

*Invited Review*

## **You Can Get There From Here: Acetone, Anionic Ketones and Even-Carbon Fatty Acids can Provide Substrates for Gluconeogenesis**

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**Summary:** Although the literature contains studies published more than 30 years ago showing that acetone is not metabolically inert, it is common to find biochemistry textbooks and current research publications asserting that acetone is a ‘dead-end’ metabolite. In fact, acetone derived from the non-enzymatic breakdown of acetoacetate in ketotic individuals or from the oxidation of ingested isopropanol can be metabolized to D-lactate and pyruvate, and ultimately glucose. This report describes the reactions and pathways that account for the metabolism of acetone in humans.

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**Keywords;** gluconeogenesis, ketones, acetone, acetoacetate, glucose, fatty acid metabolism, even-carbon fatty acids

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An adage is supposed to be a vehicle of wisdom or truth. But not all adages, no matter how old or how many times they are repeated, are necessarily correct. Following are two examples of adages you will find in most textbooks of biochemistry and physiology that cover human metabolism but which happen to be incorrect: The first states that even-numbered fatty acids cannot be converted into glucose; the second that acetone is not metabolizable, that it is a dead-end metabolite which can be eliminated from the body only through the urine or lungs. Such assertions are not hard to find in textbooks used by medical students or undergraduates and graduate students in the biomedical sciences.

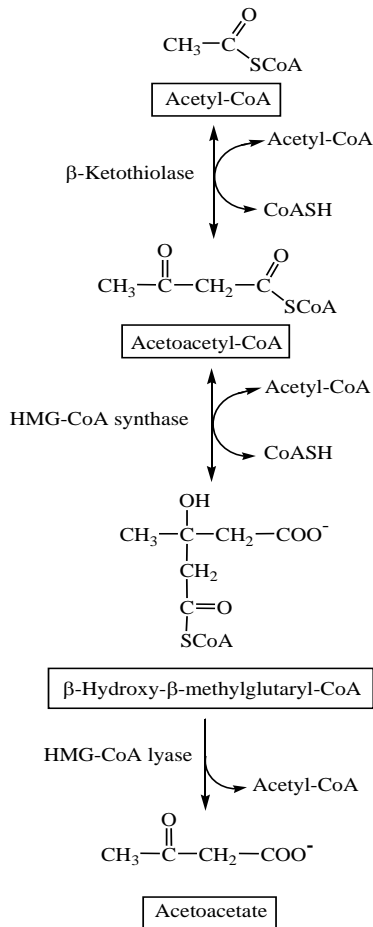
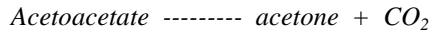
For example, in a textbook on human metabolism in health and disease, you will find a statement asserting that: “(H)umans can convert glucose into long-chain fatty acids, but they cannot convert even-carbon-numbered long-chain fatty acids into glucose.” (Rosenthal and Glew, 2009). Another example can be found in the recently published, seventh edition of Devlin’s widely popular Textbook

of Biochemistry which states that “Glucose can be synthesized from fatty acids with an odd but not an even number of carbon atoms.” (Harris, 2010) This same comprehensive 1204-page textbook asserts a few pages later that “Various amino acids, lactate, pyruvate, propionate, and glycerol are sources of carbon for the pathway of gluconeogenesis.”, and that “Since acetyl-CoA and other intermediates of even-numbered fatty acid oxidation cannot be converted to oxaloacetate or any other intermediate of gluconeogenesis, it is impossible to synthesize glucose from fatty acids.” The Devlin textbook does not mention whether or not acetone is a substrate for gluconeogenesis. However, a recent publication about isopropanol intoxication (Vujasinovic et al., 2007) does state emphatically that “2-Propanol is metabolized via ADH (alcohol dehydrogenase) to acetone (ketone) *which permits no further oxidation or metabolism* (italics added).

In fact, these claims about the metabolism of fatty acids and acetone in humans are incorrect. The literature contains reports, some of which are more

than three decades old showing that: 1) under certain physiological conditions there can be a net conversion of the carbon atoms of even-numbered long-chain fatty acids into glucose, and 2) acetone is readily oxidized by mammals, including humans.

Following is an explanation of how acetone and long-chain fatty acids comprised of an even number of carbons can be oxidized and converted into glucose. At the core of this explanation lay the three metabolic ketone ‘bodies’ acetoacetate, β-hydroxybutyrate and acetone (Figure 1). Acetone is generated when the unstable β-ketoacid acetoacetate undergoes spontaneous decarboxylation:



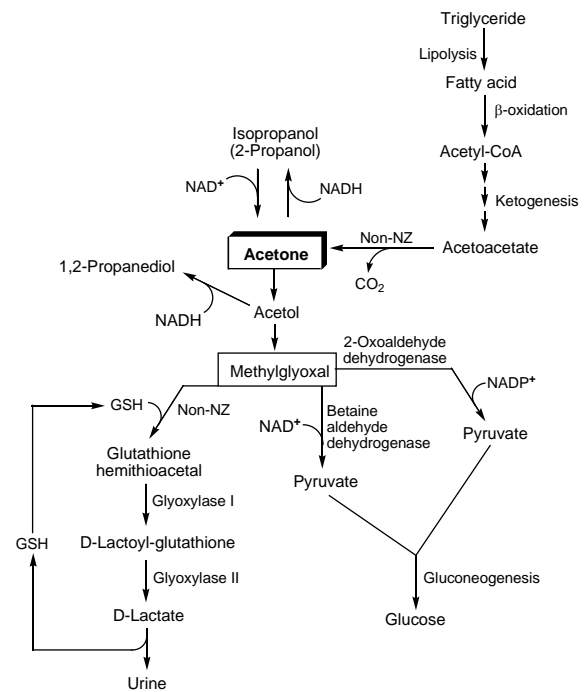
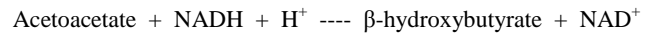
**Figure 1**  
Ketogenesis pathway.

The two most common sources of acetone are the ketogenesis pathway and intoxication with isopropanol (2-propanol).

There are two major circumstances under which ketogenesis is particularly active in humans: prolonged fasting (>2 days) and diabetic ketoacidosis. Although ketoacidosis is usually associated with type 1 diabetes, it can also occur in individuals with type 2 diabetes, especially if the person has been binge drinking. The confluence of the pathway of isopropanol oxidation and ketogenesis is shown in

Figure 2. Alcohol dehydrogenase (ADH), the same enzyme that oxidizes ethanol to acetaldehyde, uses NAD<sup>+</sup> to oxidize isopropanol to acetone. ADH also catalyzes the reverse reaction, namely the reduction of acetone to isopropanol, thereby accounting for the presence of this secondary, 3-carbon alcohol in an individual who has not consumed isopropanol. With regard to ketogenesis, as indicated above, once acetoacetate is formed some of it will decarboxylate non-enzymatically to form acetone.

The acetyl-CoA substrate for ketogenesis is derived mainly from the β-oxidation of long-chain fatty acids in mitochondria. The liver enzyme β-hydroxybutyrate dehydrogenase converts most of the acetoacetate into β-hydroxybutyrate:



**Figure 2**  
Metabolism of acetone and related metabolites. Non-NZ, non-enzymatic; GSH, reduced glutathione.

Acetone arising from isopropanol or acetoacetate is oxidized by an NADPH-dependent cytochrome designated CYP2E1 in liver to methylglyoxal. A comprehensive review by Vander Jagt (2008) of methylglyoxal metabolism in mammals, including humans, was published recently. Methylglyoxal can be further metabolized by three different routes: one leads to D-lactate, the other two produce pyruvate. Betaine aldehyde dehydrogenase and 2-oxoaldehyde dehydrogenase, which use NAD<sup>+</sup> and NADP<sup>+</sup>, respectively, generate pyruvate. In contrast, the glyoxylase pathway generates D-lactate (Figure 2). According to the glyoxylase pathway, methylglyoxal

first reacts non-enzymatically with reduced glutathione (GSH) to produce an intermediate called glutathione hemi-thioacetal which is subsequently metabolized to D-lactoyl-glutathione by glyoxylase I. Glyoxylase II then converts D-lactoyl-glutathione into D-lactate and reduced glutathione. D-lactate metabolism is slow or impaired in humans, so most of the D-lactate is excreted in the urine (Uribarri and Carroll, 1998). D-lactate derived from acetone can contribute significantly to the metabolic acidosis associated with ketosis or isopropanol intoxication.

Having metabolized acetone to pyruvate, the carbon atoms of the original acetone molecule derived from either acetoacetate or isopropanol are now available for glucose synthesis via gluconeogenesis. It has been estimated that by means of these reactions as much as two-thirds of the metabolized acetone can be converted into glucose (Reichard et al., 1974; Reichard et al., 1979; Kalapos et al., 1996), thereby disproving the two old adages that humans cannot convert even-chain fatty acids into glucose in humans and that acetone is metabolically inert.

Acetone can also be metabolized to isopropanol by ADH (Lewis et al., 1984):



This reaction explains why the blood of individuals who have not consumed or been otherwise exposed to isopropanol can contain this particular alcohol (Bailey, 1990; Jones and Summers, 2000).

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