Neuroendocrine and Other Effects on Carbohydrate Metabolism During Anesthesia

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The neuroendocrine response to anesthesia and surgery, and its role in postoperative disturbances in metabolic balance have been widely studied and are discussed elsewhere in this symposium. The role of the endocrine response, which may start as early as the induction of anesthesia with some agents, in the etiology of acute disturbances in metabolism during the operative period is less clear. That disturbances in intermediary metabolism do occur in the anesthetized patient is apparent, but the nature of these disturbances is obscured by inadequate and often conflicting data.

Total body oxygen consumption—the metabolic rate—may rise, fall, or remain unchanged, depending on the anesthetic agent and the conditions of observation. Cerebral oxygen consumption falls during anesthesia with intravenous agents, but no information is available for the inhalation agents. Diethyl ether and cyclopropane anesthesia are accompanied by moderate to marked hyperglycemia, whereas blood sugar is unchanged during anesthesia with thiopental, and evidence for the effect of halothane on blood glucose is inconclusive. A decrease in utilization of infused glucose, “glucose intolerance,” has been reported to occur with several agents, but the interpretation of the reported data has recently been challenged. Elevations in serum lactate and pyruvate during ether and cyclopropane anesthesia have been attributed to the sympatho-adrenal response associated with these agents, but this interpretation has also recently been questioned. It has been suggested that elevations in serum inorganic phosphate, which occur during ether, cyclopropane, and thiopental anesthesia, may reflect an effect of anesthesia on storage or utilization of high energy organic phosphates; but again alternative interpretations have been proposed which might indicate that these changes are secondary, rather than primary, effects of anesthesia.

It is our purpose to consider whether the observed changes reflect a direct effect of the anesthetic on energy metabolism, which may in turn deprive the nervous system of energy needed for the normal activity of the conscious state; or whether such changes may be secondary, may simply reflect the decreased metabolic need of an organism whose function has been depressed in some other manner. Accordingly, an attempt will be made to correlate, as far as possible, observations in man with current theory and experimental data concerning the mechanism of anesthesia and to consider other possible explanations for the observations presented.

It is perhaps representative of the confusion concerning metabolic effects of anesthesia that the effect of anesthesia on the metabolic rate, which surely one would consider of central importance to the issues in question, is in doubt. It has been generally assumed, largely on the basis of early studies in animals, that depression of oxygen consumption is fundamental to the process of anesthesia itself. Current evidence suggests that anesthesia with diethyl ether or with cyclopropane may result in no change or actually an increase in oxygen consumption. In a recent report, Topkins and Artusio make the interesting observation that metabolic rate in the surgical patient immediately prior to induction of anesthesia may be elevated, presumably on the basis of apprehension, and they suggest that a comparison of preinduction with postinduction oxygen consumption under these conditions has been responsible for misleading data.

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By contrast to the apparent unchanged or increased oxygen consumption during anesthesia with diethyl ether or with cyclopropane, thiopental and halothane anesthesia are reported to be accompanied by appreciable lowering of metabolic rate.\textsuperscript{6,8} A possible explanation for such differences among anesthetic agents is on the basis of differences in sympatho-adrenal response. The increase in catecholamines which has been long suspected to occur during anesthesia with diethyl ether\textsuperscript{9,10} has now been clearly demonstrated by Price and associates.\textsuperscript{11} Their observation of an elevation in norepinephrine, rather than epinephrine, during ether anesthesia in man came as somewhat of a surprise and has been considered by some to afford a less satisfactory explanation of ether's metabolic effects (see below). Concentrations of norepinephrine in peripheral blood were reported to be elevated also during anesthesia with cyclopropane, but not during anesthesia with thiopental or halothane. The calorigenic effects of norepinephrine, although somewhat less than those of epinephrine,\textsuperscript{12} are adequate to explain the differences in oxygen consumption between ether and cyclopropane on one hand, and halothane and thiopental on the other; and it is thus hard to escape the conclusion that the occurrence or failure of sympatho-adrenal response during anesthesia is an important factor in determining changes in metabolic rate.

A limited amount of evidence is available on the effects of anesthesia on oxygen consumption of the brain, based upon the measurement of cerebral blood flow and simultaneous arterio-venous oxygen differences. Such studies of cerebral oxygen consumption during anesthesia have been handicapped by the technical difficulty of measuring cerebral blood flow by the classical Kety nitrous-oxide technique in the presence of other gaseous anesthetics. However, information is available on the effects of intravenous anesthetics on cerebral oxygen consumption, and it is clear from the studies of Himwich, and of Kety and their associates\textsuperscript{13-15} that thiopental anesthesia is accompanied by a progressive depression in oxygen consumption and that the depression is closely proportional to depth of anesthesia.

The barbiturates in hypnotic doses; morphine, meperidine, chlorpromazine and promazine in therapeutic doses; and intravenous alcohol sufficient to produce mild to moderate intoxication all are devoid of measurable effect on cerebral oxygen consumption.\textsuperscript{16} By contrast, severe alcoholic intoxication is associated with profound depression of cerebral oxygen consumption\textsuperscript{17} similar to that observed in deep barbiturate anesthesia.

Information concerning effects of anesthesia on oxygen consumption of other organs is limited. Splanchnic oxygen consumption during thiopental, cyclopropane, and curare anesthesia in man has been reported to be depressed and in proportion to depression of splanchnic blood flow.\textsuperscript{18} By contrast, during spinal anesthesia and with equivalent depression of splanchnic blood flow, splanchnic oxygen consumption is apparently well maintained.\textsuperscript{19} Cardiac oxygen extraction during ether anesthesia in the intact dog is relatively well maintained,\textsuperscript{20} whereas in the heart-lung preparation oxygen consumption may be considerably depressed with a variety of agents.\textsuperscript{21}

The demonstration of a decrease in cerebral oxygen consumption \textit{in vivo} and \textit{in vitro} logically suggests that anesthesia may interfere with energy metabolism necessary for function of the nervous system, \textit{i.e.}, that depression of tissue respiration may be responsible for the phenomenon of narcosis. Quastel and associates were the first to report anesthetic-induced depression of oxygen consumption in brain cortex slices\textsuperscript{22,23} and to suggest this as a possible mechanism of anesthesia. The significance of Quastel's early work was soon questioned on the basis that the concentrations necessary to depress oxygen consumption of brain \textit{in vitro} were much greater than necessary to produce anesthesia \textit{in vivo}; the observed effects were, in fact, often irreversible,\textsuperscript{24,25} and "therapeutic" concentrations failed to depress oxygen consumption. However, oxygen consumption of unstimulated tissue preparations is considerably lower than observed \textit{in vivo}, and enthusiasm for a metabolic hypothesis was rekindled by the demonstration that concentrations of anesthetics comparable to those used clinically do depress respiration of electrically stimulated tissue preparations. Since the metabolic pathways of stimulated and resting activity may differ, the search for a specific metabolic defect again pressed for-
ward. Quastel, accepting the conclusion that oxygen consumption of unstimulated tissue is essentially unaffected at anesthetic concentrations, more recently has suggested such a specific defect might be in "an oxidative step in cell respiration concerned with the synthesis of adenosinetriphosphate." 26

The demonstration by Brody and Bain that the barbiturates in concentrations equivalent to surgical anesthesia block the transfer of energy of oxidation to creatine phosphate and adenosinetriphosphate in tissue homogenates has offered one of the most attractive metabolic explanations of narcosis. 27, 28 The evidence for and against this "uncoupling" of oxidative-phosphorylation as the mechanism of anesthesia has been summarized in detail by Hunter. 29 Perhaps the most widely quoted contrary evidence is that not all uncoupling agents produce anesthesia, and not all anesthetics have an uncoupling effect. Although it is attractive to assume that the mechanism of anesthesia is the same for all agents, it goes without saying that such need not be the case.

Currently, it is fashionable to take the position that the metabolic effects of anesthesia are secondary to depression of neuronal activity. Impressive evidence for this has been provided by the work of Larrabee and associates 30 who were able to demonstrate depression of transmission in the rabbit cervical sympathetic ganglion by a variety of anesthetic agents at concentrations which had no effect on oxygen consumption or on pyruvate utilization. In later studies, however, Edwards and Larrabee 31 observed that in contrast to their findings in the rabbit, oxygen consumption of the rat stellate ganglion was not infrequently depressed before ganglionic transmission.

Buchel and McIlwain, 32 as early as 1950, concluded that "biochemical changes found in vivo in the bulk of the brain are a result of depressed functional activity caused by the narcotic, and not, as has been urged, its cause." They based this opinion on their observation that anesthesia, in vivo, is associated with increased concentrations of energy-rich phosphates in the brain in contrast to the lowered creatine phosphate which had been observed in brain cortex in vitro; and they postulated that a direct depression of functional activity by the anesthetic, by reducing the need for energy, permits the accumulation of organic phosphate to occur.

Levy and Featherstone 33 studied the effect of xenon and of nitrous oxide on glucose and pyruvate metabolism and on oxidative-phosphorylation of guinea pig brain homogenates. At anesthetic concentrations they observed no alterations in metabolism and conclude that "theories of anesthesia involving metabolic inhibition of glucose or pyruvate oxidation or the uncoupling of phosphorylation...are not applicable to the gaseous anesthetics xenon or nitrous oxide." Carpenter, 34 commenting on Levy and Featherstone's work, suggests that inability to detect metabolic changes in brain preparations may simply reflect inadequately sensitive methods. Or, as Keith Killam has suggested to the author, such negative metabolic studies may simply reflect our ignorance of how energy necessary for neuronal activity is generated, our ignorance of the specific links between metabolism and function, and hence our inability to know where to look for specific effects.

In summarizing current evidence in his excellent review, Hunter 35 states that the "ability of general depressants...to reduce electrically stimulated oxygen consumption might be the indirect result of a decreased neuronal response to electrical stimulation or a direct result of inhibition of an enzyme in the oxidative system." Later, however, he concludes that "it seems inescapable that the primary in vivo effect of most hypnotics and anesthetics is a decrease in neuronal activity, with decreases in oxidation being largely secondary to the decreased utilization of ATP. The decrease in neuronal activity may be the result of special sensitivity to these drugs at synapses in general or at synapses of the reticular activating system."

Such a conclusion certainly would appear to be the more consistent with other current information and theory relating to the mechanism of anesthesia: effects of anesthetics on the electrical activity of the brain, and in particular the reticular activating system; 35 Pauling's and Miller's molecular theories of anesthesia 36, 37 emphasizing the possible role of physical properties of anesthetics in affecting cell function; and the impressive fact of narcosis produced by electrical current, "electronarcosis." 38
On the other hand, it must be remembered that the nature of (or perhaps even the existence of) the chemical component in electrical activity of the nerve cell and of synaptic transmission under normal conditions is still unresolved, and until the mechanism of conduction is better understood it is unreasonable to expect to resolve in detail the nature of alterations in nervous activity by drugs. That the apparent paradox may be more imaginary than real is perhaps exemplified by the studies of Elliott and associates in 1951 on the effects of anesthesia on aerobic and anaerobic glycolysis and of acetylcholine synthesis.\textsuperscript{39, 40} The small metabolic changes which they observed at drug levels sufficient to inhibit acetylcholine synthesis led them to conclude that changes in acetylcholine synthesis "are more significant in the production of narcosis \ldots than effects on energy production or formation." Regardless of the ultimate role of acetylcholine synthesis in the normal activity of the central nervous system, here is an example of a possible anesthesia-induced disturbance in neuronal activity which is at the same time a "metabolic" disturbance, although certainly not the kind of metabolic disturbance in energy metabolism for which many have sought.

I would like to return now to observations in man and in the intact experimental animal, and it must be stated that these have not contributed significantly to the solution of the above problems. The most widely known clinical metabolic disturbance is certainly the elevated blood sugar which occurs during anesthesia with ether and with cyclopropane.\textsuperscript{41, 42} Hyperglycemia does not occur during uncomplicated thiopental anesthesia, and probably not during anesthesia with halothane, although evidence on the latter is somewhat conflicting.\textsuperscript{43} The role of the sympatho-adrenal response to ether anesthesia in the etiology of hyperglycemia has been strongly suggested by the studies of Brewster et al.,\textsuperscript{45} who found no change in blood sugar when ether anesthesia was administered to dogs in the presence of a total sympathetic block and adrenalectomy. Whereas ether anesthesia in the dog is accompanied by increase in levels of epinephrine, in man there is an elevation in norepinephrine rather than epinephrine.\textsuperscript{11} The relatively lesser elevations in glucose which ether produces in man\textsuperscript{45} in comparison to those observed in the dog\textsuperscript{43} are consistent with the known but considerably smaller glycolgenolytic actions of norepinephrine.\textsuperscript{12} The occurrence of hyperglycemia during cyclopropane anesthesia, in which increased blood levels of norepinephrine are also observed, and the absence of hyperglycemia or of increased catechol amines during thiopental anesthesia provides additional suggestive evidence of the role of sympatho-adrenal activity in the etiology of hyperglycemia during anesthesia.

If it appears likely that sympatho-adrenal activity may be a cause of hyperglycemia during anesthesia, it is by no means clear that it is the only cause. The original views of Quastel and his associates, less popular now, suggest a specific depression of oxidative metabolism of glucose. The more recent in vitro studies of uncoupling of oxidative phosphorylation by some anesthetics, together with clinical observations of simultaneous elevations in blood glucose and serum inorganic phosphate, have suggested that entrance of glucose into the cell via phosphorylation may be impeded.\textsuperscript{45} Evidence for or against such possibilities has been difficult to obtain, and the evidence which is available is difficult to interpret. It has been reported that anesthesia with a variety of agents is associated with a decreased tolerance to infused glucose,\textsuperscript{46-47} and it has been suggested that this reflects decreased glucose utilization. However, Greene\textsuperscript{42} has taken serious exception to the published data on glucose tolerance studies during anesthesia, both as to validity and interpretation. He correctly points out that the apparent glucose intolerance during cyclopropane and ether anesthesia may simply reflect the superimposition of a glucose load on a changing baseline, since other studies indicate that blood glucose rises progressively during anesthesia with either of these agents. The possibility that ether anesthesia may interfere with the action of insulin has also been considered by Henneman and Vandam.\textsuperscript{48} Their conclusion that insulin resistance occurs during ether anesthesia has been questioned by Greene, again on the basis of the validity and interpretation of data.\textsuperscript{42} It has also been suggested that the marked depression of renal function which accompanies ether and cyclopropane anesthesia may contribute to the ap-
parent alterations in tolerance to infused glucose. However, since in a normal glucose tolerance test little if any glucose is spilled by the kidney, this would not appear to be an important consideration.

It is odd that Greene in his exhaustive effort at critical evaluation of the effects of anesthesia on intermediary metabolism has limited his attention to inhalation agents, omitting entirely the comparatively quite informative data obtained during anesthesia with intravenous agents, thiopental in particular. In contrast to the difficulties in interpretation presented by the cyclopropane and diethyl ether data, the demonstration of glucose intolerance during thiopental anesthesia appears to be relatively straight forward. Sympathoadrenal responses are depressed by this agent, and blood sugar remains essentially unchanged in the “fasting” patient anesthetized with thiopental. Renal function is less disturbed during anesthesia with thiopental than with cyclopropane or ether and presumably is even less apt to contribute to abnormal disposition of infused glucose during anesthesia. Thus the demonstration of consistently elevated levels of blood glucose during thiopental and infused glucose above those observed during and following infusions of glucose in normal unanesthetized patients strongly suggests an alteration in the metabolic disposition of glucose with this agent.

It would seem likely (though by no means certain, in view of the marked variation of metabolic effects in vitro) that if glucose intolerance occurs with one anesthetic agent, it might well occur with others. And, in fact, there are specific reasons, apart from any speculative effect on glucose transport or metabolic destruction, to predict such effects. The adrenal cortical response to ether and to cyclopropane anesthesia, for example, can be expected with confidence to affect the metabolic disposition of glucose, since marked glucose intolerance has been reported in normal man as early as eight and one-half hours following initiation of corticosteroid therapy.

The well-known elevations in serum lactate and pyruvate and the less consistent elevations in citrate and alpha-ketoglutarate which occur during anesthesia with diethyl ether and cyclopropane but not with thiopental may, again, be reasonably assumed to be related to increased sympatho-adrenal activity; and Brewster and associates’ demonstration that total sympathetic block and adrenalectomy prevent the rise of lactate and pyruvate of ether anesthesia in the dog specifically suggests this interpretation.

Presumably the increases in serum lactate and pyruvate occurring during ether anesthesia in normal man thus reflect increased production. Considerably greater elevations in lactate are observed during ether anesthesia in the infant or small child, who at the same time manifests other evidence of greatly increased sympatho-adrenal activity, most notably marked elevations in pulse and respirations. Large accumulations of lactate and pyruvate may also occur when ether anesthesia is administered in the presence of metabolic defects in lactate or pyruvate utilization, such as occurs in cirrhosis or in Cushing’s syndrome.

From the foregoing, it appears likely that the well-known sympatho-adrenal response to anesthesia and surgery contributes to elevations of lactate during general anesthesia. However, it has also long been a source of concern that moderate lactacidemia, which may occur during a well-conducted anesthesia, and in the absence of anoxemia, shock, or other obvious explanation, may yet reflect tissue hypoxia. This suspicion is perhaps strengthened by the demonstration by Greene that the marked lactacidosis of severe hypoxemia can be largely prevented, in the laboratory animal, by prior sympathetic block. By this token the lesser elevations in lactate, whether or not mediated via sympatho-adrenal activity, might suggest a lesser hypoxia, presumably at a peripheral site.

In more recent studies, Greene has attempted to examine this possibility by correlating metabolic changes with changes in tissue oxygen tension. Following Huckabee’s calculation of “excess lactate,” from measured concentrations of lactate and pyruvate, as an index of anaerobic glycolysis, Greene has reported an increase in excess lactate production during anesthesia with ether and with cyclopropane. He attributes these to tissue hypoxia, evidence for which at present appears to be limited to a report of moderate and variable
decrease in skin oxygen tension which occurred during ether anesthesia in two of six patients studied.\textsuperscript{57} The interpretation of changes in excess lactate as necessarily reflecting tissue hypoxia is in conflict with Huckabee’s own views;\textsuperscript{58, 59} it is also in conflict with Huckabee’s data which indicate that arterial oxygen saturation must fall approximately 50 per cent before excess lactate is affected. It might also be pointed out that the concept of excess lactate as an index of anaerobic glycolysis and oxygen debt has been questioned.\textsuperscript{60, 61}

The elevations in serum inorganic phosphate which occur during anesthesia with most agents\textsuperscript{45, 62} rank second only to anesthetic hyperglycemia in theoretical interest. The accumulation of inorganic phosphate in the peripheral circulation together with a simultaneous elevation in blood sugar, and possibly with abnormal glucose “tolerance,” appears to be precisely what one might expect in the presence of an anesthesia-induced depression of oxidative phosphorylation. But whether the observed increases in serum inorganic phosphate actually reflect an effect of anesthesia on cellular metabolism is hard to establish, and there are a variety of reasons to suspect that they do not. On a theoretical basis, uncoupling of oxidative phosphorylation as the mode of anesthetic action has many shortcomings, not the least of which is the fact that in vivo animal studies, brain levels of ATP and phosphocreatine usually rise\textsuperscript{33} rather than fall as one would expect if synthesis of high energy organic phosphates were blocked, and as already discussed. However, depression of muscle phosphocreatine, recently reported by Henneman and Vandam during ether anesthesia,\textsuperscript{63} appears to support the uncoupling theory.

In an attempt to determine the cause of increased serum inorganic phosphate as observed clinically, Henneman and Bunker\textsuperscript{45} have examined some of the factors which might be responsible. It is apparent that increase in blood levels of epinephrine or norepinephrine, or of corticosteroids, cannot in this instance be implicated, since all induce a fall in serum inorganic phosphate.\textsuperscript{12, 48} A marked fall in renal excretion of phosphate was documented in a small group of carefully studied patients,\textsuperscript{49} but there remained a very considerable amount of the calculated increase in total phosphate in the extracellular fluid which could not be accounted for by changes in renal function.

In a separate group of patients the effect of change in acid-base balance on concentrations of serum inorganic phosphate, as well as on lactate, pyruvate, citrate, and alpha-ketoglutarate was measured. The metabolic response to respiratory acidosis\textsuperscript{45} and alkalosis\textsuperscript{64} during clinical anesthesia with thiopental, nitrous oxide, and curare, and the metabolic response to respiratory acidosis during ether anesthesia were identical to those reported to occur in unanesthetized man\textsuperscript{65} and in the nephrectomized dog.\textsuperscript{66} Specifically, during induced acidosis there is a moderate to marked elevation in serum inorganic phosphate and simultaneous depression of lactic, pyruvic, and citric acids. Similarly, respiratory alkalosis is accompanied by changes in the opposite direction, a large fall in inorganic phosphate and elevations in lactic, pyruvic, and citric acids. These changes, together with reciprocal changes in serum sodium and chloride, are the basis for Giebisch’s “extra renal response”\textsuperscript{66} to acute disturbances in acid-base balance, and represent electrolyte shifts which tend to buffer change in pH in the extracellular fluid. Thus a rising concentration of inorganic phosphate in acidosis provides an important new source of base, which, by combining with hydrogen ion, helps to minimize change in pH. The alterations in other electrolytes, which are less in magnitude and less consistently observed, presumably occur in accommodation to the changing concentrations of phosphate and bicarbonate buffers to preserve electrical neutrality.

Disturbances in acid-base balance occurring during anesthesia in man and in the laboratory animal have received a great deal of attention, but unfortunately the relation of changes in pH to blood levels of the products of intermediary metabolism—lactate, pyruvate, citrate, inorganic phosphorus—has not been appreciated until recently. The effect of changes in pH which are known may occur under anesthesia, together with the probable effects of adrenocortical and adenomedullary stimulation and depression of renal function, can provide an adequate explanation of most if not
all of the changes in carbohydrate metabolism as reflected in the peripheral blood.

To take the simplest example, thiopental anesthesia is accompanied by an elevation in serum inorganic phosphate and simultaneous depression of lactate, pyruvate, citrate, and alpha-ketoglutarate. These are the changes previously reported to accompany respiratory acidosis, and they may well be secondary to respiratory depression with the resultant respiratory acidosis which may occur with this agent. That the changes observed were related to changes in acid-base balance is suggested by the small number of studies in which measurement of pH was included. When pH was unchanged, no changes in electrolytes were observed. When respiratory acidosis was induced, inorganic phosphate rose, and lactate, pyruvate, citrate and alpha-ketoglutarate remained unchanged or fell. In a separate group of patients respiratory alkalosis during thiopental, nitrous oxide, and curare anesthesia was accompanied by a fall in serum inorganic phosphate, and elevations in lactate, pyruvate, and citrate.

Comparable studies are not available for cyclopropane and are available for ether only during induced respiratory acidosis, but not during induced respiratory alkalosis. In the absence of such information it is probably fruitless to attempt to speculate in detail on the possible role of changes in pH on serum electrolyte balance during anesthesia with these agents. The possible direct effect of change in pH or of P$_{O_2}$ on cellular metabolism has been suggested as possibly of greater importance than the anesthetic; but although efforts have been made to explore this possibility, interpretation of available information on this point is even more difficult.

It is apparent that we have fallen short of the goals set forth at the outset. A variety of "metabolic" effects of anesthesia have been reported, but much of the data is fragmentary or poorly controlled. Any postulated direct effects of anesthesia on intermediary metabolism are obscured by the marked metabolic consequences of endocrine, renal, and respiratory disturbances in acid-base balance. Metabolic information which has been obtained in anesthetized man, for these reasons, does not contribute appreciably to our understanding of the mechanism of anesthesia.

Difficulties in interpretation are further compounded by the marked discrepancies between effects of anesthetics in vitro and in vivo. However, such differences as have been uncovered, rather than being considered a nuisance, should be considered a challenge and as a fortuitous opportunity for the exploration of fundamental mechanisms. It appears desirable that future in vivo studies be made at a cellular level, perhaps on the basis of serial tissue biopsies. Improved methods of handling and analyzing such biopsy material are necessary. Better in vitro systems are also needed, and it is particularly important that such systems be designed to simulate more nearly conditions which exist in intact man. Only by carefully planned studies carried out with improved methods and attempting to relate cellular events to those of the intact organism can the elucidation of the metabolic effects of anesthesia be achieved.

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References


