SHORT COMMUNICATION

Against the stream: relevance of gluconeogenesis from fatty acids for natives of the arctic regions

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Background. The question whether even-chain fatty acids can be converted into glucose has a long-standing tradition in biochemistry. Since the glyoxylate shunt is absent from mammals, the question has been considered to be solved. It is of particular relevance for understanding the metabolic state of natives of the arctic regions due to the very high fat content of their traditional diet only containing negligible amounts of carbohydrates.

Methods & Results. Using an in silico approach, we discovered several hitherto unknown routes in human metabolism that allow the conversion of even-chain fatty acids into carbohydrates in humans. These pathways proceed via ketogenesis over the intermediate of acetone and produce the gluconeogenic precursor pyruvate. While these pathways can make a contribution to glucose production during times of limited carbohydrate supply, we found that their capacity might be limited due to a high demand in reducing equivalents in acetone degradation. Considering the traditional diet of natives of the arctic regions, the detected pathways are not only important in order to improve carbohydrate supply, but moreover reduce the amount of protein that needs to be used for gluconeogenesis.

Conclusion. In summary, our study sheds new light on our understanding of the metabolic state of natives from the arctic regions on their traditional diet. Moreover, they provide an avenue for new analyses that can reveal how humans have adapted metabolically to a practically carbohydrate-free diet.

Keywords: *carbohydrate-free diet*; *gluconeogenesis*; *inuit diet*; *ketogenesis*; *even-chain fatty acids*

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While glucose can readily be converted into fatty acids in humans, the question whether the reverse conversion, gluconeogenesis from fatty acids, is also feasible has been a topic of intense debate at the beginning of the 20th century. With the discovery of the glyoxylate shunt, which allows this conversion and is present in plants, fungi, nematodes and some bacteria but not in mammals, the conclusion had been that gluconeogenesis from fatty acids is impossible at a metabolic steady state in humans. This statement can be found in many prominent biochemistry textbooks. However, it is ignored in this reasoning that there might exist other routes than the glyoxylate shunt that could allow this conversion. In a previous study, we set out to investigate whether there exist such alternative routes that would allow to convert fatty acids into carbohydrates in humans using a compendium of all metabolic reactions known to take place in humans, which had become available due to the advent of genome-scale networks (1). The above-mentioned question is of particular relevance for natives of the arctic regions, as their traditional diet contains only negligible amounts of carbohydrates, with 2% of energy coming from carbohydrates, 66% from fat and 32% from proteins (2).

Results and discussion

Our analysis was based on a genome-scale metabolic network, which represents a compendium of all metabolic reactions known to take place in humans and, hence, also provides the basis to identify hitherto unknown routes in metabolism. An in silico search for the possible routes for gluconeogenesis from even-chain fatty acids revealed a

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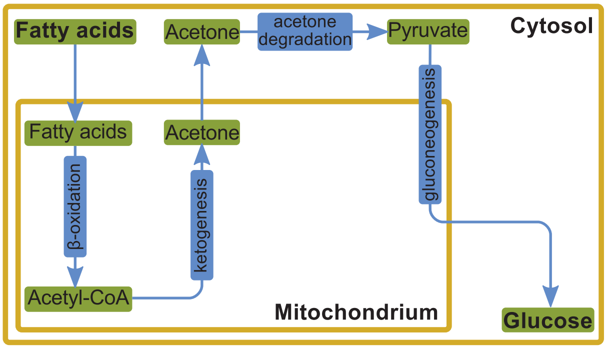

Fig. 1. Scheme of the pathway for gluconeogenesis from fatty acids. For a more detailed scheme, see Kaleta et al. (1).

large number of possible pathways (1). An important finding is that this pathway list is exhaustive; no other routes are feasible. A common denominator of these routes is that they cross the mitochondrial membrane several times, convert the product of β-oxidation of fatty acids, acetyl-CoA, into acetone (a ketone body) and subsequently degrade acetone to pyruvate (Fig. 1). The formation of acetone as well as its degradation can occur on several routes that differ in their energetic requirements. In particular, reducing equivalents in the form of reduced nicotinamide adenine dinucleotide phosphate (NADPH) required for metabolising acetone potentially limit the capacity of gluconeogenesis from fatty acids. As discussed in Ref. (1), several lines of experimental evidence support the utilisation of the detected pathways, in particular during times of ketosis as it occurs during starvation, fasting, in hibernating animals and in humans on a low-carbohydrate and ketogenic diet. In these situations, the detected pathways allow to reduce the degradation of proteins for gluconeogenesis since there is a continued need for glucose by several physiological processes, for example, in the brain, even in situations where carbohydrates are scarce.

These findings are of a particular relevance for understanding the metabolic state of Inuit and other native people of the arctic regions on a traditional diet. This diet is practically free of carbohydrates, and energy is provided by 66% from lipids and 32% from protein (2). Our results imply that, if on a traditional diet, natives of the arctic can meet their glucose requirements not only from the glycerol component of lipids and from glucogenic amino acids but from fatty acids. Additional relevance comes from the recommendation that a maximum of 37% of daily energy intake should be provided from protein (3) (at a daily energy consumption of 2,500 kcal for an individual of 65 kg). The observed figure of 32% (see above) is close to this value and in particular during times of increased protein intake; for instance, in late winter, when the hunted animals only have reduced lipid stores, symptoms associated with protein poisoning have been observed (3). Although glucogenic amino acids can, obviously, be converted into glucose, these symptoms occur when protein degradation for gluconeogenesis and energy production exceeds the body's capacity to dispose of ammonia and uric acid (3). In this context, the pathways for gluconeogenesis from fatty acids that we detected allow the body to decrease the amount of protein that needs to be degraded for gluconeogenesis from proteins and, thus, reduce the danger of protein poisoning.

In summary, our findings show that, in contrast to text-book knowledge, there do exist gluconeogenic routes from fatty acids and that these pathways can be used during times, or at places, of scarcity of carbohydrate sources. These pathways are likely to be of particular relevance for the natives of arctic regions. The conversion of part of the fatty acid components of lipids into glucose allows them to reduce the potentially toxic overstrain of the body's capacity for degradation of proteins for gluconeogenesis and energy production. In particular, the analysis of mutations in the enzymes of these pathways as well as their regulators in genome sequences from people of the arctic regions could underline this relevance.

Conflict of interest and funding

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