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NEPHROLOGY FORUM

Ketosis

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Case presentation

A 54-year-old man was admitted to the hospital in an obtunded state. A diagnosis of diabetes mellitus had been made at the age of 43, after he had experienced polydypsia, polyuria, and a 15-lb. weight loss. In the 11 years after the diagnosis of diabetes was established, he was admitted to the hospital several times for acute and chronic alcoholism and cellulitis of the face. On one of these admissions, his blood glucose was 304 mg/dl and plasma bicarbonate was 14 mEq/liter. Treatment with 60 units of regular insulin and 3 liters of normal saline over an 8-hour period restored the blood sugar and bicarbonate concentration to normal. The patient was discharged on 40 units of NPH insulin daily, but the physicians who examined him later in the clinic believed he was not complying with this therapeutic program.

Before admission, the patient had been drinking heavily, and on the morning of admission he was found in bed, incontinent, confused, and difficult to arouse. On admission he was grossly confused, unable to give a history, and combative. He was slightly obese and was taking 24 deep breaths per minute. The blood pressure was 110/70 mm Hg, and the heart rate was 104 beats per minute. The skin turgor was poor. His breath was fetid but acetone could not be detected. The neck veins were flat. There was a grade I/VI precordial systolic murmur. The lungs were clear except for scattered ronchi. The liver, which could be percussed 4 finger breadths below the right costal margin, seemed slightly tender. Ankle reflexes were absent, and pain sensation in the lower extremities was markedly decreased.

Laboratory findings included: hematocrit, 41% with normal indices; white blood cell count, 8400 per mm^3 with a normal differential; blood glucose, 193 mg/dl; BUN, 32 mg/dl; and serum creatinine, 1.6 mg/dl. Electrolyte values included: sodium, 141 mEq/liter; potassium, 5.1 mEq/liter; chloride, 105 mEq/liter; and bicarbonate, 12 mEq/liter. The blood pH was 7.30 and the $PaCO_2$ was 25 mm Hg. Ketones were positive in 1:4 dilution. Subsequent enzymatic analysis gave values of plasma acetoacetate, 1.2 mEq/liter; β-hydroxybutyrate, 9.0 mEq/liter; and lactate, 1.2 mEq/liter.

Treatment with intermittent small doses of regular insulin (10 units per hour three times) and with intravenous glucose and one-half normal saline reversed the metabolic abnormalities within 8 hours.

Discussion

Dr. George F. Cahill, Jr. *(Professor of Medicine, Harvard Medical School; Director of Research, Howard Hughes Medical Institute; and Physician, Brigham and Women's Hospital, Boston):* This man had a history of diabetes and the classic syndrome of weight loss, polydypsia, and polyuria 11 years prior to the present admission. He was and is slightly obese. The relatively mild course of his metabolic disorder permitted him to stop insulin therapy without becoming ketotic. If not for the initial event and the current episode of ketosis, he would be classified as having typical non-insulin-dependent diabetes mellitus (NIDDM). The type of diabetes in this patient contrasts with the other common variety, insulin-dependent diabetes mellitus (IDDM), which is more frequent in youth and is associated with a progressive viral and/or autoimmune destruction of the beta cells. The latter form of the disease necessitates daily insulin injections to prevent gross metabolic decompensation and ketoacidosis because a total or nearly total lack of endogenous insulin production occurs within several years. Thus this patient is a non-insulin-dependent or "maturity-onset" diabetic, whose only overt symptom of diabetes was soft-tissue infection of the face, a problem probably also related to poor hygiene. Although the diabetes was reasonably well controlled, the patient did exhibit a neurologic deficit in his lower extremities. This condition also was probably exacerbated by his alcohol intake: alcohol and diabetes act synergistically in causing peripheral neuropathy.

On admission, the patient was somewhat hyperpneic, and metabolic acidosis was discovered to be the cause of the hyperventilation. Ketosis was the cause of the acidosis, as evidenced by the elevated values of β-hydroxybutyrate, 9 mM/liter, and acetoacetate (AcAc), 1.2 mM/liter. Plasma lactate was only 1.2 mM/liter. Thus he had moderate ketoacidosis but his blood glucose concentration was only 193 mg/dl. One might have expected a glucose value of 300 or 400 mg/dl, or even higher perhaps, especially in light of the slightly elevated blood urea and serum creatinine levels. He was treated appropriately

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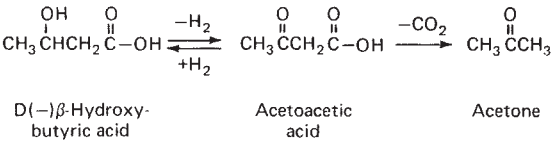

Fig. 1. *Interrelationship between acetoacetate (AcAc) and β-hydroxybutyrate (BOHB), the reaction catalyzed by the enzyme β-hydroxybutyrate dehydrogenase with NAD^+ as acceptor to produce NADH plus H^+.* Also shown is the nonenzymatic decarboxylation of AcAc to acetone, an irreversible step.

with small doses of insulin, 5 to 10 units initially, and he was given both glucose and saline; the chemical abnormalities were corrected in several hours. Had the glucose levels been in the overtly diabetic range of 400 mg/dl or higher, it would have been appropriate to treat him with larger quantities of insulin given either intramuscularly or intravenously. Although the patient was somewhat hyperglycemic, he did not have bona fide diabetic ketoacidosis and thus he was appropriately treated with small doses of insulin, saline, and glucose from the start.

What was the pathogenesis of the metabolic disorder in this patient? He had not been eating, and the ketosis probably could be attributed partially to simple starvation. But it takes 1 to 2 weeks of total starvation to cause such a severe degree of ketosis [1, 2]. In fact, in the fasting patient, increased excretion of ammonia by the kidney counterbalances the effect of the increased acid production, thus limiting the severity of acidosis. Another factor contributing to ketosis in this patient was the alcohol intake [3–5]. Alcohol is metabolized in the liver to form acetaldehyde and acetate, and the latter is released into the circulation for metabolism by other tissues. Flooding of the liver by acetate results in the production of ketoacids, especially β-hydroxybutyrate (BOHB), and this increased acetate load probably contributed to the ketoacidosis. In the presence of excessive alcohol metabolism, reduced NAD^+ (i.e., NADH) accumulates and leads to a preferential conversion of pyruvic acid to lactic acid. Although plasma lactate was nearly within the normal range when this patient was examined, the plasma lactate level might have been higher earlier. The slightly elevated BOHB/AcAc ratio (normal = 4/1) supports this contention because these two substrates, like lactate and pyruvate, are a redox couple. The lactate/pyruvate ratio represents the mean body cytosolic redox potential, and the BOHB/AcAc ratio refers to the mean of the mitochondrial redox potential. With anoxia or with an excessive production of reducing equivalents, as with alcohol metabolism, both ratios increase.

In sum, the patient had mild ketoacidosis that probably resulted from three processes, each leading to increased hepatic ketone production: starvation, alcohol consumption, and possibly diabetic decompensation.

Ketoacid metabolism. The intermediary metabolism of the ketoacids has been reviewed in great detail in several recent articles. Hepatic ketogenesis was discussed extensively by McGarry, Mannaerts, and Foster [6–8], and the peripheral metabolism of the ketoacids and their effects on other substrates was reviewed by Robinson and Williamson [9]. Fenselau detailed the biochemical reactions involved in ketogenesis and ketoacid metabolism [10], and Liljenquist discussed ketoacid regulation [11] in Brownlee's series on diabetes mellitus [12]. These reviews permit me to concentrate on the pathways of

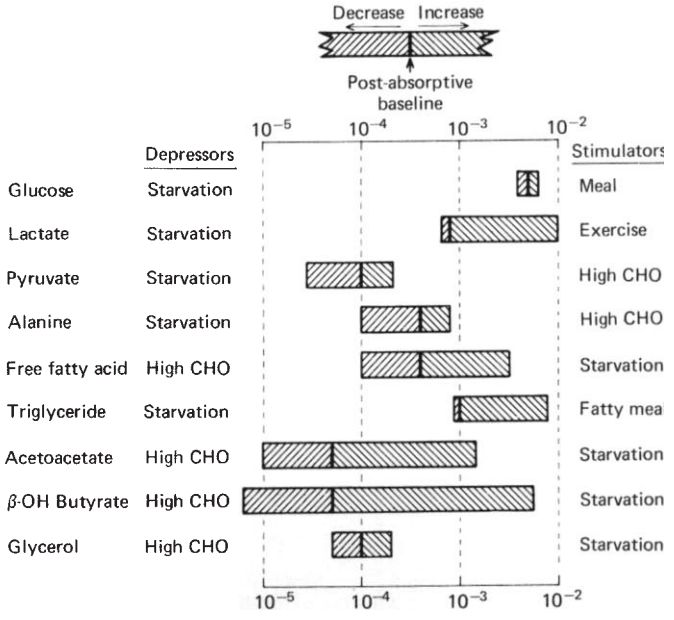

Fig. 2. *Physiologic ranges of circulating substrates in normal humans expressed on a logarithmic scale.* Of note is the narrow range of glucose concentrations and the three orders of magnitude variation in the concentration of BOHB.

ketogenesis, and I will emphasize the issues concerning substrate and sites of hormonal control.

Acetoacetate and β-hydroxybutyrate are the principal "ketone" products and are interconverted by a single step, an oxidation-reduction with NAD^+ and NADH as cofactors (Fig. 1). The enzyme for this interconversion, β-hydroxybutyrate dehydrogenase, is located primarily inside mitochondria, as compared with lactate dehydrogenase, which resides in the cytosol. Thus the BOHB/AcAc ratio reflects the mitochondrial NADH/NAD^+ ratio, and the lactate/pyruvate (L/P) ratio is indicative of the same ratio in the cytosol. The third "ketone," acetone, is thought to be the product of a nonenzymatic decarboxylation of AcAc, although its production still could be enzymatically catalyzed. Acetone production is, therefore, a function of the level of AcAc and the duration of its elevation; the presence of acetone is thus indicative of a sustained, severe ketoacidosis. Reichard et al recently showed that about one-third of AcAc metabolically produced is decarboxylated to acetone and, surprisingly, about two-thirds of the acetone is recovered as glucose [13, 14]. This is a novel observation that disproves the old adage that fat cannot be converted into carbohydrate in humans. Although this route of conversion of fatty acid to acetate to acetoacetate to acetone to glucose is a circuitous one, it might play a very important role in prolonged fasting in humans.

Acetoacetate and β-hydroxbutyrate are produced in approximately equal amounts in humans and are made primarily by the liver [15]. No other tissue makes significant amounts of these ketones except muscle and kidney, which produce them only occasionally and in small amounts. Blood levels of AcAc and BOHB in the usual postabsorptive state are less than 0.1 mM/liter, and if large carbohydrate loads are administered, these levels can fall to as low as 0.010 mM/liter. Such low basal levels

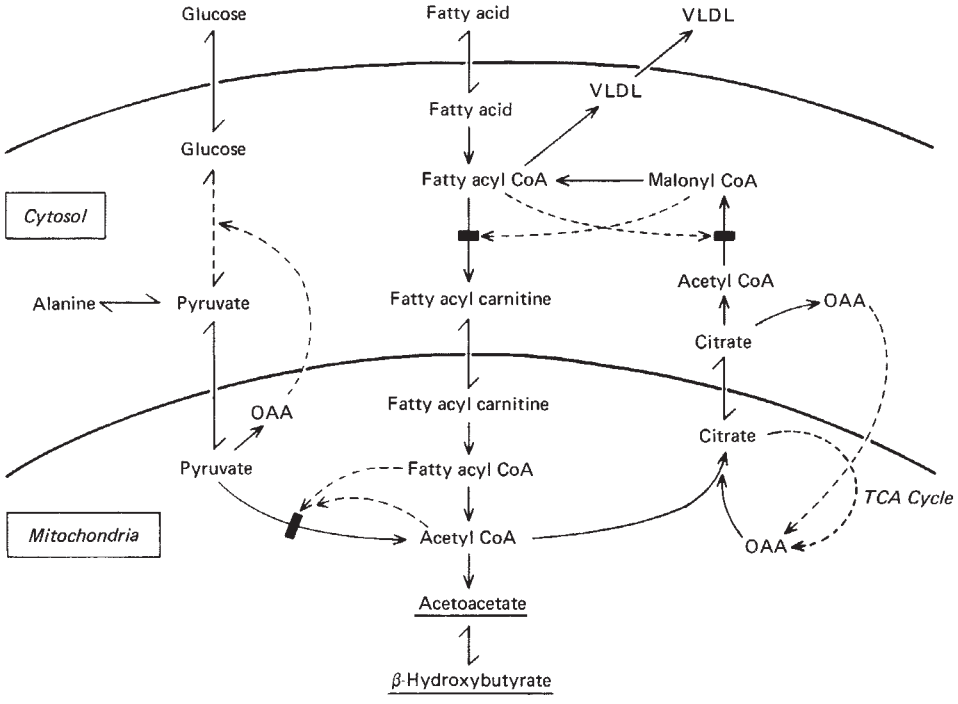

Fig. 3. *Biochemical pathways in liver connecting carbohydrate metabolism on the left, fat oxidation in the center, and acetate oxidation to CO_2 or its incorporation into long-chain fatty acid on the right.*

might consist of products of branched-chain amino acid catabolism instead of by-products of hepatic acetate metabolism; thus, fat-derived ketogenesis under these circumstances is probably near zero. In fasting humans, AcAc and BOHB levels rise to 1.2–1.6 and 6–8 mM/liter, respectively, but it takes 1 to 2 weeks to reach this plateau. Thus the variation in their concentrations may be 3 orders of magnitude; this extreme range of concentration makes these compounds unique compared to all other metabolic fuels. For example, glucose levels vary between 4 and 6 mM; other fuels such as alanine, leucine, lactate, and fatty acids vary by less than one order of magnitude (Fig. 2).

Acetoacetate and BOHB should be considered overflow products of the hepatic acetyl CoA pool. When CoA production surpasses its two routes of assimilation, ketoacid synthesis and release occur. As noted, the biochemical steps have been elucidated elsewhere in extenso [9, 10]. Figure 3 summarizes hepatic metabolism; Figure 4 contains a modified schema for the fasted (low-insulin) state. Free fatty acids released from adipose tissue are carried in plasma to the liver and by transport processes not yet clarified enter the liver cytosol where they are activated to their acyl CoA derivations. These derivatives are transacylated and the fatty acids are transported into the mitochondria as the carnitine ester. The acyl CoA ester is regenerated inside the mitochondria; then the classic "beta" oxidation of the long-chain fatty acyl CoA ester takes place, producing a number of acetyl CoAs and equal quantities of the reduced coenzymes NADH and FADH. These coenzymes donate their electrons to the mitochondrial energy chain, producing ATP and yielding their protons to oxygen to form water. One-third of the potential metabolic energy of a long-chain fatty acid is produced in this manner. When insulin levels are low and fatty acid levels are high, the metabolism of fat can supply all of the liver's energy needs. In a provocative theoretical discussion, Flatt pointed out that there must be a maximum rate for beta oxidation of long-chain fatty acids and that this rate is determined by the liver's energy utilization, since ATP cannot be accumulated above basal amounts [16].

What are the two nonketogenic pathways of acetyl CoA utilization in liver? As in any other tissue, the most significant route is the condensation of acetyl CoA with oxalacetate (OAA) in mitochondria to form citrate. Citrate formation is, of course, the first step in the primary energy-producing series of reactions known as the Krebs, tricarboxylic, or citric acid cycle. This cycle regenerates oxalacetate and picks up the next acetyl CoA for the succeeding turn of the cycle. Only acetyl groups, not the recycling four-carbon acceptor, are oxidized by this process, although isotopic oxidation or exchange does take place. Substrates such as succinate, α-ketoglutarate, or other amino acid analogs cannot be oxidized by the citric acid cycle but can be converted only to OAA. Oxaloacetate can exit from the mitochondrion only via phosphoenol pyruvate, which, in turn, can generate either glucose or pyruvate. In the latter case, acetyl CoA can be generated for eventual oxidation by the citric acid cycle. In summary, the citric acid cycle only oxidizes acetate as acetyl CoA and produces two molecules of carbon dioxide for each molecule of acetate.

The other route for acetyl CoA consumption is fat synthesis, a process that also requires mitochondrial formation of citrate (Fig. 5, Table 1). The citrate exits from the mitochondrion and is cleaved back to OAA and acetyl CoA in the cytosol. The acetyl CoA is carboxylated to malonyl CoA as the first step in long-chain fatty acid synthesis. Then, catalyzed by the fatty acid synthesis complex, the malonyl CoA units eventually form long-chain fatty acyl CoA molecules, which are incorporated into triglycerides. These triglycerides are exported by the liver as very low density lipoproteins (VLDL) to the periphery, especially adipose tissue; in adipose tissue, the triglyceride is stored in the oil vacuole at the center of the cell.

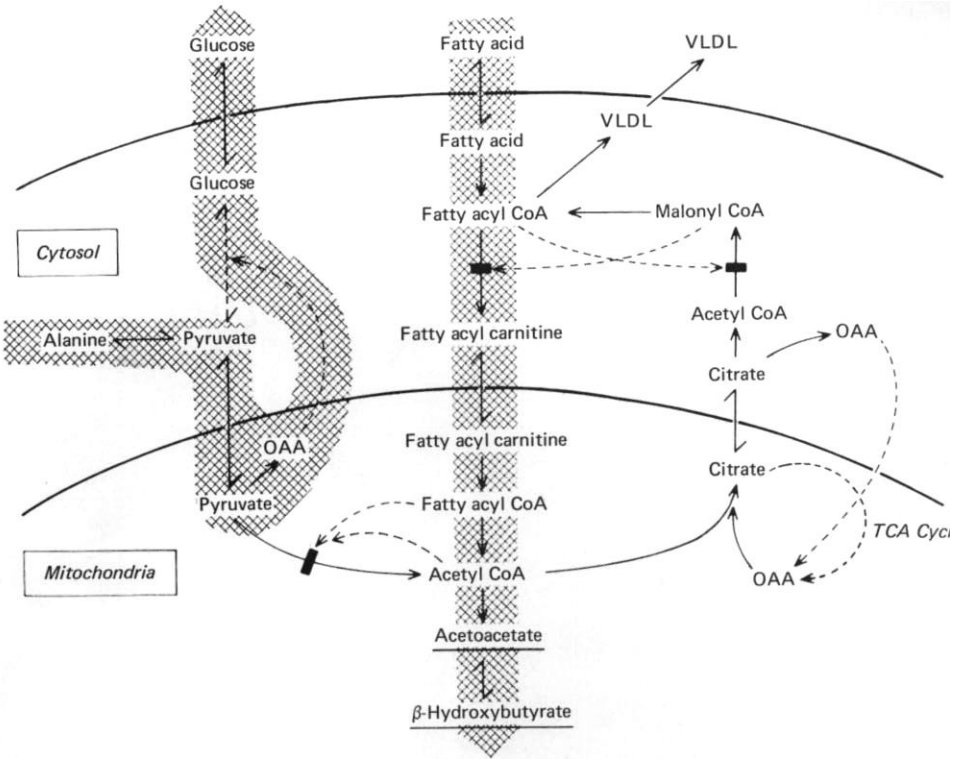

Fig. 4. *Accentuation of gluconeogenesis from muscle-derived amino acid (alanine) and fatty acid oxidation to AcAc and BOHB in fasting, a state with low insulin and normal or elevated glucagon levels.*

What are the controls of acetyl CoA disposition? Nature has devised a very simple cross-control system. When the liver is under the influence of large amounts of insulin but low levels of glucagon (e.g., after a carbohydrate meal), production of the enzyme catalyzing malonyl CoA synthesis is increased and levels of malonyl CoA increase (Fig. 5). McGarry, Mannaerts, and Foster have shown that the increased levels of malonyl CoA inhibit fatty acyl CoA entrance into mitochondria by decreasing the carnitine transferase step; thus the fatty acyl CoA moieties produced are spared from oxidation and ketone formation and are used instead for triglyceride synthesis [6–8]. By contrast, when insulin levels are low, for example during fasting, malonyl CoA production is decreased, and the fatty acyl CoA molecules coming from peripherally mobilized free fatty acids are available for ketoacid production (see Fig. 4).

How do these biochemical controls relate to glucose consumption and production by the liver? Several substrates and hormonal controls are available to direct the net flux of substrate. When mitochondria are full of acetyl CoA in the low insulin state because of fatty acid release from the periphery, and with low levels of malonyl CoA and unchecked beta oxidation, then citrate formation is brisk, and large quantities of citrate exit from the mitochondria. In the cytosol, the enzyme that cleaves citrate is low when insulin levels are low. Thus, citrate levels increase and high levels of citrate inhibit the principal glycolytic enzyme, phosphofructokinase. With glycolysis dampened by these events, the stage is set for gluconeogenesis. Mitochondrial dehydrogenation of pyruvate also is inhibited because of inactivation as well as inhibition of the active moiety of the responsible enzyme. The pyruvate that comes to the liver from the periphery as alanine is spared oxidation to acetyl CoA and instead is carboxylated to OAA. Thus, the pyruvate is processed to phosphoenolpyruvate as the first step in "reverse glycolysis" or gluconeogenesis (Fig. 4). As a result of low insulin and probably also of normal or high glucagon levels, all systems are directed toward gluconeogenesis [17]. For several reasons, the hepatic citric acid cycle activity is reduced under these circumstances. Cycle activity is decreasd first because ATP levels are ample, owing to fatty acid beta oxidation, and OAA levels are decreased both because of augmented incorporation into phosphoenolpyruvate and the accumulated NADH that accelerates the formation of malate. Second, this reduced state also inhibits the cycle by providing less free NAD^+ at the various dehydrogenation steps. Finally, to return to the upper steps in glycolysis and gluconeogenesis, inhibition of phosphofructokinase allows glucose-6-phosphate to accumulate and results in glucose production in the liver via the critical and unique enzyme, glucose-6-phosphatase.

Thus we can think of the liver as working in one of two modes: a low-insulin state characterized by gluconeogenesis, lipolysis, and ketogenesis; and a high-insulin state characterized by glycolysis, lipogenesis, and fat export. In the former, the liver's energy is provided by beta oxidation of fatty acids; in the latter state, the tricarboxylic acid cycle produces the energy. The only exception to this rule occurs when protein is ingested without carbohydrate (Fig. 6). When protein intake is high, gluconeogenesis occurs, probably because of high levels of glucagon. Yet there is little ketogenesis, and what little there is probably results from branched-chain amino acid metabolism. This metabolic state is probably explained by a high insulin as well as a high glucagon level [17, 18]. Fatty acid synthesis can proceed in humans and carnivores when the diet

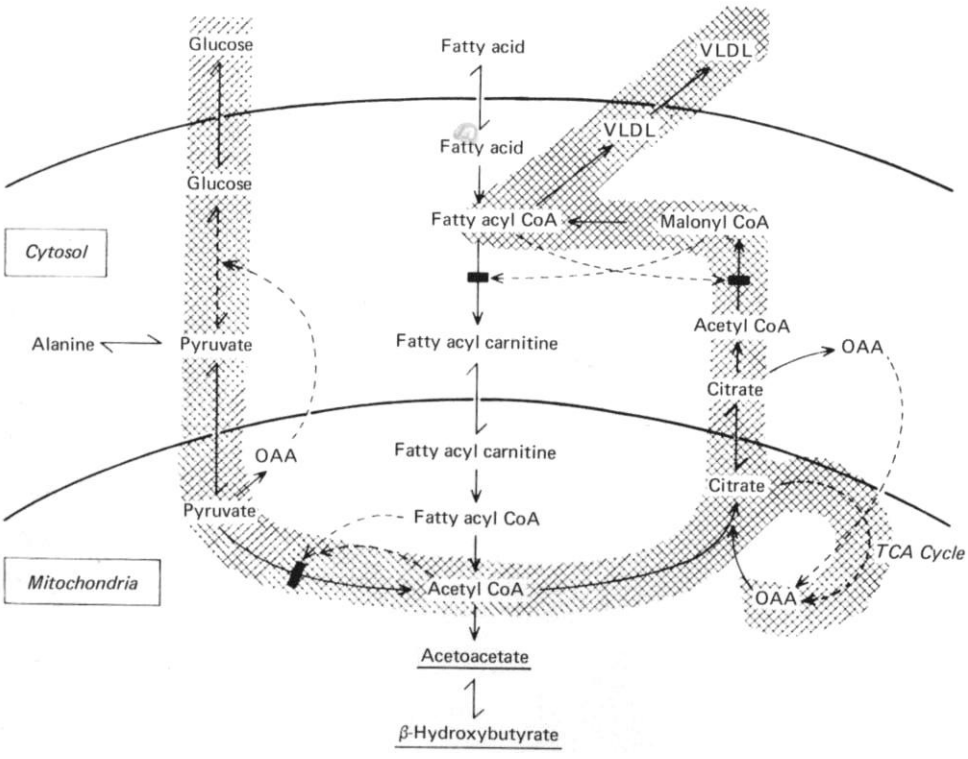

Fig. 5. *The high-insulin–low-glucagon state in which there is glycolysis to pyruvate, then to acetyl CoA and oxidation of some of the acetate to CO_2 via the TCA cycle for energy.* The remainder is used for fat synthesis via export from the mitochondria as citrate, cleavage to CoA, and subsequently fatty acyl CoA synthesis via the insulin-activated fatty acid synthetase system. The fatty acyl CoAs are used for triglyceride synthesis and then exported from the liver as very low density lipoprotein (VLDL).

Table 1. Acetate (acetyl CoA) metabolism

Nutritional state	Source	Disposition
High insulin (feeding)	Pyruvate Amino acids Ethyl alcohol	Oxidation by tricarboxylic acid cycle Fatty acid synthesis
Low insulin (fasting)	Free fatty acids Amino acids Ethyl alcohol	Ketoacid export (± acetate export)

consists of a high protein intake. A small amount of carbohydrate in the diet, however, suppresses glucagon production and inhibits gluconeogenesis (Fig. 7). This observation should not be taken to signify that insulin and glucagon are inhibitory of each other in the liver, but that insulin also has secondary effects independent of glucagon levels. Recent research in phosphorylation of proteins in the liver after exposure to insulin, glucagon, or both shows that some proteins are uniquely phosphorylated by each of these hormones but at different sites and with differing metabolic effects [19]. These data support the separate messenger concept.

Ambient ketoacid levels are controlled by hepatic production and peripheral disposition. The latter is composed of two processes, renal excretion and oxidation by peripheral tissues, mainly muscle but also kidney. Evidence suggests that in prolonged ketoacidosis, renal conservation of ketoacids becomes more efficient [20]. Peripheral tissues, perhaps because of increased fatty acid utilization and thus a high $NADH/NAD^+$ ratio, decrease their utilization of ketoacids, as evidenced by production of one mole of BOHB for each mole of AcAc taken up [21, 22]. Thus a major contribution to the ambient levels of ketoacids is their reduced peripheral metabolism.

The physiology of ketosis. The ketoacids are derived from the partial hepatic oxidation of long-chain fatty acids to 2-carbon fragments, or acetate, and then are exported to other tissues where they are oxidized. To a much lesser degree, the ketoacids are derived from the metabolism of the branched-chain amino acids and also can be formed from other sources of acetate, such as ethyl alcohol. In ruminants, a considerable quantity of acetate is produced in the rumen and in the liver from the large load of other short-chain fatty acids, such as butyrate, coming from the gut. In the fed state, ruminants can maintain appreciable levels of circulating ketoacids, which are utilized by skeletal muscle and mammary tissue for the synthesis of milk fat. Ketoacids also have another function in suckling mammalian young including humans [9]. The medium-chain fatty acids found in high proportion in milk enter mitochondria for oxidation more readily than do long-chain fatty acids because they bypass the carnitine transfer step and thus are not inhibited by high levels of malonyl CoA. Mild ketoacidosis therefore can occur in suckling animals, especially those consuming milk low in carbohydrate, such as the carnivores. In fact, porpoise and seal milk is almost devoid of lactose, and the pups are on a "ketogenic" diet very high in fat and protein. What purpose does this mild ketoacidosis serve? Increased ketoacids probably spare carbohydrate and in turn spare protein, but in these aquatic mammals, transfer of calories as extraaqueous lipid instead of water-soluble carbohydrate might be even more important as a water-conserving process.

Two events in human evolution have created a relatively unique metabolic predicament. The blood-brain barrier, shared by all vertebrates, prevents the extracellular fluid of the central

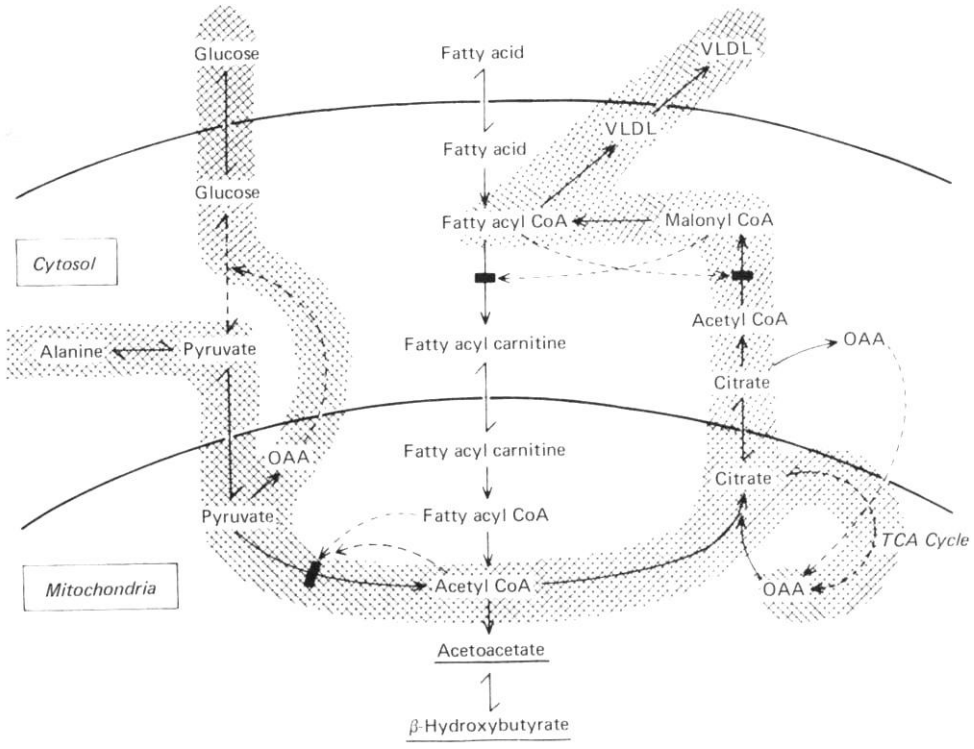

Fig. 6. *The combined high-insulin and high-glucagon state in which both glucose synthesis (an effect of glucagon) and fat synthesis (an effect of insulin) occur.*

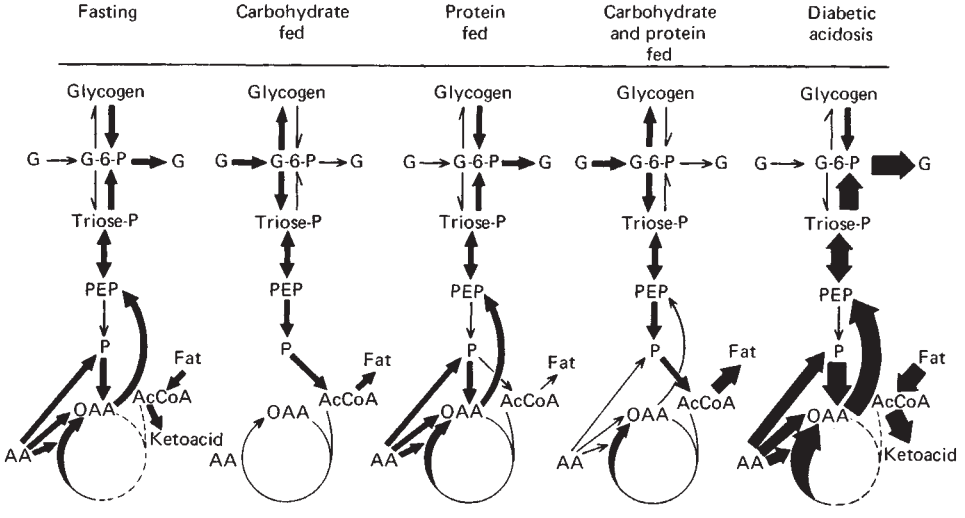

Fig. 7. *Summary scheme of liver as in Figures 3 through 6, but also containing a scheme of mixed carbohydrate-protein intake, in which glucagon is suppressed, and there is net glucose intake.* On the right is the super-fasted state of diabetic ketoacidosis in which insulin-controlled processes are lacking.

nervous system from exchanging substances by simple diffusion with the blood [23]. Numerous tight junctions bridge and occlude the endothelial cells of the brain capillaries and preclude the flux of macromolecules; only simple, small, water-soluble molecules with specific transport processes can overcome this barrier. Lipoprotein complexes and the albumin-fatty acid complex are excluded from the adult human brain, and the only remaining fuel of significant concentration in the circulation that can provide calories is glucose. Glucose is thus the standard fuel for the central nervous system in all animals studied. At times amino acids can provide a small amount of energy, but use of this fuel requires disposition of their amino groups, usually as glutamine, so amino acid utilization is relatively trivial.

The second unique evolutionary component is the disproportionate size of the human brain and its relatively large fuel demand. In adults, the brain consumes one-fifth to one-quarter of the total calories; in children, the brain uses as much as one-half. Between meals, this energy demand relies on hepatic glycogen to provide blood glucose. At most, only one day's supply of glucose can be stored as liver glycogen, and fasting for a longer period necessitates gluconeogenesis. The adult

brain consumes about 500 kcal daily, and that of a 5-year-old child uses only slightly less, perhaps 450 kcal. If these calories were derived solely from protein, about 0.5 kg of muscle would be consumed daily. It is obvious that such total reliance on protein would limit survival, especially in the child; but the brain's ability to utilize selectively the increased circulating ketoacids instead of glucose diminishes to one-fifth or one-fourth the otherwise obligatory rate of protein breakdown [24].

Of further assistance in gluconeogenesis is the glycerol from the lipolyzed adipose triglyceride [1, 25]. About 10% of fat by weight is the glycerol moiety; thus, the 160 to 180 g of triglyceride metabolized daily by a fasting human provides about 16 to 18 g of glycerol. In addition, 10 to 15 g of glucose can be derived from acetoacetate via acetone [14]. Thus, the brain can even maintain some glucose utilization without relying on protein as a source. In fact, it is probably glycerol derived from triglyceride that provides glucose for the brain in the fasting black bear [26] and the nesting emperor penguin [27], both of which survive months of starvation without ketosis and without relying on gluconeogenesis. Also, their relatively small brains contribute to their ability to survive without exogenous protein.

The fasting human. In fasting ketosis, AcAc and BOHB serve as a fat-derived, water-soluble fuel capable of crossing the blood-brain barrier. Transport of these substances occurs via facilitated diffusion, a "downhill" process, and requires an adequate concentration of ketones in the circulation to provide the diffusion gradient. Fasting ketosis occurs after 1 to 2 weeks of starvation [1, 2, 24, 25] and is produced by a rapid increase in hepatic production of ketones in the first few days [13–15], a diminished peripheral utilization of ketones [21], and more efficient renal conservation of these substances [20]. Thus with plasma levels of BOHB and AcAc of 6–8 and 1–2 mM, respectively, two-thirds or more of brain energy needs are supplied. Gottstein et al have shown, by measurement of brain arteriovenous differences during ketoacid infusion, that the level of ketoacids determines their rate of utilization [28, 29]. The brain's dependency on ketoacids was shown in humans by Drenick et al [30], Flatt et al [31], and Müller et al in dogs in which glucose levels rapidly lowered with insulin produced no subjective or objective indices of "hypoglycemia" [32]. I should point out that fasting ketosis evolves over several days in humans, and that this time period matches that required by the kidney to increase ammoniagenesis [33]. One might speculate that the primary function of renal ammoniagenesis is to conserve cations during fasting ketoacidosis; the parallel development of ketosis and ammoniagenesis in fasting supports this concept.

As ketosis becomes sufficient to provide the brain's energy needs, glucose utilization is diminished [24]. Ruderman et al have shown that the mechanism of decreased glucose utilization is inhibition of phosphofructokinase by citrate, which dams up hexose phosphate and in turn inhibits brain hexokinase [34]. The net result is the sparing of gluconeogenesis and, pari passu, the sparing of muscle protein, extending survival time several-fold, from weeks to months.

How does muscle sense that it no longer should provide amino acids, primarily alanine and glutamine [35–40], for gluconeogenesis? It has been suggested that fat oxidation spares both ketoacid utilization [21] and perhaps the oxidation of the keto analogs of the branched-chain amino acids [41]. If so, resynthesis of muscle protein, inhibition of muscle breakdown, or both would be facilitated. This hypothesis is supported by the observation that administration of the keto analogs of the branched-chain amino acids in fasting humans reduces nitrogen excretion [42, 43]. The ketoacids also might directly contribute to this diminished proteolysis by acting as direct inhibitors [44], but further characterization of this process is critical, because aberrations in the normal efficiency of this process are the basis of the hypercatabolic states associated with trauma, sepsis, denervation disuse, and diabetic ketosis.

In summary, ketosis is a normal physiologic state in which fat-derived, water-soluble molecules capable of crossing the blood-brain barrier displace glucose as brain fuel. The primary signal for ketoacid production by the liver is a low insulin level, but ketoacid production is also modulated by formation of acetate both from long-chain fatty acids and from other sources such as ethyl alcohol, ketogenic amino acids, and medium- or short-chain fatty acids in the diet.

Questions and answers

DR. JEROME P. KASSIRER: Dr. Cahill, what is the mechanism of the rapid reversal of the metabolic abnormalities in patients with alcoholic ketoacidosis? Typically small amounts of glucose, sodium chloride, and water are all that are needed to reverse ketosis and acidosis.

DR. CAHILL: When insulin levels are increased by glucose infusion, ketoacid production by the liver is terminated, and ketoacid levels fall to zero within a few hours. Also, if volume depletion occurs, insulin release may be suppressed by adrenergic nerve endings in the islets of Langerhans as well as by circulating catecholamines. Volume repletion thus is necessary to correct this inhibition of insulin release.

As ketoacid levels fall, plasma bicarbonate rises and pH returns to normal. This is why we are reluctant to use intravenous alkali. In fact, the same principle holds true in the therapy of diabetic ketoacidosis. We avoid using alkali unless it becomes absolutely necessary. Some consider a pH below 7.1 the indication for using alkali. I prefer to make a clinical judgment. If the patient's pulse is becoming weak, thready, and rapid, and blood pressure is falling, then I would administer alkali. Further, if the patient's PCO_2 is 20 mm Hg or so, as a result of hyperventilation to compensate for the metabolic acidosis, I would be reluctant to use alkali. But if the patient is deteriorating rapidly because weakness is preventing hyperventilation, and the PCO_2 is rising as high as 35 mm Hg, alkali therapy is indicated.

DR. KASSIRER: Under what circumstances is it appropriate to use insulin to treat alcoholic ketoacidosis?

DR. CAHILL: These patients usually do not require insulin. Administering intravenous glucose is usually sufficient unless there is concomitant volume depletion; if so, dextrose and saline should be used.

DR. JORDAN J. COHEN: It seems clear from the literature as well as from our own experience that some individuals are particularly susceptible to the development of alcoholic ketoacidosis. This is evidenced by numerous reports of recurrent episodes in the same person and by the relatively small percentage of alcoholics who manifest the condition. Is there a metabolic explanation for this susceptibility?

DR. CAHILL: I can't explain this susceptibility but I do wonder why it's so relatively rare. Despite the millions of alcoholics who fast for days while ingesting large amounts of ethanol, very few of these individuals appear at the hospital.

DR. JOHN T. HARRINGTON: Is there any direct quantitative relationship between blood ethanol levels and the severity of the acidosis in patients who have repeated episodes of alcoholic ketoacidosis? Secondly, can ketoacidosis be induced in normal fasted individuals simply by infusing ethanol?

DR. CAHILL: I don't know, nor do I know whether anyone has tried inducing ketoacidosis by giving alcohol experimentally to fasted people.

DR. HARRINGTON: Does one ever see ketoacidosis in association with hypoglycemia?

DR. CAHILL: Yes, especially when hypoglycemia is severe. A large reducing load to the liver such as alcohol will reduce oxalacetate to malate, making this substrate unavailable for gluconeogenesis. These circumstances may lead to alcoholic ketoacidosis complicated by severe hypoglycemia, that is, with a blood sugar of 20 or 30 mg/dl. In this instance the most acute problem is to treat the hypoglycemia.

DR. KASSIRER: I would like to return to the question of alkali therapy in severe diabetic ketoacidosis and alcohol ketoacidosis. Although it is true that patients with severe acidosis may recover uneventfully merely by treatment of ketosis, I have serious reservations about withholding alkali therapy when acidosis is extreme. Even with robust respiratory adaptation, patients with plasma bicarbonate concentrations of 2–3 mEq/liter typically have blood pH values less than 7.0, a state that in itself impairs the function of many organs and threatens life. When plasma bicarbonate concentration is this low, a further reduction of only 1 mEq/liter, consequent to a delay in initiation of therapy or a slight delay in response to therapy, will result in lethal acidosis. For this reason I believe that bicarbonate therapy is warranted in severe acidosis. The amount to give, however, is the critical issue. I would advocate giving enough to raise plasma bicarbonate only 4–5 mEq/liter: this increase should raise blood pH only modestly and protect the patient. A greater increase in plasma bicarbonate is to be avoided. Given the propensity of hyperventilation to persist during the early phase of correction of acidosis, a large increase in plasma bicarbonate induced by alkali therapy can yield remarkable alkalemia. I know that opinions differ on this issue, but do you disagree with me?

DR. CAHILL: No, I agree with your view. But I would not allow alkali therapy to supplant or delay attempts to expand volume. Diabetic ketoacidosis is one of the few conditions in medicine in which expedience is critical. It is important to insert a large-bore needle in a large vein promptly and to administer isotonic saline rapidly. The only other crucial factor is the serum potassium concentration. If serum potassium is low or even normal, potassium should be given as soon as therapy with insulin has begun.

DR. NICOLAOS MADIAS (*Renal Service, NEMC*): Dr. Lemieux and coworkers have shown that ketone bodies depress renal ammoniagenesis [45, 46]. Do you have any thoughts about this?

DR. CAHILL: No, I don't. I believe that the mechanisms that control ammoniagenesis by the kidney are still an open area for research. The controls and rate-limiting steps of ammonia production and even the pathway for ammonia production remain controversial.

DR. COHEN: Dr. Cahill, you noted that this patient had a relatively low blood sugar given the degree of ketosis he had. Some investigators claim that a small percentage of patients with classic diabetic ketoacidosis are euglycemic [47]. Do you agree?

DR. CAHILL: One can't have euglycemia and diabetes; it's a matter of semantics. After a week of fasting it is possible to have ketosis with normal blood sugar, with plasma ketone levels as high as 6 mEq/liter. But there must be a net negative carbohydrate loss from the body to produce more ketosis. Let me illustrate by a small clinical "pearl": If a patient calls me in the evening to report that her urine tests strongly for sugar, that she cannot remember having taken her insulin in the morning, and that she is worried about developing ketoacidosis, the dietary history alone usually suffices to determine whether there are grounds for concern. If the patient has eaten her usual lunch and dinner, the chance of her having ketoacidosis is virtually zero. In fact, she may be insulin deficient but her glycosuria is the result of dietary "spillage": that is, her hyperglycemia is not endogenous. If, on the other hand, the patient failed to eat lunch and ate little at dinner, there is a considerable probability that she is ketotic. She has sustained a net carbohydrate loss associated with gluconeogenesis and its accompanying ketosis. In others words, one can draw a parallel between the net negative carbohydrate balance and the degree of ketosis. Thus, I do not believe diabetic ketoacidosis can develop without copious urinary spillage of endogenously derived glucose.

DR. MADIAS: It has been suggested that hypophosphatemia can cause insulin resistance and glucose intolerance [48]. In your opinion, does hypophosphatemia have important pathogenetic and/or therapeutic implications for the patient with diabetic ketoacidosis?

DR. CAHILL: If the patient has had chronic ketoacidosis with substantial lean tissue loss, phosphate depletion is almost certainly a concomitant feature. Once one gives insulin, phosphate moves into cells. For this reason potassium should be given as the phosphate salt. I am not convinced that administering phosphate ordinarily is critical, but if the individual is debilitated, I prefer to give potassium as phosphate rather than as chloride.

DR. COHEN: The starving person who uses ketone bodies instead of glucose to fuel the brain must, as a consequence, develop some degree of acidosis. Is there any metabolic advantage to the acidosis per se?

DR. CAHILL: That is an important question, because ketosis is the basis of the protein-sparing effect of modified fast. Namely, if one completely deprives people of food and then gives them a little bit of protein, they maintain nitrogen balance. But the process is very inefficient. One has to administer approximately 80 to 100 grams of protein to spare about 20 grams. This 20 grams would be lost if no protein were given.

DR. COHEN: There is no reason, I gather, to think that the inevitable acidosis is advantageous.

DR. CAHILL: No, but there are normal people in the world who are chronically acidotic. The blubber-eating eskimo is the prototype.

DR. COHEN: As illustrated by today's patient, the ratio of β-hydroxybutyric acid to acetoacetic acid is unusually high in alcoholic ketoacidosis. This circumstance often poses a diagnostic problem on the wards because the nitroprusside reaction does not detect β-hydroxybutyrate. Is there any convenient way for the clinician or, for that matter, the routine clinical laboratory to estimate the concentration of this substance?

DR. CAHILL: The best approach is to measure plasma bicarbonate concentration and obtain a rough estimation of acetoacetate using one of the crude bedside tests. A positive acetoacetate level and a very low plasma bicarbonate concentration suggest ketosis with a high level of β-hydroxybutyrate. The combination of a barely positive acetoacetate test and a very low plasma bicarbonate concentration signifies either a very reduced state with high concentrations of β-hydroxybutyrate or else a coincidental lactic acidosis. Fortunately, as far as treatment is concerned, it does not make too much difference because therapy is directed at correcting volume deficiency, at returning blood sugar toward normal with insulin, and at correcting acidosis with alkali if the situation is life threatening.

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