

Hepatic glucose and lipid metabolism

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Abstract The liver has a central role in the regulation of systemic glucose and lipid fluxes during feeding and fasting and also relies on these substrates for its own energy needs. These parallel requirements are met by coordinated control of carbohydrate and lipid fluxes into and out of the Krebs cycle, which is highly tuned to nutrient availability and heavily regulated by insulin and glucagon. During progression of type 2 diabetes, hepatic carbohydrate and lipid biosynthesis fluxes become elevated, thus contributing to hyperglycaemia and hypertriacylglycerolaemia. Over this interval there are also significant fluctuations in hepatic energy state. To date, it is not known to what extent abnormal glucose and lipid fluxes are causally linked to altered energy states. Recent evidence that the glucose-lowering effects of metformin appear to be mediated by attenuation of hepatic energy generation places an additional spotlight on the interdependence of hepatic biosynthetic and oxidative fluxes. The transition from fasting to feeding results in a significant re-direction of hepatic glucose and lipid fluxes and may also incur a temporary hepatic energy deficit. At present, it is not known to what extent these variables are additionally modified by type 2 diabetes and/or non-alcoholic fatty liver disease. Thus, there is a compelling need to measure fluxes through oxidative, gluconeogenic and lipogenic pathways and determine their relationship with hepatic energy state in both fasting and fed conditions. New

magnetic resonance-based technologies allow these variables to be non-invasively studied in animal models and humans. This review summarises a presentation given at the symposium entitled ‘The liver in focus’ at the 2015 annual meeting of the EASD. It is accompanied by two other reviews on topics from this symposium (by Kenneth Cusi, DOI: [10.1007/s00125-016-3952-1](https://doi.org/10.1007/s00125-016-3952-1), and by Hannele Yki-Järvinen, DOI: [10.1007/s00125-016-3944-1](https://doi.org/10.1007/s00125-016-3944-1)) and a commentary by the Session Chair, Michael Roden (DOI: [10.1007/s00125-016-3911-x](https://doi.org/10.1007/s00125-016-3911-x)).

Keywords Anaplerosis · De novo lipogenesis · Deuterated water · ¹³C Isotopomer analysis · Krebs cycle · Magnetic resonance spectroscopy · Pyruvate cycling · Review

Abbreviations

NAFLD	Non-alcoholic fatty liver disease
PC	Pyruvate carboxylase
PDH	Pyruvate dehydrogenase
SCFA	Short-chain fatty acid

Relationship between hepatic glucose, lipid, and energy metabolism

As the major site in the body for carbohydrate and lipid biosynthesis, the liver has a central role in the regulation of systemic glucose and lipid fluxes during feeding and fasting. At the same time, it is also dependent to a considerable degree on the oxidation of these substrates for its own energy needs. Under normal conditions, these activities are highly attuned to carbohydrate and lipid inflow from feeding, and uptake of NEFA derived from adipose tissue lipolysis during fasting. In the setting of type 2 diabetes and non-alcoholic fatty liver disease (NAFLD), control of glucose and lipid biosynthesis is loosened, contributing to

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excessive systemic glucose and lipid levels. These changes in glucose and lipid fluxes are also accompanied by alterations in hepatocellular energy levels. The benign early stages of NAFLD are associated with an elevated energy state, while the later more severe stages of both NAFLD and type 2 diabetes are associated with a depressed energy state [1]. A key question is: how are the changes in hepatic energy state related to those of hepatic glucose and lipid metabolic fluxes?

Hepatic Krebs cycle as the central link for carbohydrate, lipid and energy metabolism

The liver has the capacity to sustain high rates of both carbohydrate and lipid biosynthesis. In addition to diverting carbons from energy production, these pathways also consume energy and reducing equivalents. The hepatic energy balance is therefore in part determined by the partitioning of carbons between carbohydrate and lipid biosynthesis pathways and oxidation. Under fasting conditions, the profiles of hepatic oxidative and biosynthetic fluxes are relatively well understood. In essence, there is a high flux through fatty acid β -oxidation, sustained by the inflow of NEFA from peripheral adipose tissue lipolysis, with the acetyl-CoA product being fully oxidised to CO_2 by the Krebs cycle. This process generates an abundance of ATP and reducing equivalents that sustain the conversion of pyruvate and other anaplerotic substrates into glucose via gluconeogenesis. Under conditions where acetyl-CoA generation from β -oxidation exceeds the oxidative capacity of the Krebs cycle, the acetyl-CoA overflow is diverted into ketone body synthesis. Based on the known rates of hepatic fatty acid oxidation, oxidative Krebs cycle fluxes and gluconeogenesis, and considering that the overwhelming fraction of acetyl-CoA is derived from β -oxidation, the overall process has a positive energy balance. Moreover, the carbon flows are conceptually straightforward, with the catabolic inflow of fatty acid carbons into the Krebs cycle driving the gluconeogenic outflow of anaplerotic carbons. This metabolic model has been confirmed in both fasted humans and animal models in many different laboratories [2–9]. In the setting of mild hepatic insulin resistance, it explains how elevated rates of fasting glucose production are energetically sustainable through systematic increases in both anaplerotic and oxidative Krebs cycle fluxes [5, 10].

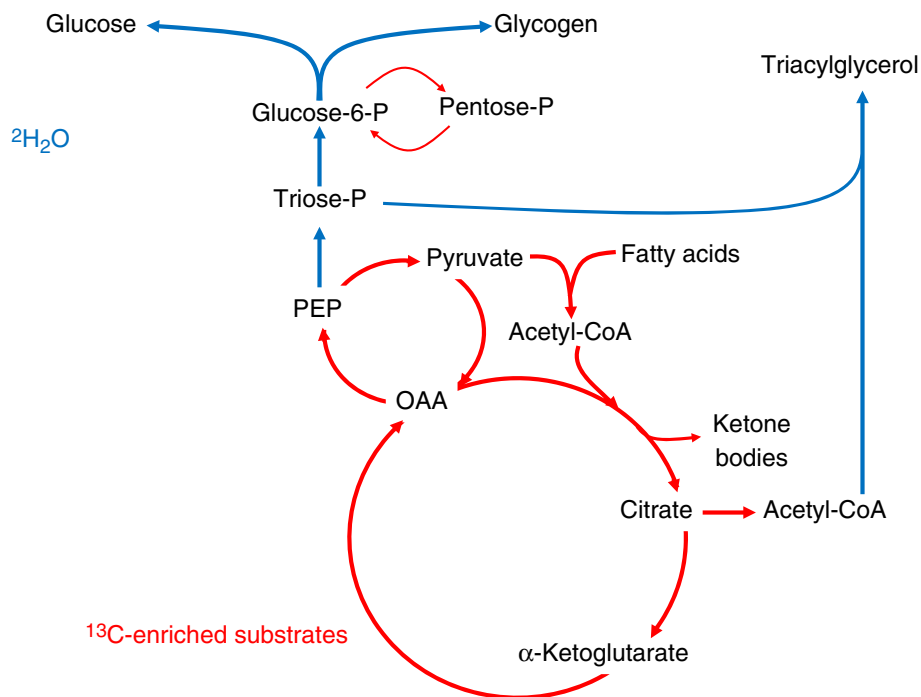
If the generation of mitochondrial ATP and reducing equivalents is restricted, then gluconeogenesis from pyruvate is also restrained. Thus, the antihyperglycaemic actions of metformin have been explained through blockade of respiration redox reactions via inhibition of mitochondrial glycerol-3-phosphate dehydrogenase [11] and by direct inhibition of complex I and ATP synthase [12]. Compounds or formulations that reduce energy generation through mild mitochondrial uncoupling have also been shown to improve glucose intolerance and reverse steatosis [13, 14] and have been

proposed as a new class of glucose-lowering medications. In this setting, uncoupling agents have an additional advantage over respiration blockers in that they also accelerate fatty acid oxidation, thereby promoting the clearance of excess fat as well as reducing gluconeogenesis.

Measuring hepatic Krebs cycle fluxes under basal fasting conditions

The hepatic Krebs cycle is of high importance in both the manifestation of abnormal hepatic glucose and lipid fluxes and as a target for therapeutic interventions. To date, hepatic Krebs cycle fluxes have been assayed by measuring the flow and distribution of carbon-labelled tracers through its constituent metabolite pools and into biosynthetic products such as glucose. Initial studies using ^{14}C tracers and laborious metabolite carbon-by-carbon degradation methods for obtaining positional labelling information were fundamental in describing the principal carbon flows through the hepatic Krebs cycle [15–17] and provided the foundations for developing stable isotope ^{13}C tracers whose distributions can be analysed more conveniently and in greater detail by MS and NMR methods. While positron emission tomography (PET) has also been used to measure hepatic fatty acid oxidation in humans using [^{11}C]palmitate [18], it does not provide sufficient labelling information for de-convoluting oxidative and anaplerotic Krebs cycle fluxes. With ^{13}C -enriched substrates, the required positional labelling information can be non-invasively acquired by two complementary approaches. In vivo ^{13}C NMR spectroscopy permits direct real-time assessment of positional ^{13}C -enrichment of hepatic Krebs cycle carbon skeletons through the observation of hepatic glutamate and glutamine, whose carbon skeletons are exchanged with that of α -ketoglutarate [19–21]. Ex vivo analysis involves ^{13}C NMR or gas chromatography-mass spectrometry (GC-MS) measurements of circulating or excreted metabolites that can be traced back to the hepatic Krebs cycle (Fig. 1). These include plasma glucose, hepatic uridine diphosphate glucose (UDP-glucose) and hepatic glutamine—the latter two being non-invasively sampled in urine following conjugation with paracetamol and phenylacetic acid, respectively [3, 5, 8, 10, 22–25]. To date, only a very small number of studies describing hepatic Krebs cycle fluxes in individuals with type 2 diabetes or NAFLD have been published. In NAFLD patients with elevated levels of intrahepatic triacylglycerol but relatively mild hepatic insulin resistance, ex vivo ^{13}C -isotopomer and ^2H -enrichment analysis of plasma glucose following administration of [3,4- $^{13}\text{C}_2$]glucose, [U- ^{13}C]propionate and $^2\text{H}_2\text{O}$ revealed systematically higher rates of hepatic oxidative Krebs cycle and gluconeogenic fluxes compared with individuals with normal hepatic triacylglycerol levels [5]. These findings were recapitulated in mouse models of high-fat feeding and hepatic insulin resistance [10]. In

Fig. 1 Coverage of the principal catabolic, anaplerotic and biosynthetic fluxes of hepatic carbohydrate and lipid metabolism using deuterated water ($^2\text{H}_2\text{O}$), shown in blue, and ^{13}C -enriched substrates, shown in red. OAA, oxaloacetate; -P, phosphate; PEP, phosphoenolpyruvate



overnight-fasted individuals with type 2 diabetes who had moderately increased rates of fasting endogenous glucose production over healthy controls, no significant differences in oxidative and anaplerotic Krebs cycle fluxes were found [3]. More such studies are required to better understand the evolution of hepatic Krebs cycle fluxes with NAFLD and type 2 diabetes pathogenesis and to investigate how they are modulated by medications that target mitochondrial energy generation, such as metformin. Stable isotope tracer methodologies can in principle be integrated with in vivo ^{31}P magnetic resonance measurements of hepatic high-energy phosphate metabolites [26] to precisely determine the relationship between hepatic energy state and Krebs cycle fluxes.

Hepatic carbohydrate, lipid and Krebs cycle fluxes in the fed state

The fed state presents a more complex and perhaps more challenging setting for hepatic control of glucose, lipid and energy metabolism. Under these conditions, the liver receives a range of different nutrients via the portal vein, including simple sugars, amino acids and short-chain fatty acids. Some, such as fructose, glycerol, butyrate and propionate, are efficiently extracted and rapidly incorporated into hepatic intermediary metabolism. Others, such as glucose and lactate, are only partially cleared from the circulation. The abundance of these substrates in portal vein blood, in conjunction with high levels of insulin resulting from beta cell stimulation, promote hepatic glycogen synthesis and de novo lipogenesis, while fatty acid oxidation and

endogenous glucose production are suppressed [27]. Ex vivo analysis of plasma glucose, hepatic lipid, and hepatic glycogen deuterium (^2H) enrichment from deuterated water ($^2\text{H}_2\text{O}$) provides information on their fractional synthesis or appearance rates and can also provide details of the metabolic carbon sources that sustain these activities (Fig. 1). In rodent models, these analyses reveal that gluconeogenesis contributes a significant fraction of both plasma glucose and hepatic glycogen appearance under natural feeding conditions [28, 29] or following a glucose tolerance test [30]. When the rodent feed was supplemented with sucrose in the drinking water, glucose and glycogen synthesis via anaplerotic fluxes were largely replaced by synthesis from fructose [31]. Analysis of hepatic triacylglycerol or plasma VLDL enrichment from $^2\text{H}_2\text{O}$ [32] as well as ^{13}C -enriched precursors provides information on fractional de novo lipogenesis [33–35], as well as fractional elongation and desaturation rates of the fatty acid moiety and turnover of the glycerol moiety [32, 36]. In animal models of diet-induced NAFLD and insulin resistance, these activities are highly dependent on the constituents of the diet. Fractional lipogenic rates are promoted by diets high in sugar [37] but suppressed by diets high in fat [36, 38]. In humans, elevated lipogenic rates were found in insulin-resistant NAFLD patients [39, 40], as well as in healthy individuals following both acute intake as well as longer term consumption of diets made hyperenergetic with excess fructose [41–43].

Collectively, glycolytic and lipogenic biosynthetic activities consume a significant proportion of mitochondrially generated ATP and reducing equivalents. In addition, ATP can be sequestered during the initial metabolic processing of nutrients, most notably by fructose. At the same time, NEFA availability is

reduced, thereby curtailing hepatocyte energy production from NEFA oxidation. Under these conditions, pyruvate dehydrogenase (PDH) is activated via its dephosphorylation, thereby promoting acetyl-CoA generation from glycolytic substrates. The relatively low levels of mitochondrial acetyl-CoA also attenuate pyruvate carboxylase (PC) activity, hence, the ratio of PDH:PC flux—which is very low during fasting—is increased. Once incorporated into citrate, acetyl-CoA may be oxidised or made available for de novo lipogenesis via the citrate shuttle. Despite the central role of these fluxes in rebalancing hepatic lipid, carbohydrate and energy fluxes during the transition from fasting to feeding, very few *in situ* measurements of Krebs cycle fluxes have been performed under fed conditions in either animal models or humans. Alves et al measured fractional PDH flux contributions to hepatic Krebs cycle fluxes in rats under both fasting state and under hyperinsulinaemic–hyperglycaemic clamp conditions, where the availability of glucose as a substrate is maximal [44]. Their studies confirmed the very low PDH contribution to Krebs cycle fluxes during fasting. While the PDH contribution was significantly increased under the clamp conditions, it accounted for less than half of oxidative Krebs cycle flux, and in rats fed high-fat diets, this contribution fell to about 20% [44]. Magnusson et al measured Krebs cycle fluxes in overnight-fasted healthy volunteers infused with glucose and glucagon [2]. They found that PDH accounted for 40–60% of oxidative Krebs cycle flux under these conditions compared with ~5% in 60-h-fasted individuals.

Given that, under fed conditions, glycolytic substrates appear to contribute at most ~50% of the acetyl-CoA requirements for oxidation and that NEFA oxidation is efficiently repressed by malonyl-CoA, are there alternative substrates that could contribute to mitochondrial energy generation? Short-chain fatty acids (SCFAs) are derived from intestinal fermentation of complex carbohydrates and their mitochondrial uptake is independent of carnitine palmitoyltransferase 1a (CPT-1a) and therefore unaffected by cytosolic malonyl-CoA levels. It is not known to what extent the liver is dependent on these or other substrates as alternative energy sources during feeding. Acetate, typically the most abundant intestinally generated SCFA, can also be converted to acetyl-CoA in the cytosol via acetyl-CoA synthase [45, 46], thereby potentially competing for de novo lipogenesis against mitochondrially generated acetyl-CoA. Recent studies suggest that altered intestinal SCFA production is an important link between intestinal microbiome dysbiosis and hepatic insulin resistance and NAFLD [47, 48].

Conclusions

The onset and progression of type 2 diabetes/NAFLD is associated with a progressive impairment in hepatic control of glucose and lipid fluxes. Recent studies also suggest that these changes are also accompanied by alterations in hepatocellular

energy state. These alterations in carbon flows and energy status are linked by the hepatic Krebs cycle. To date, there have been very few measurements of human hepatic Krebs cycle fluxes in type 2 diabetes/NAFLD and none have examined the relationship between these variables and hepatic energy state. The transition from fasting to feeding also transforms carbohydrate and lipid carbon fluxes through the Krebs cycle and, depending on the nutrient composition, the hepatic energy state can be acutely compromised, even in healthy individuals. Currently, we have no knowledge of hepatic Krebs cycle fluxes in this setting for either healthy or type 2 diabetic/NAFLD individuals. Finally, the actions of glucose-lowering medications such as metformin appear to be based on compromising the capacity for hepatocellular mitochondrial energy generation. How these effects interplay with acute hepatic energy depletion induced by nutrients such as fructose, as well as underlying impairments of hepatic mitochondrial function in type 2 diabetes/NAFLD, are not well understood. The development of non-invasive tracer approaches that provide comprehensive coverage of hepatic glucose, lipid and Krebs cycle fluxes coupled with non-invasive measurements of hepatocellular energy state should improve our understanding of hepatic glucose and lipid metabolism in healthy humans and better explain the metabolic derangements associated with diabetes and NAFLD.

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