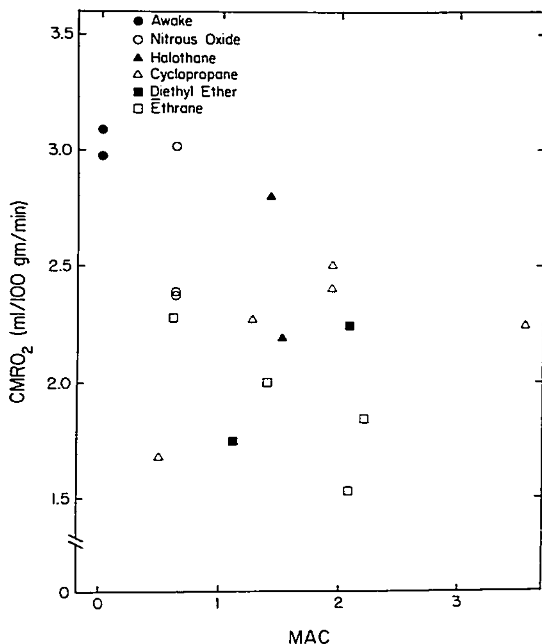

FIG. 1. Cerebral metabolic rate for oxygen as a function of MAC (Smith, AL, Wollman, H, ANESTHESIOLOGY 36:385, 1972.

Detailed discussions are available elsewhere,[46] and only a few particulars will be given here. It has long been plain that the oxygen uptake of brain slices *in vitro* reflects the basal needs for the maintenance of cellular integrity, and occurs at about half the normal *in-vivo* rate,[47] or approximately the same rate as in brain deeply depressed by barbiturate anesthesia. The *in-vitro* rate can be doubled by electrical stimulation.[48] Stimulated excess respiration is inhibited by anesthetics, but this again may reflect a primary effect of the anesthetic on electrical excitability rather than on metabolism. In potassium-stimulated brain slices, 50 per cent cyclopropane or 5 per cent ether causes a significant and reversible decrease of oxygen consumption.[49] The measurements, of course, do not distinguish between the oxygen consumed by neurons and the oxygen consumed by neuroglia.

Michenfelder and Theye [50] set out to answer the question by examining the ATP and lactate levels in canine brain. They produced cerebral anoxia, or more precisely ischemia, by the time-honored expedient of decapitation, and observed the post-decapitation rates of ATP depletion and lactate accumulation. At 37 C these were uninfluenced either by the presence of halothane or by halothane with thiopental, although the premortem CMR_{O_2} had been reduced 40 per cent below control. Lowering the temperature to 30 C without anesthetic likewise reduced CMR_{O_2} 40 per cent below control, but in this case the post-decapitation ATP depletion and lactate accumulation rates also were reduced 40 per cent. Thus, anes-

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thesia and hypothermia had similar effects on CMR_{O_2} while the dog was alive, but had entirely different effects on the rate of depletion of ATP and lactate accumulation after decapitation. Michenfelder and Theye thought it significant that, anesthetized or not, the cerebral ATP content following decapitation decreased at an approximately constant rate down to 25 or 30 per cent of the pre-decapitation level and thereafter decreased at a much slower rate. They had previously shown that reductions in CMR_{O_2} during anesthesia and hypothermia are accompanied by quantitatively similar reductions in cerebral glucose consumption, indicating continued aerobic energy production. Michenfelder and Theye reasoned, therefore, that reduction in CMR_{O_2} was accompanied by quantitatively similar reductions in the rate of ATP synthesis and the rate of ATP utilization. If similar levels of ATP are obtained during anesthesia and hypothermia, why, then, was there not a similar degree of cerebral protection against anoxia? The answer was that the rate of utilization of the ATP by the decapitated brain was so different in the two states; anesthesia alters only that aspect of ATP utilization responsible for the conscious state but not that required for cellular integrity. Hypothermia reduces both. In the anesthetized brain, once the EEG was abolished by anoxia, the energy requirement for maintenance of cellular integrity would be unaffected by anesthetics.

The results of Michenfelder and Theye have been described in some detail because their conclusions are at variance with the above-discussed survival experiments. Michenfelder and Theye argue that the anoxic brain undergoes irreparable damage within 3 or 4 minutes, whereas the experiments of Schneider *et al.*[42] have shown that irreparable damage within this time is contingent on failure of the circulation in the recovery phase. When glucose transport to the brain is present after the period of anoxia, the levels of ATP and P-creatine are well maintained.[51] The weakness of the experiments of Michenfelder and Theye is that they do not show that recovery cannot occur after 3 minutes of complete anoxia. They only show that this does not occur in the decapitated dog's head, which is hardly surprising. If the concentration of ATP is limiting, then the rate of ATP utilization may be decreasing continuously as the ATP level falls. This would account quite well for the published data. By the same token, some caution may also apply to their conclusion that anesthetic reduction of cerebral metabolism does not afford any protection against hypoxia. There is some evidence to the contrary from experiments on living animals. Dhruva *et al.*[52] reported that halothane anesthesia could increase the tolerance of the brain to anoxia. Goldstein[53] showed that in dogs pentobarbital, 30 mg/kg, extended the tolerance of cerebral ischemia—total interruption of cerebral circulation—by several minutes; however, this study lacked precise temperature control. Cox and colleagues[54] reported that the addition of halothane to a 3-to-1 nitrous oxide–oxygen mixture markedly increased the tolerance of the rabbit brain to ischemia at normothermia. Bain *et al.*[55] used the pneumatic tourniquet around the rabbit's neck to produce isolated cerebral ischemia while maintaining artificial ventilation, normal blood gases, and normal temperature. The absence of cortical electrical activity throughout the period of occlusion was considered evidence of cerebral ischemia. The addition of halothane to the standard nitrous oxide–oxygen mixture increased the 24-hour survival rate following 3 minutes of cerebral ischemia from 36 to 95 per cent; survival following 6 minutes of cerebral ischemia increased to 72 per cent (from 21 per cent) with halothane, methoxyflurane, or cyclopropane anesthesia.

This discussion should not persuade anyone to make light of the threat of disaster. Its message is that if a disaster does occur, immediate recovery of effective cardiac function is a generally hopeful portent.

Glucose Metabolism

What is the oxygen consumed by the brain used for? The short answer is, to burn glucose. The complete oxidation by cerebral tissue of glucose to carbon dioxide and water appears to be the principal source of energy metabolism in this organ. Except for glycerol and mannose,[56] none of the other substrates that have been tested is significantly metabolized. The normal rate of utilization of

glucose amounts to 27.8 nanomoles/100 g brain/min, or about 70 mg/min for the entire brain, and in the process approximately 5.5 millimoles oxygen per millimole glucose are consumed.[57] After crossing the cell membrane, glucose is immediately phosphorylated, thereby facilitating further glucose entry. Consistent with the conclusion that brain respires almost entirely at the expense of glucose is the observation that hypoglycemia produces a definite decrease in cerebral oxygen consumption and that the decrease correlates well with the arterial blood glucose level and with the mental state. Consciousness lost in hypoglycemia is restored with intravenous administration of glucose.[58] In brain slices the amount of glucose disappearing is approximately equal to the total expected from the oxygen consumption (assuming complete oxidation) and from the amount of lactic acid formed in anaerobic glycolysis.[40] It may be noted that dependence of the human brain on glucose is lessened during prolonged fasting, presumably thanks to induction of enzymes capable of oxidizing keto acids.[59]

Some of the glucose entering the brain cells is not metabolized directly, but serves as a precursor of various intermediates. Evidence for this is the observation that when labeled glucose is utilized, the resultant carbon dioxide has a lower specific radioactivity than the original glucose substrate. The glucose label becomes diluted because some of the glucose is initially used to synthesize other compounds such as amino acids and lipids. These are then metabolized together with unlabeled intermediates already in the pool.[60] In the perfused brain of the cat, glucose is taken up at the rate of 10 mg/min/100 g of tissue[61, 62] under "resting" conditions; 30–35 per cent of the glucose absorbed is oxidized directly, and another 20–30 per cent is taken up and rapidly transformed into acid-soluble components such as amino acid and lipids. During this time the amount of oxygen consumed by the perfused brain corresponds to that necessary to oxidize all of the glucose to carbon dioxide.

What effect does anesthesia have on the intermediary metabolism and, more particularly, on the metabolism of glucose? Unfortunately, many of the results to be cited have been obtained at uncertain body temperatures and blood levels of anesthetic, from animals coincidentally suffering from unknown degrees of hypoxia and acidosis. All the more importance attaches to the rare studies in man, such as those of Cohen *et al.*[15] These workers observed a cerebral glucose uptake of 8.1 mg/100 ml blood during inhalation of 1.2 per cent halothane vapor. The normal value is about 9.5 mg/100 ml blood, with 92 per cent of the glucose being oxidized and the rest appearing as lactate. Since glucose appears to be the principal substrate for the metabolism of cerebral tissue, one may assume that oxygen consumption is really an indirect measurement of glucose metabolism.

In vitro, barbiturates stimulate glycolysis by rat brain,[63] but so far as is known the human brain does not respond to barbiturates by increased glycolysis. Thiopental anesthesia in man has been shown to reduce the CMR_{O_2} by an average of 55 per cent, but the respiratory quotient was 0.99.[13] In isolated ganglia, where anesthetics "selectively" inhibit synaptic transmission,[64, 65] pentobarbital depression of the postganglionic action potential accelerates the rates of glucose consumption and lactate production while decreasing oxygen uptake. Diethyl ether, on the other hand, with a similar reduction in action potentials, has no measurable effect on oxygen uptake. Thus, so far as carbohydrate metabolism is concerned, the results with excised ganglia closely resemble those with slices of brain tissue.[66] Of the glucose utilized by the ganglia *in vitro*, 64 per cent appears as carbon dioxide and 24 per cent as lactate.[66] These results are quite similar to those of Geiger[61] with the perfused brain of the cat. One may conclude that the much greater production of lactate by the *in-vitro* preparations compared with the intact brain probably reflects the drastic difference in conditions of oxygenation occasioned by the absence of circulating blood.

One indication of an anesthetic's influence on brain glucose metabolism is a change in the rate of appearance of metabolites from freshly administered glucose. The specific radioactivity of carbon dioxide produced by the brain during continuous infusion of ^{14}C-labeled glucose has been measured by Barkai and Allweis[67] in the intact cat narcotized with

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pentobarbital (after induction of anesthesia with diethyl ether). At apparent isotopic equilibrium, the relative specific activity of the carbon dioxide produced by the brain amounted to 45 per cent compared with 32 per cent observed in the unanesthetized cat brain. An even larger increase in the specific radioactivity of the CO_2 formed by glucose oxidation was found by Geiger *et al.*[68]; the addition of pentobarbital to the perfusion fluid roughly doubled the amount of label appearing in the CO_2 carbon. Possibly the anesthetic depressed the incorporation of the glucose into other components and therefore made more substrate available for direct oxidation. Experiments by Bachelard *et al.*[69] indicate that the incorporation of ^{14}C from uniformly labeled glucose into amino acids in the rat brain is significantly retarded by diethyl ether and by pentobarbital (75 mg/kg). On the other hand, experiments with the anesthetized dog have shown that the relative specific radioactivity of the CO_2 produced by the brain remained at 100 per cent for most of the time of the experiment.[70] At present it is not clear whether the difference between the results with cats and with dogs is due to species or technique. Sacks[71] estimated that in man little more than half the cerebral CO_2 production comes directly from glucose.

Brain Levels of Glucose and Glycogen

Glucose is stored in the brain mainly in the form of glycogen. In the mammalian brain the total amount of glycogen is equivalent to 2 g glucose.[72] This is sufficient substrate for approximately 24 minutes of oxidative metabolism at the normal rate. However, in an animal deprived of oxygen, the glycogen would be used up at five or six times this rate because of the greatly increased rate of glycolysis.[73] Since such a rapid exhaustion of substrate may be a principal factor in causing irreversible damage to the brain during circulatory arrest, especially in the newborn,[74] it is of interest to examine the effect of anesthetics upon this phenomenon in case any protective effect is present. With barbiturate narcosis, a time-dependent increase in cerebral glycogen has been found, six hours of anesthesia producing a two- to threefold increase.[75,76,77] Higher levels of plasma glucose are not a sufficient explanation for this increase in the cerebral levels. Central depression of glycolysis may be involved.[78]

Brunner *et al.*[79] have observed that the volatile anesthetics affect the intracerebral concentration of glucose in a manner similar to the barbiturates. Upon administration of 4.5 per cent diethyl ether, plasma and cerebral glucose were both elevated. However, the ratio of cerebral glucose to plasma glucose increased. After two hours plasma glucose had increased 40 per cent; cerebral glucose increased 80 per cent, and glucose-6-phosphate increased approximately 56 per cent. Glycogen also increased approximately 80 per cent in two hours, but after four hours began to decrease. All of these substances represent energy stores which accumulate in the brain during general anesthesia. Halothane, methoxyflurane, and enflurane in equivalent concentrations were also studied; their effects on levels of cerebral glucose, cerebral glycogen, and plasma glucose were generally similar to those of diethyl ether. All the general anesthetics depressed the cerebral metabolic rate about 50 per cent and tended to decrease body temperature, but a 10-degree C fall in temperature in the absence of anesthetic did not affect the intracellular concentration of glycogen.

Takemori[80] has reported that certain depressants like pentobarbital, diethyl ether, and chloroform increase the glucose-6-phosphate dehydrogenase activity in rat cerebral cortex, implying an increased utilization of glucose via the pentose phosphate pathway.

A conflicting note from the laboratory of Biebuyck and Hawkins[81] mentions a reduction in rat brain glucose-6-phosphate, 3-phosphoglycerate, and α-ketoglutarate with pentobarbital (50 mg/kg, intraperitoneal) or halothane (1.5 per cent in oxygen). The divergence probably arises from differences in methodology. Estler[82] found a small increase in cerebral glycogen in mice after one hour of 4.5 per cent ether anesthesia.

The distribution of glycogen in the brain is not uniform, and neither is the increase occasioned by anesthesia. In unanesthetized animals glycogen levels are higher in the white matter than in the cortex.[83] Phenobarbital (200 mg/kg) increases the glycogen more

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in layer 1 than in the remaining layers, but does not change the glycogen content in the subjacent white matter. Glucose and phosphocreatine are also increased. At the electron-microscopic level, prolonged barbiturate anesthesia (6 hours, phenobarbital, 250 mg/kg) produces large increases of particulate glycogen in the astrocytes of the hippocampus and frontal cortex.[84] Smaller increases occur in cerebellar cortex, but none in the hypothalamus or midbrain reticular formation. Interestingly, in this study glycogen was present only in astrocytes and not in neurons, oligodendroglia, or microglia.

High-energy Phosphates

Oxygen consumption as a measure of the "health" of tissue is somewhat crude and may, in fact, be misleading. The major oxygen consumption of tissues is through the electron-transport system, at a rate controlled by and coupled to the phosphorylation of ADP to ATP. This control may be lost and electron transport, and, thereby, oxygen consumption may be uncoupled from phosphorylation and proceed at an uncontrolled or even supernormal rate. Unreplenished, the cell's store of ATP would soon be depleted and the cell would in fact be dying, although consuming oxygen in abundance.

Interest in the brain levels of high-energy phosphates during anesthesia was stimulated by the hope of casting light on the role of energy metabolism in narcosis. Depleted levels might incriminate inhibition of oxidative metabolism as a primary cause of anesthesia, whereas an excess could suggest that decreased oxidative metabolism is secondary to the primary effect of the anesthetic. Because of the extremely rapid breakdown of labile phosphates during decapitation and complete freezing of the brain, critical importance attaches to the experimental procedure. It is because of this difficulty in technique that much of the earlier work must be critically re-evaluated. An investigation of methodology by Weiner[85] indicated no change in ATP content with ether or pentobarbital anesthesia, although a higher level of phosphocreatine was found. In the above-cited work of Brunner *et al.*,[79] it was also found that animals anesthetized with ether, halothane, methoxyflurane, or enflurane all had approximately 30–50 per cent increases in brain energy stores. However, these were principally a result of increased glucose and glycogen levels, not large increases in ATP or phosphocreatine. Other workers, using barbiturate anesthetics, also found the cortical levels of ATP and phosphocreatine stabilized or only slightly increased during anesthesia.[86, 87] The weight of evidence indicates a small increase in phosphocreatine and no change in ATP levels during narcosis.[88, 89]

The mechanism of the inhibition of oxygen uptake by anesthetics may involve several control points in the energy-generating and energy-utilizing machinery of the cell. Cohen and Marshall[90] have shown how this can occur at the NAD reductase step in the oxidative phosphorylation system with halothane. In addition to a direct effect of anesthetics on this pathway, Quastel[46] postulated a model in which a Na^+–K^+-linked ATPase in the plasma membrane is seen as one of the possible sites of anesthetic inhibition leading to a decrease of cellular oxygen uptake. Inhibition of ATP breakdown in the plasma membrane would increase the ATP/ADP ratio and consequently decrease the ADP available for phosphorylation. Indirectly, then, the effect is again upon the oxidative phosphorylation system. Ueda and Mietani[91] looked for a direct effect of general anesthetics on the ouabain-sensitive Na^+–K^+-linked ATPase of microsomal fractions of rabbit brain. Decreased ATPase activity was demonstrated only with ether and with halothane when the partial pressures were eight to ten times pressures used clinically. However, microsomal ATPase may not be bound to lipoprotein membrane in the same way as the Na^+–K^+-sensitive ATPase of plasma membrane. On the other hand, firefly luciferase,[92] an enzyme with ATPase activity, is inhibited by therapeutic concentrations of diethyl ether and halothane.

Chance *et al.*[93] have shown that the site of action of an inhibitor of electron flow can be identified by the crossover point, the point in the respiratory chain where reduced cofactor accumulates upstream and reduced forms are depleted downstream. With barbital and other oxybarbiturates, this crossover point is found between reduced nicotinamide (NADH)

and flavin. Several sites of inhibition may be postulated.[94] Cohen's study[90] of the action of halothane on the rate of phosphorylation of ADP in liver mitochondrial preparations is of particular interest. It demonstrated that 50 per cent inhibition is produced by approximately 1.6 per cent halothane. The ability of succinate to reverse the inhibition suggests that halothane may interfere with the oxidation of reduced NADH by flavoprotein. Even greater sensitivity of oxidative metabolism to volatile anesthetics has been observed in certain cell culture strains.[94] However, a factor often discounted in studies with volatile anesthetics is the possibility of an effect due to the oxygen which is used as carrier gas. Williams and Haugaard[96] found that 100 per cent oxygen at 1 atmosphere depresses ATP synthesis in rat brain homogenates. This depression occurs earlier than depression of substrate utilization, indicating that oxidative phosphorylation is particularly sensitive to inactivation by oxygen *in vitro*. On the other hand, there is a report[97] that hyperbaric oxygen (3–6 atm) shortens the sleeping time of mice anesthetized with sodium pentobarbital.

In the above-mentioned studies of high-energy phosphate, the investigators measured only the total concentration of the pool of the various compounds. The study of cerebral levels as such has an inherent limitation. For example, an increase can result from either increased production or decreased utilization. One must also be aware that constancy in the size of a pool of a high-energy compound does not necessarily mean that it is being turned over at a constant rate. An anesthetic could affect the turnover rate without altering the absolute level. It must also be remembered that compartmentalization of high-energy phosphates in various areas of the cell may exist, and that the nucleotide may be displaced from one compartment of the cell to another without any change in the size of the total pool. At present there is no good evidence for or against such compartmentalization.

Amino-acid and Protein Metabolism

Protein turnover in the living brain takes place at a high rate relative to turnover in liver and in secreting glands. The reason for such high turnover is better understood now that proteins are known to be exported continuously from the perikaryon to the nerve ending. Such transport occurs at speeds ranging from 1 to 400 mm/day or more. The rapid transport is oxygen dependent but is unaffected during general anesthesia. Lidocaine, 0.4 per cent, inhibits the rapid axonal transport of proteins *in vitro*,[98] and so does 0.5 per cent procaine (G. Aasheim *et al.*, to be published). The inhibition of transport by lidocaine precedes the loss of microtubules from the axon,[99] but it is not yet known whether either effect occurs during therapeutic nerve blocks. If found, this will represent a toxic effect rather than a physiologic component of nerve block, since the minimum concentration of local anesthetic blocking protein transport is more than ten times as high as that necessary for conduction block.[98]

As previously mentioned, the amino acids necessary for the functioning of the brain are partially synthesized in the brain cells from glucose and partially transported across the blood–brain barrier. The transport of amino acids into the brain is slow,[100] but rapid turnover inside the brain is maintained by uptake from the free amino acid pool[101] derived from the intermediary metabolism of glucose. In the brain of the rat the rate of incorporation of ^{35}S from labeled methionine into the proteins can replace all of the methionine in cerebral proteins in 20 days.[102] The effect of anesthetics on uptake of labeled amino acids was unequivocal. Ether anesthesia in rats maintained at normal body temperature decreased the rate of uptake of intracisternal ^{35}S into brain proteins by 34 per cent. Intraperitoneal injection of pentobarbital, 75 mg/kg, diminished uptake by 24 per cent. The effect was greatest in animals that were most deeply anesthetized. Nechaeva *et al.*[103] obtained generally similar results with radioactive methionine and glycine.

That the brain can rapidly synthesize amino acids from glucose was first demonstrated in brain slices by Beloff *et al.*,[104] and Barkulis *et al.*[105] confirmed this in cortical slices of perfused cat brain. They reported that narcosis with pentobarbital did not appreciably change the pattern of labeling. However, Tsuji *et al.*[106] observed a decrease in cortical levels of γ-aminobutyric acid (GABA) and

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glutamic acid in rat brain after intraperitoneal injection of pentobarbital (30 mg/kg). Cyclopropane, 10–15 per cent, also provoked a decrease in GABA level. The findings are of interest because GABA is a transmitter at inhibitory synapses; nevertheless, it seems doubtful that these changes play any direct part in causing the anesthetic state, since they also occur under certain conditions that do not give rise to anesthesia.

Besides effects of anesthetics on protein biosynthesis in brain, Lajtha and Toth [107] noted that the excitement stage may lower the normal resting level of glutamine. (Malhotra [108] concluded that anesthetic excitement depressed the acetylcholine content of brain.) Apparently, increased activity of the brain generaly is associated with a lowering of the glutamine level. Under ordinary conditions, this decrease of glutamine is not noticed because cerebral stimulation also has the effect of liberating ammonia in the brain, which in turn promotes increased *de novo* synthesis of glutamine; in anesthesia it is noticed because anesthesia prevents production of free ammonia in the brain, as does ethanol intoxication. Dobkin [109] has confirmed these observations, adding that the stimulus of decapitation, in itself, significantly decreased the glutamine content of the brain in the rat. However, Biebuyck and Hawkins [81] have noted a 30 per cent *increase* of the glutamine concentration in rat brain 10–40 minutes after the onset of halothane, pentobarbital or ketamine anesthesia. Here again, technique doubtless plays a determining part. Biebuyck did not decapitate his animals but blew their brains out.

Cremer and Lucas [110] have presented evidence that the pool of glutamate is not metabolically homogeneous within the cell and that pentobarbital affects the hypothesized compartments unevenly.

A distinctive effect of halothane on the permeability of brain cells to an enzyme, glutamate oxalacetate-transaminase (GOT), was observed by Amakata and Greene [111] *in vitro*. Normally the permeability of cellular membranes to this enzyme is very low, and it exists entirely as an intracellular enzyme. Halothane in concentrations of 1 and 2 per cent significantly increased the efflux of GOT from slices of cerebral cortex. This effect was specific inasmuch as it was not present in midbrain, heart, and liver slices, and did not occur with ether. While halothane increased membrane permeability, it did not affect GOT activity. The functional significance of the observation is unknown. An interesting sidelight on the modification of protein metabolism by general anesthetics was contributed by Ungar.[112] All the common ones inhibited a protease obtained from rat cerebral cortex. The ID_{50} was several times higher than the anesthetic AD_{50} for goldfish, but the correlation was excellent ($r = 0.9911$) and was interpreted as pointing to the combination of anesthetics with structured water surrounding the protein molecules, in other words, supporting the Pauling–Miller microhydrate-crystal theory of anesthesia.

Neurotransmitters

Once the doctrine of chemical transmission of nerve impulses became firmly established, attempts were made to determine whether the cerebral content of neurotransmitters or their precursors varied with the functional state. What is more important, now that labeled precursors are freely available, the rate of turnover of many substances can be determined. Thus, the studies of effects of anesthetics on concentrations in brain, or on regional distribution within the brain, are giving way to measurements of effects on turnover rates. The earliest neurotransmitter to be studied was acetylcholine; more recently, the monoamines have been gaining much attention.

Acetylcholine

Diethyl ether and pentobarbital, examined by Crossland and Merrick,[113] produce little change in the acetylcholine content of various regions of the brain—the cerebral hemispheres, the upper brainstem, the cerebellum (the medulla is an exception)—at least in adult rats. In young rats the results were different. All parts of the young brain underwent an increase in acetylcholine during light anesthesia with either agent and a further increase during deep anesthesia. Schmidt [114] reported increases in various regions of the brain with halothane anesthesia, presumably expressing decreased liberation of acetylcholine

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from cholinergic neurons secondary to anesthetic depression of cerebral activity. It appears that the acetylcholine content of the brain increases inversely with the state of functional activity and eventually reaches a plateau. The plateau is explained by the limited capacity of the tissue to accumulate the substance. It has been known for many years that acetylcholine is released continuously from the cerebral cortex [115] and also from the ventral surface of the cat brain [116] and from brain slices.[117] The amount of "weeping" of acetylcholine from the cortex decreases with increasing anesthetic depression. In sheep lightly anesthetized with ether, cyclopropane, or pentobarbital, the rate of release of acetylcholine is 1.0–3.54 ng/min/cm^2 of cortex and is roughly proportional to the electrical activity of the brain.[118] In the visual cortex of conscious, free-moving rabbits,[119] the rate of release of acetylcholine is also related to the activity and state of arousal; it is three times higher in the free-moving animal than in animals anesthetized with pentobarbital, 30 mg/kg, intravenously.

Monoamines

An interesting new aspect of the influence of anesthetics and narcotics on amino-acid metabolism in brain is their effect on catecholamine and dopamine biosynthesis. Subject to the usual cautions concerning species differences, there is reason to suppose that the narcotic effect of morphine may be bound up with the action of morphine on dopamine metabolism. In normal rats the accumulation of dopamine from tyrosine injected intracisternally is increased in the hypothalamus and striatum approximately 1.3-fold one hour after injection of morphine (60 mg/kg). In rats made tolerant to morphine the increase was more than twofold.[120] Further arguments for the mediation of the analgesic action of morphine through metabolism of dopamine have been presented by Fukui and Takagi.[121] Analgesic doses of morphine (10 mg/kg, sc) increased the content of the dopamine metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), in the brain of the normal mouse. The time course of the increase of the dopamine metabolites was approximately the same as the time course of the morphine analgesia. In morphine-tolerant mice, the concentrations of DOPAC and HVA were not different from normal. The next question to be asked is, what is the mechanism of the increase in DOPAC and HVA? There are, as usual, several possibilities: 1) Increased biosynthesis of dopamine, leading to enhanced formation of the metabolites. 2) Impeded resorption of dopamine into the storage form, thereby leaving more available for degradation. 3) Inhibited removal of the dopamine metabolites. We suggest that the work of Smith *et al.*[122] and Clouet and Ratner,[120] cited above, favors the first of these possibilities.

Levorphanol is about ten times more potent than morphine in its ability to increase locomotor activity and to deplete cerebral catecholamines.[123] The analgesic action supposedly results from a decrease in the brain catecholamine concentration which results in a corresponding increase in the amount of dopamine. Chlordiazepoxide (Librium) and diazepam are reported to decrease norepinephrine turnover in the thalamus–midbrain, cortex, and cerebellum, and dopamine turnover in the striate region.[124] However, the dosage of the drugs, 10 mg/kg injected subcutaneously, seems remarkably high by human standards, and the suggestion of the authors that the mode of action of these minor tranquilizers involves catecholamines in the central nervous system can hardly be accepted on this basis.

The effect of general anesthesia on brain monoamine content is much less striking than that of the narcotics. Bonnycastle and colleagues,[125] using a biological assay, reported finding increases in 5-hydroxytryptamine after the administration of a variety of central nervous system depressants, including pentobarbital, thiopental, diethyl ether, ethanol, meperidine, and morphine. However, Diaz *et al.*,[126] using a more refined spectrofluorimetric method, could find little effect in the cerebral level of serotonin (5-HT) with 15 per cent cyclopropane, 3 per cent diethyl ether, or 0.75 per cent halothane. The main metabolite of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), was increased, presumably because its removal was prevented. They concluded that these anesthetics probably block the 5-HIAA transport mechanism; there was no evidence of

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inhibition of monoamine oxidase activity. Sung[127] reported that ketamine, 40 mg/kg, in the rat produces in the brain a significant increase in serotonin and a decrease in norepinephrine concentration. Thiopental did not affect the concentration of the monoamines. The turnover rate of cerebral serotonin was markedly depressed after ketamine. Cardier[128] examined *in vitro* the effect of cyclopropane on catecholamine-O-methyltransferase, but found little effect. On the whole, there is still little to suggest that an effect on neurotransmitter metabolism is important in the establishment or maintenance of general anesthesia.

A metabolic basis for the anesthetic state is at present a discredited idea because electrical excitability at synapses becomes a casualty at concentrations of anesthetic that have had little or no demonstrable metabolic effect *in vitro*.

Efforts are presently being made to link impairment of mitochondrial pumping of Ca^{++} with the presence of a "clinical" concentration of anesthetic.[129] Such an effect could produce hyperpolarization of the neuronal membrane and reduce excitability,[130] and would represent an effect at a lipoprotein membrane, that of the mitochondrion, but whether this is merely another of the multitudinous correlations with lipophilic properties of anesthetic molecules or the key to anesthetic depression of the nervous system remains entirely unsettled.

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