Anesthesia and Hepatic Metabolism:
Current Concepts of Carbohydrate Homeostasis

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There have been many advances in recent years in our knowledge of the fundamental reactions important in normal hepatic function and metabolism. In addition, there have been advances in our understanding of the effects of anesthetic agents on such reactions and on endocrine control mechanisms. It is not possible here to comment on the numerous significant and basic contributions relating to hepatic metabolism in general. Instead, this survey is concerned with advances and new concepts in three areas: 1) the control of carbohydrate metabolism (including gluconeogenesis) in the liver, and the role of cyclic AMP; 2) hepatic fuel availability and utilization during starvation and anesthesia; 3) advances in the assessment of the redox state of the liver cell and its relation to hepatic function. Many of these advances have possible relevance to present clinical anesthetic practice and future directions of anesthetic research.

Sympathetic Regulation of Carbohydrate Metabolism

The hyperglycemic action of epinephrine has been considered by many to be one of the best understood metabolic effects of the hormone.1 Recently,2 it has become apparent that its mechanism may be exceedingly complicated (see fig. 1), that it is not very well understood, and that increased glycogenolysis, increased gluconeogenesis, and decreased peripheral glucose utilization may all contribute to the hyperglycemia.

The hyperglycemia which follows the injection of epinephrine is the result of at least three separate effects: 1) The direct effect on the liver. This results not only in a net increase in the rate of conversion of glycogen to glucose, but also in stimulation of the rate of gluconeogenesis. 2) A direct effect on muscle. This results in an increased rate of conversion of muscle glycogen to lactic acid, which is released into the blood. Part of this lactic acid is reconverted by the liver to glucose (by gluconeogenesis). Thus, gluconeogenesis is stimulated by epinephrine, not only by its direct effect on the liver, but also by increased availability of substrate. 3) A direct effect on the pancreas to suppress the release of insulin which would normally occur in response to the increase in blood glucose levels.3 This leads to inhibition of peripheral utilization of glucose, thus enhancing and prolonging the hyperglycemia which results from the direct effect of epinephrine on the liver.

The mobilization of hepatic glycogen, secondary to catecholamine release, has been accepted as the mechanism whereby hyperglycemia occurs during diethyl ether anesthesia.5 However, the multiplicity of factors involved is borne out by the fact that diethyl ether causes similar increases in blood sugar in both fed and starved rats.4 In starved animals, the content of glycogen in the liver is extremely low and cannot be the source of the hyperglycemic response. Brunner6 has shown that diethyl ether causes a significant decrease in glucose uptake by isolated skeletal muscle, and it may be that this decreased peripheral utilization accounts in part for the increase in blood glucose seen in the starved state.

Other factors, including the release of free fatty acids from adipose tissue, and the presence or absence of steroids and other hormones, may also influence the response to catecholamines.

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Role of Cyclic AMP in Control of Hepatic Metabolism

Epinephrine increases the rate of glucose production in the liver by stimulating both glycogenolysis and gluconeogenesis. The effort to understand the factors involved in the stimulation of hepatic glycogenolysis led to the discovery of cyclic AMP.\(^7\) It is now known that the conversion of hepatic glycogen to glucose occurs as the result of phosphorylase activation,\(^6\) as well as inactivation of glycogen synthetase.\(^9\) That these hepatic effects of epinephrine are mediated by cyclic AMP seems well established.\(^10\)

Cyclic AMP has been implicated as an intracellular mediator in the actions of a variety of hormones on their target tissues. The role of cyclic AMP in hormonal actions as it is understood today\(^11\) is shown in figure 2. After release from an endocrine gland and transport to its effector cell, a hormone interacts with a component of the cell membrane, the adenylyl cyclase system, a hormone-sensitive constituent of cell membrane. As a result of this interaction, the rate of transformation of ATP to cyclic AMP intracellularly is altered. Cyclic AMP, acting inside the cell, carries out the work of the hormone by effecting the activities of enzymes or permeability processes of the target cell. In some cases the synthesis or release of other hormones is part of the physiologic event under the control of cyclic AMP.

Another hepatic response to epinephrine is potassium release. This also occurs in response to glucagon and exogenous cyclic AMP,\(^12,13\) suggesting that it is probably mediated, at least in part, by cyclic AMP. The efflux of potassium is an early event following the arrival of epinephrine or glucagon at the liver, either coincident with or slightly preceding the efflux of glucose.\(^12,14\)

Cyclic AMP and Catecholamines

Catecholamines stimulate adenylyl cyclase in the liver (presumably in the hepatic parenchymal cells) and in all forms of muscle. The
adrenergic receptors mediating this effect in muscle are characteristically β-receptors, in that isoproterenol is a more potent agonist than either of the naturally occurring catecholamines, and their effects can be selectively blocked by β-adrenergic blocking agents. These characteristics are shared by the receptors in the liver in many species. Although the hepatic responses to catecholamines can be inhibited by ergotamine, the β-adrenergic blocking agents are more effective.\textsuperscript{15}

In the liver, the increased levels of cyclic AMP lead to an increased rate of glucose production by at least three mechanisms\textsuperscript{12}: activation of phosphorylase, inactivation of glycogen synthetase, and stimulation of gluconeogenesis.

Glucagon and Insulin Interaction in Hepatic Metabolism

It is now well established that insulin exerts direct effects on the liver to inhibit the production of glucose and urea, and to promote the uptake of potassium ions. It has been proposed that these effects of insulin may be partly due to a decrease in cyclic AMP in the liver.\textsuperscript{16} Glucagon and epinephrine (which raise the level of cyclic AMP and exogenous cyclic AMP) produce in the liver effects opposite to those of insulin.\textsuperscript{17} The reduction of the intracellular levels of free cyclic AMP by insulin could result from inhibition of adenyl cyclase, or from activation of phosphodiesterase or some other enzyme that metabolizes cyclic AMP.

The antagonistic actions of insulin and glucagon on glycogenolysis, gluconeogenesis, and glycogen synthesis in the liver provide an effective control system for glucose homeostasis and fuel consumption.\textsuperscript{17} Insulin secretion is greatly increased by metabolites (e.g., glucose and fatty acids) that decrease glucagon secretion, and vice versa. During acute or chronic hypoglycemia, inhibition of insulin secretion and stimulation of glucagon secretion cause mobilization of hepatic glycogen and enhanced gluconeogenesis. These changes may be reinforced by activation of the sympathetic nervous system which would increase glucose production and possibly inhibit insulin secretion (see fig. 1).

The advent of radioimmunoassay techniques\textsuperscript{15,19} for the measurement of polypeptide hormones has proven a major factor in advancing our knowledge concerning the ef-

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**Fig. 2.** Cyclic AMP and hormone actions at the effector cell (from Butcher RW\textsuperscript{11}).
Effects of anesthetic agents on the secretions and actions of hormones. A failure of insulin response to injected glucose during surgery has been shown by Allison, Frowse and Chamberlain, using such techniques. It has been suggested that this suppression of insulin release is a nonspecific response to stress, mediated by increased epinephrine secretion and sympathetic activity, as reported by Porte and associates. The occurrence of glucose intolerance and insulin resistance during halothane anesthesia is further suggested by the work of others.

Halothane has been shown to result in an increased rate of glycogenolysis in the isolated perfused liver in the absence of any endocrine influence. In the perfused liver this increased glycogenolysis results in a rise in perfusate lactate concentration, whereas in the intact animal stimulated glycogenolysis following exposure to halothane results in an increase in the blood glucose concentration. Why exposure to halothane has different effects on the possible pathways at the crucial glucose-6-phosphate step (see fig. 3) in the presence and in the absence of endocrine influences is not known. The conversion of glucose-6-phosphate to glucose is catalyzed by a specific phosphatase, glucose-6-phosphatase. It is present in intestine, liver, and kidney, where it allows these particular tissues to add glucose to the blood. The enzyme, which is microsomal, is absent from muscle and adipose tissue. The different effects of halothane on the isolated organ, and on the liver in vivo, may be resolved by future specific investigation of the effects of the anesthetic agent on cyclic AMP formation and phosphofructokinase activity. Phosphofructokinase is known to act as a rate-limiting enzyme within the Embden-Meyerhoff scheme.

**Hepatic Fuel Availability and Utilization**

There are three forms of potential fuels in man: carbohydrate, fat and protein. Fat is the most important, but there is also a relatively abundant supply of calories in the form of protein, the majority of which is in muscle. The amounts of fuel which can be stored in the form of carbohydrate are very limited.

Carbohydrate, primarily in the form of liver and muscle glycogen, provides a trivial energy supply when compared with protein or fat. The 40–75 g of glycogen in liver could maintain blood glucose for a few hours, and the approximately 200 g in muscle could provide...
only 12 hours worth of basal calories should fat not be available.29 As a reserve for acute anaerobic production of high-energy phosphate by glycolysis to lactate, either directly in muscle or by release as glucose from liver into blood and then to muscle, this small glycogen mass is crucial for survival in the emergency situation, and its preservation is therefore essential. Longer-term glucose requirements, however, must be met by gluconeogenesis.

An understanding of the main factors which govern the utilization of fuels by tissues during a brief period of fasting is essential to a logical approach to the situation pertaining during anesthesia and postoperatively. These factors are 29, 30: 1) The release of substrates from tissue stores of triglycerides and glycogen. 2) The concentration of the fuel in blood plasma. 3) The entry of fuels from plasma into tissues (controlled by hormones such as insulin, epinephrine, and corticosteroids, and by cyclic AMP). 4) The concentration of the fuel in the tissue. 5) The presence in the tissue of the enzymes necessary for the degradation of the fuel.

Man has only two major fuel depots, fat and protein. Table 1 lists the various fuel components in a normally proportioned 70-kg man with a basal expenditure of approximately 1,800 cal per day. The relatively small caloric value of the circulating fuels and liver and muscle glycogen compared with the adipose tissue reserves 31 is evident.

During a brief (24-hour) period of fasting, a normal man who consumes 1,800 cal per day burns about 75 g of protein, primarily from muscle, and 160 g of adipose-tissue triglyceride. Splanchnic output of glucose approximates 180 g, of which almost 50 per cent is used by nerve (mainly brain) and is completely oxidized to carbon dioxide and water. Other glycolytic tissues—erythrocytes, leukocytes, bone marrow, renal medulla, and peripheral nerve, and probably, to a lesser degree, normal muscle—metabolize glucose but convert it primarily to lactate. The lactate is released back into the blood-stream and carried to the liver and kidney, where it can be resynthesized to glucose. The liver is the center of this central mechanism—glycerol, lactate, pyruvate, and glucogenic acids are all converted into glucose.

The remainder of the organism—heart, kidney cortex, skeletal muscle, and liver—uses either fatty acids released directly into the circulation or fatty acids partially oxidized to acetoacetate or $\beta$-hydroxybutyrate (the "ketone bodies") by liver. The liver derives its energy from fatty-acid oxidation, but by two stages: the partial oxidation of fatty acids to acetate (acetyl CoA), and the terminal combustion of acetate in the tricarboxylic acid cycle. Glucose is oxidized to a very small extent by the liver, both fasting and in the normal fed state.32

In summary, fasting man has two major sources of fuel, muscle protein and adipose tissue triglyceride; and three patterns of fuel utilization: terminal glucose combustion, mainly in the brain; glycolysis, occurring primarily in the erythrocytes; and the utilization of fatty acids and ketones in the remainder of the body. The liver serves as the transformer, synthesizing glucose from its precursors and using fatty-acid oxidation to ketones as its main source of energy.

Biebuyck, Lund, and Krebs32 have demonstrated that a fatty acid (oleate) can have a protective effect against the metabolic changes produced by halothane 26 in the perfused liver, inasmuch as oleate decreases the inhibition of oxygen consumption and maintains the ATP content of the liver and a normal rate of urea synthesis during exposure to halothane. Biebuyck and Lund 24 have further shown that the hepatic metabolic changes of halothane in vivo are reversed in situations in which
Fig. 4. The pathway of gluconeogenesis from various precursors, showing the stages where amino acids (alanine), glycerol, and lactate join it. The reactions which are common to gluconeogenesis and glycolysis are indicated by straight arrows, downward arrows showing the direction of gluconeogenesis, upward arrows the direction of glycolysis. The curved arrows represent the reactions which circumvent the energy barriers obstructing the direct reversal of glycolysis.

Greater plasma concentrations of fatty acids are available to the liver (i.e., during starvation or ingestion of a high-fat content diet). Ko and Paradise have also shown that to achieve 50 per cent depression of the force of contraction of atria from starved rats a greater concentration of halothane is necessary than when atria from fed rats are used. It is known that the myocardium obtains energy mainly from fatty acids and it is probable that higher fatty-acid and ketone-body levels were present in the starved preparation used by Ko and Paradise.

During even brief starvation, man undergoes a series of metabolic adaptations in order to derive energy from adipose tissue and to conserve as efficiently as possible his protein reserves. Insulin appears to be that dominant hormone (others being glucagon, growth hormone, and glucocorticoid) in controlling fuel mobilization and homeostasis during starvation. Probably the most important adaptation during starvation, and one of some importance in anesthesia, is the ability of brain to utilize ketone bodies produced by the liver. Recent evidence has shown that ketone bodies can make a major contribution to the fuel of respiration in the brain, and the major factor controlling this uptake is the circulating concentration of ketone bodies.

Gluconeogenesis

That gluconeogenesis is a biosynthetic process of major importance has been truly recognized only in the past ten years. The liver is normally the major site of gluconeogenesis, with the kidney becoming an important site during starvation and acidosis. Gluconeogenesis is a biosynthetic process which requires the intactness of the energy-transforming apparatus of the cell and is therefore a valuable indicator of the metabolic function of the liver.
thetic functions suffer very early when a tissue deteriorates and, in liver, the most exciting
syntheses in terms of ATP requirements are gluconeogenesis and urea formation. Gluco-
neogenesis involves some reactions of glycolysis in reverse and some additional reactions (see
Fig. 1) which overcome the energy barriers, preventing a direct reversal of glycolysis.29
Gluconeogenesis performs several functions im-
portant to the maintenance of physiologic
stability during anesthesia. First is the pro-
vision of glucose to the body during situations
where carbohydrate intake from the alimentary
tract is limited, and the body glycogen stores
are depleted. Second is the re-utilization of
lactate and glycerol produced in constant
amounts under basal conditions (by erythro-
cytes and adipose tissue, respectively), and
the lactate released from muscle during exer-
cise, sympathetic activity, and circulatory
shock states. Third is the provision of NH\textsubscript{3}
in the kidney to counteract acidosis. Fourth is
the metabolism of amino acids absorbed from
the alimentary tract or released during protein
breakdown in muscle and other tissues.

Resynthesis of glucose in the Cori cycle is
a major route of lactate disposal in the body.
During exercise, enhanced gluconeogenesis
limits lactacidosis from the lactate production
of muscle. Following exercise, ATP consump-
tion in the liver for lactate gluconeogenesis
is a major factor in the "oxygen debt" phe-
nomenon.30

Hepatic gluconeogenesis is negligible in the
fetus and increases during the first week of
life, paralleling the induction of the specific
enzymes involved.31 Following birth, the in-
creased release of free fatty acids,32 consequent
on activation of the sympathetic nervous sys-
tem and cyclic AMP, leads to increased ketone
body formation. It is likely that the availabil-
ity of ketones for utilization by the brain33,34
accounts for the well-known resistance of new-
born infants to hypoglycemia.35

Another aspect of impairment of gluconeogenic-
ness important in anesthesia, particularly in
premature infants, relates to lactate disposal.
Children who have hyaline membrane disease
or other respiratory disorders produce large
amounts of lactate because of the increased
effort of breathing and the presence of tissue
hypoxia.36 Any deficiency of gluconeogenesis
due to diminished levels or impaired activa-
tion of gluconeogenic enzymes contributes to
the lactic acidosis, which is a serious problem
in the management of these children.

Biebuyck et al.36 have demonstrated in the
isolated, perfused liver that halothane de-
creases the rate of gluconeogenesis from lac-
Fatty-acid oxidation was unaffected by halo-
thane, and the presence of a fatty acid in the
perfusion medium was found to decrease32 the
degree of inhibition by halothane of gluco-
neogenesis from lactate. Gluconeogenesis re-
quires the transport of various anions across
the mitochondrial membrane, and it is possible
that the mechanism by which halothane inter-
feres with gluconeogenesis is related to this
membrane transport.

Of further importance to the anesthesiologist
is that the underfed or starved patient who has
ingested alcohol may have unsuspected, severe
hypoglycemia.32 There is strong evidence
suggesting that this hypoglycemia is the result
of inhibition of gluconeogenesis,40 the primary
effect being a shift in the [free NAD\textsuperscript{+}]/[free
NADH] ratio in the cytoplasm of the liver cell.
The concentration of alcohol that causes major
inhibition is reached in the blood after a mod-
erate intake of alcoholic beverages.

Effects of Hypoxia on the Liver

A potentially important factor in the con-
rol of hepatic metabolism is hepatic blood
flow. In abnormal states such as septic shock,
hemorrhage, cardiac failure, partial intestinal
obstruction, hyperventilation, and various
forms of hepatic disease, hepatic portal blood
flow may decline markedly. Anoxia has been
shown40 to cause inhibition of gluconeogenesis
in the perfused liver.

Berry and Scheuer42 have shown that hy-
perventilation, or shock induced by trimetha-
pharn, produces an increase in blood lactate
due to an outpouring of lactate from the splanchic bed. Impaired hepatic metabolism
following hepatic ischemia may be a major
consuming factor in many cases of lactic
dicosis. Schröder et al.46 have concluded
from their experiments that the liver is the
organ responsible for the development of lactic
dicosis in low-flow states, either by failure to
clear lactate from the portal blood (by gluconeogenesis) or by lactate production.

Total splanchnic blood flow has been shown to decrease during halothane anesthesia in man \(^{47}\) and animals.\(^{48}\) Further work in this field is indicated, particularly in view of the interference by halothane with gluconeogenesis,\(^{25}\) which is the main mechanism for disposal of lactate from the blood. It is of interest that the direct influence of halothane on hepatic blood flow—as evidenced in the isolated perfused liver\(^ {26}\)—is to increase blood flow through the liver, supporting the conclusions of Epstein et al.,\(^ {11}\) that the reduction in splanchnic flow in man is the result of a decline in perfusion pressure, rather than altered vascular resistance.

Tissue Redox State and Function

By the use of rapid freezing methods and sensitive assays, it is possible to assay the hepatic content of many intermediates. Changes in the levels of regulating metabolites can then be correlated with changes in the metabolic pathways they influence. (The physiologically important effects of various anesthetic agents on metabolic pathways can be attributed to their effects on control processes of known mechanisms at the enzymic level.) Whole-tissue measurements of metabolites, however, can be misleading, since not all metabolites are uniformly distributed through the intracellular space.

The disadvantage of the so-called “freeze-stop” technique,\(^ {49}\) which has the virtue of fixing cell constituents near their states in vivo, is that fractionation into individual cell compartments is impossible because the distribution of nucleotides is liable to undergo very rapid changes during the process. Therefore, methods by which compartmented (cytosol and mitochondria) values may be derived from whole-tissue data have been developed (for review see ref.\(^ {51}\)). One of the procedures for doing this is the calculation of the redox state of the nicotinamide nucleotides in the cytosolic and mitochondrial compartments.

Oxidation-reduction reactions (also called “oxido-reductions” or “redox” reactions) are those in which there is a transfer of electrons from an electron donor (the reducing agent or reductant) to an electron acceptor (the oxidizing agent or oxidant). Oxidizing and reducing agents function as conjugate redox pairs, or couples. An equilibrium constant may be used to express the tendency of a reducing agent to lose electrons.

Pyridine-linked dehydrogenases, which require either NAD or NADP as coenzyme, participate in the mainstream of electron transport from organic substrates to molecular oxygen. The pyridine-linked dehydrogenases catalyze the following general reaction:

\[
\text{Reduced substrate} + \text{NAD}^+ \rightleftharpoons \text{oxidized substrate} + \text{NADH} + \text{H}^+
\]

The pyridine-linked dehydrogenases transfer reversibly two reducing equivalents from the substrate to the oxidized form of the pyridine nucleotide.

The redox state\(^ {51}\) of the NAD couple is characterized by the ratio:

\[
\frac{\text{Concentration of free NAD}^+}{\text{Concentration of free NADH}}
\]

The redox states of the NAD system are very different in the cytoplasm and in the mitochondria of the same cell. This fact led to one of the major criticisms\(^ {52}\) of Huckabee's concept of "excess lactate,"\(^ {53}\) viz., that the [lactate]/[pyruvate] ratio in the blood, a ratio which is determined by cytoplasmic lactic dehydrogenase, may or may not reflect the state of oxidation: reduction of the mitochondrial NAD couple. Olson's criticism\(^ {52}\) is that the blood [lactate]/[pyruvate] ratio is not an accurate indicator of the state of oxidation of the whole tissue. This criticism is valid in that measurement of the [3-hydroxybutyrate]/[acetocetate] ratio, which indicates the hepatic mitochondrial [free NAD\(^ +\)]/[free NADH] ratio,\(^ {54}\) is necessary for full assessment of tissue oxidation.
The physiologic significance of the difference between the redox states of mitochondria and cytoplasm is connected to the functions of the two compartments. The cytoplasm of the liver cell is the main site of glycolysis and gluconeogenesis. The direction of these reactions depends on the redox state of the hydrogen-carrier systems. In the mitochondria the main function of the NAD system is to channel hydrogen atoms to the electron-transport chain from the substrates of respiration.

The lactate-dehydrogenase system reflects the [NAD⁺]/[NADH] ratio in the cytoplasm, the β-hydroxybutyrate dehydrogenase that in the mitochondrial cristae, and the glutamate dehydrogenase that in the mitochondrial matrix. The substrates of these dehydrogenases are likely to be in equilibrium with free NAD⁺ and NADH, and the ratio of the free dimucleotides can be calculated from the measured concentrations of the substrates and the equilibrium constants.

The calculated [free NAD⁺]/[free NADH] ratios in both cytoplasm and mitochondria were found to be lower in halothane-exposed perfused livers than in controls. This effect of halothane and the others reported in the same paper can be explained on the assumption that inhibition of electron transport between NADH and O₂ is the primary event. Fatty-acid oxidation was found to be relatively unaffected by halothane. In isolated mitochondria, reoxidation of NADH through the electron-transport chain is inhibited by halothane, but succinate oxidation is not affected. The results in the isolated perfused liver and in isolated mitochondria suggest the NADH dehydrogenase stage as the site of inhibition by halothane, since both succinate oxidation and the β-oxidation of fatty acids are largely dependent on flavoprotein-linked enzymes.

Barbiturates, substances of an entirely different chemical structure but with similar pharmacologic effects, also block electron transfer between NADH and flavoproteins.

Future Developments

Better understanding of the changes in physiologic control mechanisms which take place during anesthesia can come only from further study of the effects of anesthetic agents at an organ level, as well as at the cellular and even subcellular levels. However, it is essential that the study of such effects should be correlated with the changes in function they produce.

Transport systems in the plasma membrane and in intracellular membranes, such as the mitochondrial membrane, are of increasing importance in the control and hence operation of metabolic pathways. The realization of the role of these transport systems suggests the basis for further investigation of the cellular effects of anesthetic agents. Greene has pointed out the importance of the study of such membrane effects.

The radical change during the last five years in emphasis on cell utilization and supply in the body has been mainly due to the contributions of Cahill and Dudrick, (for review, see Moore). These advances, together with the knowledge of the effects of different fuels on anesthetic effects, should stimulate anesthesiologists to re-evaluate the types of intravenous fluids administered intra- and postoperatively, and to consider whether “intravenous hyperalimentation” techniques may be applied during prolonged anesthesia and in the postoperative recovery period. It is possible that many of the adverse changes in function, so elegantly monitored in operating and recovery rooms, may actually be avoided or reversed by supplying the appropriate metabolic fuel to the organ concerned. It is to be hoped, specifically, that more refined forms of fatty-acid infusion will be developed for general use, since fatty acids or ketone bodies have been shown to be the primary metabolic fuel in several organs (e.g., myocardium, liver, and muscle). Furthermore, fatty-acid metabolism does not appear to be affected to the same extent as carbohydrate metabolism during anesthesia.

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