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## The Randle cycle revisited: a new head for an old hat

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### Abstract

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In 1963, *Lancet* published a paper by Randle et al. that proposed a “glucose-fatty acid cycle” to describe fuel flux between and fuel selection by tissues. The original biochemical mechanism explained the inhibition of glucose oxidation by fatty acids. Since then, the principle has been confirmed by many investigators. At the same time, many new mechanisms controlling the utilization of glucose and fatty acids have been discovered. Here, we review the known short- and long-term mechanisms involved in the control of glucose and fatty acid utilization at the cytoplasmic and mitochondrial level in mammalian muscle and liver under normal and pathophysiological conditions. They include allosteric control, reversible phosphorylation, and the expression of key enzymes. However, the complexity is formidable. We suggest that not all chapters of the Randle cycle have been written.

**Keywords:** adenosine 5'-monophosphate-activated protein kinase, fatty acids, glucose, heart, insulin resistance, liver, mitochondria, peroxisome proliferator-activated receptor, skeletal muscle, type 2 diabetes

IN 1963, Philip Randle, Peter Garland, Nick Hales, and Eric Newsholme ([142](#)) proposed a “glucose-fatty acid cycle,” which describes fuel flux between and fuel selection by mammalian organs. This type of cycle must not be confused with metabolic cycles, the prototype of which is the citric acid cycle. In a metabolic cycle, an overall chemical change is brought about by a cyclic chemical reaction sequence ([9](#)), whereas the glucose-fatty acid cycle describes the dynamic interactions between substrates.

Specifically, the Randle cycle draws attention to competition between glucose and fatty acids for their oxidation in muscle and adipose tissue ([142](#)) (for historical aspects, see Refs. [63](#), [146](#), and [168](#)). At the time, the effects of hormones on fuel metabolism were already well known. For example, it was known that the high insulin/glucagon ratio of the postabsorptive state promotes lipid and carbohydrate storage. And it was also known that a high glucagon/insulin ratio, characteristic of the fasted state, stimulates adipose tissue lipolysis and hepatic glucose production to preserve glucose supply to those tissues that rely exclusively on this sugar. The novelty of the glucose-fatty acid cycle was that it introduced a new dimension of control<sup>1</sup> by adding a nutrient-mediated fine tuning on top of the more coarse hormonal control. In isolated heart and skeletal muscle preparations, Randle and colleagues ([142–146](#)) demonstrated that the utilization of one nutrient inhibited the use of the other directly and without hormonal mediation. The glucose-fatty acid cycle is thus a biochemical mechanism that controls fuel selection and adapts substrate supply and demand in normal tissues in coordination with hormones controlling substrate

concentrations in the circulation. As Randle et al. proposed ([142](#)), this dynamic adaptation to nutrient availability perfectly applies to the interaction between adipose tissue and muscle ([Fig. 1](#)). Hormones that control adipose tissue lipolysis affect circulating concentrations of fatty acids, and fatty acids, in turn, control fuel selection in muscle ([64](#), [146](#)).

Although the biochemical mechanism by which fatty acid oxidation inhibits glucose utilization in muscle seemed clear ([142–146](#)), the reciprocal aspect, namely inhibition of fatty oxidation by glucose ([169](#)), received a plausible mechanistic explanation only much later ([114](#)). Another aspect of the Randle cycle often not appreciated is the inhibition of adipose tissue lipolysis by glucose and insulin via a mechanism involving stimulation of glucose uptake and reesterification of fatty acids in the presence of glucose-derived glycerol 3-phosphate ([142](#)). Last, the glucose-fatty acid cycle also provides an explanation for the pathophysiology of dysregulated fuel metabolism, referred to as “fatty acid syndrome” in the original article ([142](#)). Inhibition of glucose utilization by fatty acids is a form of glucose intolerance that resembles, or may lead to, insulin resistance, i.e., the impaired capacity of insulin to increase glucose uptake by muscle and adipose tissue accompanied by increased lipolysis and increased hepatic glucose production.

Much has been learned during the last four decades about the cross-talk between pathways of energy substrate metabolism. We take this occasion to integrate both old and new mechanisms involved in the control of glucose as well as fatty acid utilization and oxidation mainly in muscle and liver. A central theme is the control of glucose and lipid metabolism.

### Glucose is Spared and Rerouted

In the fasted state, activation of lipolysis provides tissues with fatty acids, which become the preferred fuel for respiration. In the liver,  $\beta$ -oxidation of fatty acids fulfills the local energy needs and may lead to ketogenesis. As “predigested fatty acids,” ketone bodies are preferentially oxidized in extrahepatic tissues. By inhibiting glucose oxidation, fatty acids and ketone bodies so contribute to a glucose-sparing effect, an essential survival mechanism for the brain during starvation. In addition, inhibition of glucose oxidation at the level of pyruvate dehydrogenase (PDH) preserves pyruvate and lactate, both of which are gluconeogenic precursors ([69](#)). Inhibition of glucose utilization by fatty acids was originally demonstrated in heart ([142](#)). It was later also found in liver ([13](#), [84](#)) and in the  $\beta$ -cells of the pancreas, where a permissive effect of fatty acids on glucose-induced insulin secretion has been established ([146](#)). Interestingly, the cycle can be extended to lactate in heart and liver ([36](#), [37](#), [39](#), [74](#), [169](#), [182](#)), two lactate-consuming organs. Here, lactate inhibits the oxidation of both glucose and fatty acids. Much experimental evidence accumulated thus far confirms that the Randle cycle is actually working in whole animals as well as in humans ([63](#), [64](#), [146](#)).

The glucose fatty acid cycle is not restricted to the fasting state and is readily observed in the fed state after a high-fat meal or during exercise, when plasma concentrations of fatty acids or ketone bodies increase. Under these conditions, part of the glucose that is not oxidized is rerouted to glycogen, which may explain the rapid resynthesis of muscle glycogen after exercise ([37](#), [39](#), [68](#)). Rerouting of glucose toward glycogen also explains the increased glycogen content in muscles found in starvation or diabetes ([142](#)). Similarly, pyruvate in excess of the mitochondrial oxidative capacity (suggested by high levels of acetyl-CoA) is carboxylated and used by the anaplerotic route to form oxaloacetate. Anaplerosis replenishes citric acid cycle intermediates ([31](#), [71](#), [109](#), [153](#)).

### Fatty Acids Rule

Randle ([146](#)) demonstrated that impairment of glucose metabolism by fatty acid (or ketone body) oxidation was mediated by a short-term inhibition of several glycolytic steps, namely glucose transport and phosphorylation, 6-phosphofructo-1-kinase (PFK-1), and PDH. The extent of inhibition is graded and increases along the glycolytic pathway, being most severe at the level of PDH and less severe at the level of glucose uptake and PFK. This sequence occurs because the initial event, triggered by fatty acid

oxidation, is an increase in the mitochondrial ratios of [acetyl-CoA]/[CoA] and [NADH]/[NAD<sup>+</sup>], both of which inhibit PDH activity. It has been proposed that these changes lead to an accumulation of cytosolic citrate, which in turn inhibits PFK-1, followed by an increase in glucose 6-phosphate, which eventually inhibits hexokinase (70) (Fig. 2). New mechanisms have been added to this first scheme and are summarized below.

**PDH.** The control of PDH activity is complex and involves control by substrates and products, covalent modification by reversible phosphorylation, and long-term adaptation of transcript and protein levels (reviewed in Refs. 81, 145, 166, and 167). The products of PDH exert a feedback inhibition on its activity. PDH activity is also controlled by reversible phosphorylation of three serine residues in the  $\alpha$ -subunit of E1 (pyruvate decarboxylase), one of the three components of the PDH complex. Dedicated mitochondrial kinases [pyruvate dehydrogenase kinase (PDK)] phosphorylate and inactivate PDH, whereas pyruvate dehydrogenase phosphatases (PDPs) have the opposite effect (Fig. 3). Control of PDH activity depends on the relative activities of PDK and PDP and on the extent of phosphorylation of the E1 subunit sites. Four and two different isoforms of PDK and PDP, respectively, with different tissue expression and phosphorylation site specificity are known (19, 101, 167). Site 1 is responsible mainly for PDH inactivation and is phosphorylated by all PDK. The ubiquitously expressed PDK2 is the most active kinase on site 1 and is responsible for the inactivation of PDH in muscles and livers of starved animals. Phosphorylation of sites 2 (mainly by PDK4) and 3 (by PDK1 only) introduces hierarchical control by retarding site 1 dephosphorylation and PDH reactivation, thus locking PDH in its inactive state. Therefore, multisite phosphorylation is expected to be complete in tissues expressing PDK1 on top of the other PDKs. This mechanism explains the delayed reactivation of PDH in heart, which expresses PDK1 as well as PDK2 and -4, compared with liver, which expresses only PDK2 and PDK4 (165, 167).

PDH substrates and products also control PDK activity. Pyruvate, or its analog dichloroacetate, inhibits, whereas acetyl-CoA and NADH stimulate PDK, with isoform-specific differences in sensitivity (19). The relative insensitivity of PDK4 toward pyruvate maintains PDH in its inactive (phosphorylated) state, as evidenced in heart and skeletal muscle, after prolonged starvation (141, 165). On the other hand, both PDP isoforms require magnesium ions, and PDP1, but not PDP2, is stimulated by Ca<sup>2+</sup> (85). Ca<sup>2+</sup> also increases ATP production by the citric acid cycle through stimulation of isocitrate and 2-oxoglutarate dehydrogenases (reviewed in Ref. 113).

In mouse models, the genetic suppression of PDH in cardiac and skeletal muscles results in dramatic effects in male (pups die on weaning) but not in female offspring. These PDH-deficient mice can survive if fed a high-fat diet, but they then go on to develop muscle hypertrophy and heart dysfunction (162). In contrast, upregulation of PDK by genetic manipulation (196) or in response to high-fat diet, starvation, or insulin deficiency (166) keeps glucose oxidation at a low level, whereas fatty acid oxidation is increased. This situation mimics a state of “metabolic inflexibility” (failure to adapt metabolism to the fasted-to-fed state transition), which is a feature of insulin resistance (see below and Ref. 92). Conversely, the blood glucose level in starved PDK4-deficient mice is lower than in the wild types (89), probably because the active PDH diverts pyruvate, a gluconeogenic substrate, to acetyl-CoA. These observations underline the crucial role of PDH in glucose and lipid homeostasis.

**PFKs.** Inhibition of glycolysis by fatty acid oxidation is relatively small (20–30% for glucose uptake and 40–60% for PFK-1 flux) compared with the almost complete inhibition of PDH (Fig. 2) (39, 143). As initially proposed, PFK-1 inhibition results from the accumulation of citrate (70, 125), a well-known allosteric inhibitor of PFK-1, and of PFK-2, as later demonstrated in liver and heart (38, 83). PFK-2 catalyzes the synthesis of fructose-2,6-bisphosphate, a potent activator of PFK-1, and inhibitor of fructose-1,6-bisphosphatase (36, 149). Therefore, the cytosolic accumulation of citrate inhibits PFK-1 through a dual lock imposed on both PFKs. In liver, this mechanism also participates in the stimulation of gluconeogenesis by fatty acids.

**Glucose uptake.** The mechanisms involved in the inhibition of glucose uptake differ in muscle and liver and are still not entirely elucidated. In skeletal and cardiac muscle, glucose uptake is controlled mainly by the translocation of glucose transporter (GLUT)4 and not by hexokinase, whose catalytic rate exceeds that of GLUT4 (for reviews, see Refs. [36](#), [82](#), and [156](#)). These kinetics explain the low intracellular glucose concentration and the “unidirectionality” of glucose transport in these tissues. The vesicular traffic of GLUT4 from intracellular stores to the plasma membrane is stimulated by insulin, muscle contraction, and energy stress ([82](#), [156](#)). Hexokinase inhibition by accumulation of its product glucose 6-phosphate, initially proposed by Randle et al. ([142](#)), probably has little impact on the overall glucose uptake under basal conditions. Accumulation of glucose 6-phosphate has not been confirmed, at least not in human skeletal muscle oxidizing fatty acids ([151](#)), which suggests that hexokinase is not responsible for the control of glucose uptake. Inhibition of GLUT4 translocation has been observed ([53](#), [143](#)), although the mechanism for this inhibition remains elusive. However, hexokinase may become rate limiting when glucose transport exceeds glycolytic flux, for instance, with acute inotropic stimulation of the heart. Glucose then accumulates in the cell and inhibits glycogen phosphorylase ([13](#), [72](#)).

In liver, the rate of glucose transport by GLUT2 far exceeds the rate of glucose phosphorylation by hexokinase IV, also known as glucokinase. The enzyme actually controls glucose uptake in this organ ([88](#)). Interestingly, long-chain acyl-CoA derivatives directly inhibit glucokinase but do not inhibit the other hexokinases ([34](#), [173](#), [178](#)), thus offering a plausible mechanism for inhibition of glucose uptake by fatty acids in liver.

The preponderant role of PDH inactivation in the control of glucose utilization by fatty acids has been questioned, and an alternative hypothesis has been proposed. In vivo studies on human subjects by Roden et al. ([151](#)) demonstrated that, in muscles oxidizing fatty acids, the decrease in glucose uptake was twice as large as the decrease in both glucose oxidation and glycogen synthesis. These results indicate that control of glucose metabolism by fatty acids is exerted mainly at the level of glucose uptake and not at the level of PDH, as reported initially ([142](#)). However, it is presently not known whether this conclusion applies to tissues other than skeletal muscle.

**Long-term effects.** The discovery that fatty acids exert transcriptional effects has added another new regulatory dimension to the glucose-fatty acid cycle ([44](#), [59](#)). Certain fatty acids can bind to peroxisome proliferator-activated receptors (PPARs), a class of transcription factors endowed with hypolipidemic action, which regulate lipid metabolism through their long-term transcriptional effects. PPARs do not act on one single target but rather orchestrate several pathways whereby nutrients regulate their own metabolism ([40](#)). They are particularly interesting because they integrate biochemical mechanisms allowing for both lipid storage and oxidation together with a capacity to prevent oxidative stress, which turns them into challenging, interesting therapeutic targets ([40](#), [130](#)).

The three members of the PPAR family (PPAR $\alpha$ , - $\beta$  or - $\delta$ , and - $\gamma$ ) differ by their effects and their tissue distribution. PPAR $\alpha$  is the target of hypolipidemic fibrate drugs that induce peroxisomal proliferation in rodents. It is expressed mainly in liver, kidney, and heart and stimulates the transcription of genes that are involved in fatty acid uptake and in mitochondrial and peroxisomal  $\beta$ -oxidation of fatty acids ([45](#), [159](#), [189](#), [190](#)). These transcriptional “feedforward” effects allow fatty acids to prime specific organs for fatty acid oxidation. The crucial role of PPAR $\alpha$  in hepatic lipid metabolism is clearly underlined by excess triglyceride accumulation in the liver of PPAR $\alpha$ -null mice that are starved or fed a high-fat diet ([96](#)). Similarly, overexpression of PPAR $\alpha$  in muscle and in heart also favors fatty acid uptake and oxidation and induces triglyceride accumulation as well as glucose intolerance and insulin resistance ([57](#)), whereas PPAR $\alpha$  deletion downregulates fatty acid oxidation but increases glucose oxidation and glycolysis ([23](#)). Taken together, these results identify this transcription factor as a link between fatty acid oxidation and glucose metabolism ([22](#), [23](#), [57–59](#)). It is also worth noting that, in the metabolically adapted hypertrophied heart, PPAR $\alpha$  activation results in contractile dysfunction, most likely due to metabolic maladaptation ([188](#)), and that the mitochondrial biogenesis response observed in the insulin-resistant heart



is likely to be driven by the PPAR $\alpha$ /PPAR $\gamma$  coactivator-1 gene regulatory pathway (46). Last, it should also be remembered that PPAR $\alpha$  controls systemic lipid metabolism by controlling the expression of lipoprotein lipase, which probably explains the therapeutic effects of fibrates (47).

PPAR $\beta/\delta$  is ubiquitously expressed, and in metabolic tissues its target genes are involved in fatty acid and glucose metabolism and in mitochondrial respiration (22, 130). These metabolic effects are probably not as essential as those of PPAR $\alpha$ , although they have been proposed as a possible drug target for heart failure treatment (22). Besides several abnormalities in various cell functions, PPAR $\delta$ -null mice present little disturbance in their blood lipid levels, probably because the remaining PPAR $\alpha$  compensates for the lack of PPAR $\beta/\delta$  (10, 136).

PPAR $\gamma$ , the target of thiazolidinediones, is expressed mainly in adipose tissue. It is a necessary component of the adipocyte differentiation program and favors fatty acid uptake and storage, thereby improving insulin sensitivity (80). It also seems to be required for normal rates of fatty acid uptake in muscle (129).

The effects of PPARs are not restricted to lipid metabolism, and, as mentioned above, PPAR $\alpha$  affects glucose metabolism. In addition, both PPAR $\alpha$  and  $\delta$  increase PDK4 mRNA and protein in liver and muscle of fasted animals, whereas PPAR $\gamma$  prevents these changes (see above; also reviewed in Ref. 81). By keeping glucose oxidation at a low level, the PDK upregulation in response to high-fat diet or starvation contributes to metabolic inflexibility and is an early feature of the maladapted heart (171, 172). Collectively, the evidence indicates that PPARs contribute to both lipid and glucose homeostasis and thus mediate long-term adaptations of the glucose-fatty acid cycle. Although beyond the scope of our review, it should be added that PPARs also control several inflammatory processes (12), which is relevant to pathological conditions such as atherosclerosis and type 2 diabetes.

### Stress Overrides Fatty Acid Inhibition of Glucose Metabolism

Under hemodynamic stress conditions, the inhibition of carbohydrate oxidation by fatty acids is abrogated (72, 74). This abrogation applies to metabolic stresses, leading to an activation of AMP-activated protein kinase (AMPK), a protein kinase that holds the stage in metabolic regulation (Fig. 4). As the name says, AMPK is activated when cytosolic concentrations of AMP rise. It acts as a sensor of cellular energy status and plays a critical role in systemic energy homeostasis (reviewed in Refs. 76, 78, and 85). AMPK is a highly conserved eukaryotic serine/threonine kinase containing one catalytic ( $\alpha$ ) and two ( $\beta$  and  $\gamma$ ) regulatory subunits. Each subunit has multiple isoforms ( $\alpha$ 1,  $\alpha$ 2,  $\beta$ 1,  $\beta$ 2,  $\gamma$ 1,  $\gamma$ 2,  $\gamma$ 3), giving rise to 12 possible combinations. AMPK is activated by metabolic stresses, such as a decrease in substrate supply (glucose or oxygen deprivation) or an increase in energy demand (muscle exercise), both of which increase the [AMP]/[ATP] ratio (76, 78). Changes in [Ca<sup>2+</sup>] can also activate AMPK independently of adenine nucleotide changes (90, 185).

At a molecular level, AMPK is activated by phosphorylation of its  $\alpha$ -subunit Thr<sup>172</sup> by upstream kinases (90, 185). Specifically, there are at least two pathways that lead to AMPK activation in intact cells. The first one senses energy depletion and is mediated by AMP and LKB1 (Peutz-Jeghers protein), a constitutively active protein kinase. AMP binds to the  $\gamma$ -subunit and allosterically stimulates AMPK. It also inhibits Thr<sup>172</sup> dephosphorylation by protein phosphatase, thus leading to increased Thr<sup>172</sup> phosphorylation and AMPK activation (157). The second pathway involves changes in intracellular [Ca<sup>2+</sup>] and is mediated by calcium/calmodulin-dependent protein kinase kinase- $\beta$ .

Exercise and physical activity lead to AMPK activation in skeletal muscle (86, 179), and the extent of this activation depends on the intensity and duration of exercise (reviewed in Ref. 148). Similarly, oxygen deprivation activates AMPK, as is the case in the ischemic heart (99, 110). Once activated, AMPK regulates energy balance by turning on catabolic ATP-generating pathways (fatty acid oxidation and glycolysis) while switching off anabolic ATP-consuming processes (lipid and protein synthesis) (reviewed in Refs. 76 and 85). The interest in AMPK also stems from its insulin-independent stimulation of glucose

transport, e.g., in muscles and in oxygen-deprived hearts ([118](#), [154](#)), and its involvement in the antidiabetic action of biguanides and thiazolidinediones (reviewed in Ref. [77](#)). This regulatory capacity of AMPK is due to the fact that key enzymes involved in the control of carbohydrate, lipid, and protein metabolism have been identified as AMPK substrates (reviewed in Ref. [85](#)). This is the case for acetyl-CoA carboxylase (ACC)2 ([48](#)), heart PFK-2 ([110](#)), and Akt substrate 160, a Rab GTPase-activating protein that controls GLUT4 recruitment to the plasma membrane ([174](#)). For example, stimulation of glycolysis in ischemic hearts results from the concomitant increase in glucose 6-phosphate supply (enhanced glucose uptake and glycogenolysis) and from the stimulation of PFK-1 directly by AMP and indirectly through the AMPK-mediated PFK-2 activation. When oxygen is available, AMPK activation also favors fatty acid oxidation by decreasing malonyl-CoA as a result of ACC inactivation ([Fig. 4](#)) (see below and Refs. [85](#) and [90](#)). Under these conditions, efficient utilization of both substrates maximizes ATP production, providing an immediate metabolic adaptation to the stress conditions responsible for AMPK activation and protecting the heart during ischemic stress ([51](#), [195](#)). Therefore, AMPK overrules the biochemical mechanisms involved in the Randle cycle, and inhibition of glucose uptake by fatty acids no longer prevails ([24](#)). However, that AMPK also favors glucose oxidation does not seem to be the case in the presence of fatty acids ([51](#)).

A similar stress situation is observed in hearts stimulated by epinephrine. Stimulation of heart glycolysis by this hormone and its second messenger cyclic AMP overrules the control by other oxidizable substrates ([30](#), [38](#), [183](#)). This results from a concerted action of adrenergic receptor activation on glucose uptake, glycogen breakdown, PFK flux, and PDH activity mediated by cyclic AMP and intramitochondrial  $[Ca^{2+}]$  accumulation ([38](#), [112](#), [113](#)). This hierarchic control has obvious implications for the situation in vivo and predicts that, after epinephrine treatment, the fatty acids originating from adipose tissue are unable to inhibit glycolysis. In addition, epinephrine promotes fatty acid oxidation as a result of ACC inactivation by the cyclic AMP-dependent protein kinase (PKA; see below). Under these conditions, the heart oxidizes both glucose and fatty acids, but it uses carbohydrates to sustain the large increase in heart function induced by epinephrine ([72](#), [74](#)).

### There is Also a “Sweet” Side to the Glucose-Fatty Acid Cycle

Control of fatty acid oxidation by glucose, which corresponds to the other part of the glucose-fatty acid cycle, was mentioned by Randle et al. ([142](#)). However, the report lacked a convincing molecular explanation for the glucose effect, except for those mediated by insulin. Since then, considerable progress has been made, especially as a result of the seminal work of McGarry et al. ([114](#)). These authors discovered a plausible mechanism for the glucose-induced inhibition of fatty acid oxidation and ketogenesis in the liver. They demonstrated that malonyl-CoA, a lipogenic intermediate, plays a crucial role in fatty acid oxidation. Like fructose-2,6-bisphosphate, malonyl-CoA signals glucose utilization, but unlike fructose-2,6-bisphosphate, malonyl-CoA also controls long-chain fatty acid (LCFA) entry and oxidation in the mitochondria. Later work by a number of laboratories focused on the control of malonyl-CoA concentration, fatty acid uptake, and, more recently, mitochondrial events. We next consider the mechanism by which glucose inhibits LCFA oxidation in liver as well as in extrahepatic tissues ([Fig. 5](#)).

**Glucose signaling by malonyl-CoA.** The mechanism by which glucose alone inhibits fatty acid oxidation depends on the tissue. The relatively high  $K_m$  of liver glucokinase for glucose (10–15 mM, i.e., about twice the normal glycemic level) predicts that any increase in circulating glucose stimulates its uptake ([88](#), [177](#)). The resulting increase in fructose-2,6-bisphosphate stimulates glycolysis and leads to pyruvate production and its mitochondrial oxidation through the pyruvate-induced inhibition of PDK and the ensuing activation of PDH. Acetyl-CoA can then be oxidized in the citric acid cycle after condensation with oxaloacetate and its transformation into citrate. However, some of the citrate escapes oxidation and is transported to the cytosol ([25](#)), where it inhibits both PFKs but also regenerates acetyl-CoA, which in turn may be carboxylated to malonyl-CoA by ACC. Malonyl-CoA inhibits carnitine palmitoyltransferase

(CPT) I, which controls the entry and oxidation of LCFA in mitochondria. By this mechanism, glucose-derived malonyl-CoA prevents the futile oxidation of newly formed fatty acids and favors fatty acid esterification. The inhibition of LCFA oxidation in liver reroutes fatty acids toward esterification, eventually leading to hepatic steatosis. In addition, long-term effects of glucose on lipogenesis could explain the effect of a high-fat, high-carbohydrate diet in liver (see below).

This sequence of events also occurs not only in lipogenic but also in “nonlipogenic” tissues such as heart and skeletal muscle, which contain the ACC2 isoform. ACC2 differs from the liver isoform (ACC1) and binds to the outer mitochondrial membrane ([1](#), [2](#)). In these tissues, the metabolic role of ACC2 is restricted to the control of LCFA oxidation through the inhibition of CPT I by malonyl-CoA. In addition, there is no clear evidence that, in these tissues, the effect of glucose alone would be the same as in the liver and results in de novo lipogenesis. The control of glucose uptake in tissues devoid of glucokinase relies mainly on GLUT4, which is almost saturated by circulating glucose concentrations, and therefore cannot signal hyperglycemia. The only way to increase glucose uptake is to stimulate GLUT4 recruitment to the plasma membrane either by insulin or by other insulin-independent mechanisms such as AMPK activation. Therefore, it is suggested that, in cardiac and skeletal muscle, inhibition of LCFA oxidation by glucose also implies a stimulation of glucose uptake ([Fig. 5](#)). In agreement with this hypothesis, glucose infusion before exercise was found to cause hyperinsulinemia and to inhibit palmitate oxidation without affecting octanoate oxidation, the entry of which into mitochondria bypasses CPT I ([32](#)).

Heart and skeletal muscles also contain GLUT1, and one may wonder whether this transporter could participate in glucose uptake. GLUT1, which is ubiquitously expressed, is less abundant than GLUT4 in these insulin-sensitive tissues. The relative expression of GLUT1 is highest in fetal heart ([147](#)). GLUT1 is located mainly at the plasma membrane even under basal conditions, and it has a lower affinity for glucose than GLUT4 ( $K_m \sim 20\text{--}27$  mM for GLUT1 vs.  $5\text{--}7$  mM for GLUT4) ([126](#), [132](#)). At low glucose concentrations, glucose transport by GLUT4 is thought to predominate over that by GLUT1, especially in response to insulin ([60](#), [126](#), [132](#)). However, increasing glucose concentration in the absence of insulin, as can be tested in vitro, is due to favor GLUT1 because of its relatively high  $K_m$  for glucose.

Before we leave the subject, a word of caution must be added on the tissue concentrations of malonyl-CoA compared with the sensitivity of CPT I to this inhibitor ([193](#), [194](#)). The liver and muscle isoforms of CPT I differ in their sensitivity to malonyl-CoA, with half-maximal inhibition at  $\sim 2$  and  $0.02$   $\mu\text{M}$ , respectively. The concentrations of malonyl-CoA are in the micromolar range ( $\sim 1\text{--}5$   $\mu\text{M}$ ) in both rat tissues, but they are  $\sim 10$ -fold lower in human muscle, and concentration changes do not exceed severalfold. From these values, we infer that liver is  $\sim 100$ -fold less sensitive to malonyl-CoA than muscle and that muscle CPT I would always be inactive if no other mechanism were to modulate its sensitivity. Recent work indicates that muscle CPT I sensitivity is indeed modulated by interaction between its  $\text{NH}_2$  and  $\text{COOH}$  termini, depending on the physiological state ([55](#)).

**Long-term effects of glucose.** A carbohydrate-enriched diet increases the hepatic content of glycolytic (glucokinase and L-type pyruvate kinase) and lipogenic (ATP citrate lyase, ACC, fatty acid synthase, and stearoyl-CoA desaturase) enzymes. This long-term adaptation involves transcriptional effects assigned to both insulin and glucose metabolism, which are mediated by sterol regulatory element-binding protein-1c (SREBP-1c) and carbohydrate response element-binding protein (ChREBP), respectively (for reviews, see Refs. [56](#), [62](#), [137](#), [138](#), and [176](#)). These two transcription factors have effects on their own but also act in synergy. ChREBP is required for the effects of glucose on L-pyruvate kinase. It acts in synergy with SREBP-1c for ACC and fatty acid synthase induction, whereas SREBP-1c stimulates liver glucokinase expression and also inhibits the expression of two gluconeogenic enzymes, glucose-6-phosphatase and phosphoenolpyruvate carboxykinase ([62](#), [137](#)). Interestingly, the long-term effect of glucose, which is in part mediated by insulin, is involved mainly in the control of lipogenesis. It focuses on carbohydrate storage into lipid rather than on glucose oxidation itself. Also remarkable, the liver is the main target of this carbohydrate-enriched diet.



## Cytosolic Events Control Fatty Acid Oxidation

As proposed above, LCFA oxidation depends on malonyl-CoA concentrations. We will now describe the determinants of malonyl-CoA concentration and analyze other potential control steps of fatty acid oxidation, keeping in mind the relevance of these mechanisms to the glucose-fatty acid cycle.

**Control of malonyl-CoA concentration.** Steady-state malonyl-CoA concentrations depend on the balance between the activities of ACC and malonyl-CoA decarboxylase (MCD), whose activities and expressions are under tight control (74, 189). As stated above, expression of ACC and lipogenic enzymes is under the control of SREBP-1c, whereas MCD expression is regulated by PPAR $\alpha$  in heart and skeletal muscle (23, 189, 190). ACC activity is also controlled by reversible phosphorylation, the active form being dephosphorylated. PKA was first reported to phosphorylate and inactivate liver ACC1, thereby decreasing malonyl-CoA concentration and explaining the stimulation of fatty acid oxidation and ketogenesis by glucagon in the liver. AMPK phosphorylates and inactivates both ACC isoforms. Whether AMPK also phosphorylates MCD is not clear, and initial reports of MCD activation by AMPK (133, 155) have not been confirmed (75). In the isolated working rat heart subjected to inotropic stimulation, increased rates of fatty acid oxidation result almost exclusively from the increased malonyl-CoA degradation by MCD (73).

**Integration of AMPK and ACC in the glucose-fatty acid cycle.** Fatty acid oxidation and the ensuing inhibition of glucose utilization require that both malonyl-CoA concentration and ACC activity are kept low and/or that MCD is active (Fig. 4) even under basal conditions, when AMPK is supposedly inactive. However, a partial AMPK activation may follow the accumulation of AMP that results from the acyl-CoA synthase-mediated activation of long-chain fatty acids into their CoA derivatives, which produces AMP. Such a feedforward mechanism for fatty acid oxidation has been reported in the heart (28). Whether it applies to other tissues remains to be demonstrated. Conversely, the inhibition of fatty acid oxidation by glucose implies that ACC is active and that both MCD and AMPK are inactive, provided that glucose uptake is stimulated. LCFAs are then rerouted toward esterification (Fig. 5). These conditions are readily found in well-oxygenated tissues, in which AMPK is inactive. In addition, glucose inactivates AMPK, at least in skeletal muscle (87). By contrast, and as stated above, AMPK activation “overrides” the glucose-fatty acid cycle and stimulates both glucose and fatty acid oxidation (Fig. 4).

The relative importance of ACC, MCD, and AMPK in the control of fatty acid oxidation has been further evaluated by the analysis of the phenotypes of genetically modified mice. The different roles of ACC1 and -2 have been confirmed in knockout mice. Whole body suppression of ACC1 results in embryonic lethality, indicating that de novo lipogenesis is crucial for normal development (5). Liver-specific ACC1 suppression decreases de novo lipogenesis and impairs triglyceride accumulation in the liver without affecting fatty acid oxidation or glucose homeostasis (111). ACC2-mutant mice are viable; they accumulate less fat and have an increased total energy expenditure compared with control mice (3). Their fatty acid oxidation rate is increased and associated with an increased expression of uncoupling proteins (UCP), UCP2 and UCP3. The mutant mice are also protected against obesity and insulin resistance induced by a high-fat and -carbohydrate diet (3, 4, 27, 131). Taken together, these results confirm that ACC1 is concerned mainly with liver de novo lipogenesis, whereas ACC2 controls LCFA oxidation in muscles and (indirectly) improves insulin sensitivity. However, the Randle cycle seems to be overruled in muscles of mice lacking ACC2. The increased fatty acid oxidation in hearts of ACC2-null mice did not inhibit glucose utilization, which was even increased (54). This resembles the effect of AMPK and epinephrine and suggests that in one way or another ACC2 actively participates in the inhibition of glucose utilization by fatty acid oxidation by a still-unknown mechanism. In addition, mTOR signaling was also decreased in these mutant hearts, indicating that ACC2 may exert unpredicted pleiotropic effects.

Repression or inhibition of MCD is expected to increase malonyl-CoA and promote glucose utilization and limit LCFA oxidation, thus mimicking the fasting-to-fed transition (Fig. 4). Pharmacological inhibition of MCD decreases fatty acid oxidation and stimulates glucose oxidation as expected (49). However, no



difference in fatty acid and glucose oxidation is observed in aerobic hearts from MCD-deficient mice, which overexpress genes regulating fatty acid utilization, thus possibly compensating for the loss of MCD (50). Interestingly, in both models, deletion or inhibition of cardiac MCD improves functional recovery after ischemia (49, 50). In addition, reducing MCD expression in myocytes by small interfering MCD RNA expression increased malonyl-CoA concentration, decreased palmitate oxidation, and increased glucose uptake without affecting insulin signaling (18). The model also shows that metabolic switching from lipid to glucose is independent of insulin signaling (18). Conversely, overexpression of hepatic MCD decreases circulating fatty acid concentrations and reverses high-fat-induced whole body insulin resistance (7). Overexpression (or repression) of liver AMPK confirmed the role of AMPK in the control of liver LCFA oxidation (61, 180, 181). Overexpression of a constitutively active  $\alpha 2$ -subunit stimulated fatty acid oxidation (increased phosphorylation of ACC1, increased production of ketone bodies, and decreased concentration of malonyl-CoA) and inhibited triglyceride synthesis in liver. The liver-specific repression of both catalytic subunits of AMPK revealed the opposite phenotype, namely decreased fatty acid oxidation and increased lipogenesis and triglyceride synthesis with accumulation of lipid droplets.

**Fatty acid uptake.** LCFA uptake is mediated by several transporters, including FAT (fatty acid translocase)/CD36, plasma membrane-bound fatty acid-binding protein, and fatty acid transport protein (107, 108). Recent evidence underlines the importance of CD36, whose deletion rescues lipotoxic cardiomyopathy (187). Moreover, FAT/CD36 may be controlled by insulin and AMPK via a mechanism resembling that involved in GLUT4 recruitment to the plasma membrane, which increases the functional transporter pool at the plasma membrane. However, it is not clear whether CD36 and GLUT4 share the same intracellular vesicular compartment or whether the same protein machinery recruits them to the plasma membrane (reviewed in Ref. 160). Increased transport coupled to the formation of the CoA derivatives and the resulting AMPK activation should ensure efficient fatty acid uptake and metabolism toward either esterification or oxidation if malonyl-CoA permits.

### Mitochondrial Events Control Fuel Selection

The emphasis generally given to malonyl-CoA in the control of LCFA oxidation has diverted attention from the consideration of other potential regulatory steps. However, a series of recent publications have incriminated mitochondrial dysfunction in type 2 diabetes (see below). And the study of octanoate oxidation, the transport of which into mitochondria does not depend on CPT I, has confirmed that fatty acids are preferentially oxidized, suggesting that mitochondrial metabolism as a whole might control fuel selection (52, 102, 161). This section briefly describes the effects of fatty acids on mitochondrial oxygen consumption and the putative mechanisms involved in fuel selection.

**Mitochondrial control of fatty acid oxidation and fuel selection.** The stimulation of cell respiration by fatty acids is well known and has been studied in detail in isolated hepatocytes (128). The increased respiration goes along with a large increase in the mitochondrial NADH/NAD ratio and a small but significant increase in mitochondrial membrane potential ( $\Delta\Psi$ ), suggesting that energy provision overtakes energy consumption (Fig. 6). However, increased energy supply does not entirely explain the stimulation of respiration, because at any given rate of respiration,  $\Delta\Psi$  is significantly lower with fatty acids, indicating increased energy consumption and/or a loss of efficiency of oxidative phosphorylation. Such a loss could result from “intrinsic uncoupling” due to a change in the proportion of electrons delivered to the first or to the second coupling site (16, 102, 150). Switching from glucose to fatty acid oxidation leads to a greater proportion of electrons being transferred to complex 2 rather than to complex 1 of the respiratory chain. This difference is reflected in a less efficient oxidative phosphorylation (ATP/O), because electrons entering complex 1 result in a higher ATP/O ratio than those entering complex 2, being equivalent to a form of “intrinsic uncoupling.” A loss of efficiency could also result from “redox slipping,” i.e., inefficient coupling between electron and proton fluxes (102, 104, 150), or from proton leak across the mitochondrial inner membrane, which also contributes to the stimulation of respiration by fatty acids (20, 21, 127, 186).

To maintain  $\Delta\Psi$  and ATP synthesis, mitochondria have no other choice but to increase respiration. Moreover, high values of  $\Delta\Psi$  can prevent normal electron flow and lead to reversed electron flow and eventually to enhanced production of reactive oxygen species (ROS) (Fig. 7) (8, 103). Therefore, by oxidizing fatty acids, mitochondria increase their respiration, their membrane potential, and the production of ROS (102, 128).

Although the preceding considerations may explain how mitochondria adapt to fatty acid oxidation, they do not explain why mitochondria prefer fatty acids to glucose. This preference implies that a step in glucose oxidation is inhibited by fatty acid oxidation. Clearly, the almost complete inactivation of PDH by fatty acid oxidation participates in this mechanism. However, PDH inactivation does not explain why complex 1 prefers NADH from  $\beta$ -oxidation rather than cytosolic NADH transported to the mitochondria via the malate/aspartate shuttle (Fig. 7). Two different (and complementary) mechanisms can be suggested. One is the compartmentation of complex 1 between supramolecular complexes containing either complexes 1 and 2 or complexes 1 and 3, the former being involved in fatty acid oxidation and the latter in any other oxidation of NADH. The formal demonstration of the actual working of these complexes is lacking, although some experimental evidence has been presented for the presence of various supramolecular complexes and for substrate channeling (6, 66, 175). The other possibility takes into account the proton electrochemical gradient ( $\Delta p$ ) in establishing a priority for electrons coming from either glucose or fatty acids. High values of  $\Delta p$  promote the transport and accumulation of metabolic anions, such as malate and glutamate via the malate/aspartate shuttle, into the mitochondrial matrix. The glutamate-aspartate carrier exchanges glutamate plus a proton for aspartate, and high values of  $\Delta p$  favor glutamate uptake together with aspartate expulsion (reviewed in Ref. 100). Once inside, these imported substrates provide the electron transfer chain with NADH that competes with NADH from fatty acids.

Conversely, decreasing  $\Delta p$  leads to an inhibition of the mitochondrial transport of these metabolic anions and favors fatty acid oxidation. Experimentally, decreasing  $\Delta p$  by uncouplers in hepatocytes results in a progressive inhibition of respiration from glycolytic substrates but not from fatty acids, thus confirming that low values of  $\Delta p$  favor fatty acid oxidation (161). In addition, it is known that increased UCP content, resulting from PPAR $\alpha$  activation or during fasting (95, 130, 190), goes along with increased fatty acid oxidation. Similarly, one may also speculate that the increase in cytosolic  $\text{Ca}^{2+}$  brought about by muscle contraction could decrease  $\Delta p$  through its transport into the mitochondria via the  $\text{Ca}^{2+}$  uniport and so favor fatty acid oxidation. The accumulation of matrix  $\text{Ca}^{2+}$  would also stimulate the local dehydrogenases, thus contributing to the overall increase in energy production (41, 112, 113). We conclude that the control of fatty acid oxidation extends well beyond malonyl-CoA and that mitochondria have a critical role to play in fuel selection.

**Glucose toxicity.** High values of  $\Delta\Psi$  lead to proton leak, reversed electron flow, and ROS production (Fig. 7). As described above, active fatty acid oxidation induces such a state. Flooding the system with glucose on top of fatty acids is expected to induce considerable damage to the mitochondria if energy demand is not concomitantly increased. An overabundant diet rich in carbohydrates and fat (184) should force-feed electrons from glucose into the respiratory chain, in which the already prevailing high  $\Delta\Psi$  prevents electron flow. This excessive energy supply, not matched by energy demand, will further worsen the jamming of electrons in the respiratory chain and eventually result in massive ROS production and mitochondrial damage (Fig. 7). In addition, a saturated flux through the glycolytic pathway could result in an overflow into the hexosamine biosynthetic pathway leading to protein glycosylation by *O*-linked  $\beta$ -*N*-acetylglucosamine (67, 106, 192). The persistent combination of these two effects probably explains glucose toxicity. By contrast, the beneficial effects of physical activity and muscle exercise could prevent mitochondrial damage by decreasing  $\Delta\Psi$  and favoring the overall oxidation of substrates to fulfill the increased energy demand. Last, one might even wonder whether glucose intolerance and insulin resistance are not a protective mechanism that prevents glucose toxicity.

**Cross-talk between mitochondria and cytosol.** MCD inhibition in myocytes induces a clear transition from fatty acid to glucose oxidation. In these cells, glucose uptake is increased and mediated by an insulin-independent mechanism that is triggered by the collapsing LFCA oxidation ([18](#), [98](#)). These results suggest that mitochondria cross-talk with signaling pathways controlling glucose uptake. In this context, one must consider the translocation and binding of hexokinase to mitochondria, which increases its efficiency and decreases its product inhibition ([134](#)). In the heart, insulin and ischemia increase mitochondrial hexokinase binding, whereas oleate has the opposite effect ([164](#)). One can speculate that, when fatty acid oxidation is inhibited, hexokinase translocates to the mitochondria and so promotes glucose metabolism. Another interesting cross-talk is the inhibition of mitochondrial oxidative phosphorylation by fructose-1,6-bisphosphate, which could participate in the inhibition of cell respiration by high glucose concentrations (the Crabtree effect) ([42](#)). The underlying mechanisms of these cross-talks require further investigation.

Unexpectedly, both in the fed and fasted states, it is the same molecule, citrate, that signals in the cytosol the ongoing mitochondrial oxidation of either glucose or fatty acids. The activity of ATP citrate lyase is the key element that allows the cytosol to distinguish between the two nutritional states by decreasing citrate concentration and producing acetyl-CoA in the cytosol at the price of one ATP per citrate cleaved. ATP citrate lyase is under tight nutritional and hormonal control, and its activity is upregulated by the long-term effects of glucose and insulin, i.e., when lipogenesis prevails. The enzyme is also the substrate of several protein kinases ([135](#), [139](#)), but there is uncertainty about the effects of phosphorylation on its kinetic properties ([14](#)).

### The “Fatty Acid Syndrome” is a Form of Insulin Resistance

In their 1963 article, Randle et al. ([142](#)) noted that “Several abnormalities of carbohydrate metabolism common to many endocrine and nutritional disorders (including starvation, diabetes, and Cushing's syndrome) are associated with a high plasma concentration of fatty acids.” They added that “The high concentration of fatty acids stands in a causal relationship to these abnormalities of carbohydrate metabolism and suggests that this is a distinct biochemical syndrome which could appropriately be called the fatty acid syndrome.” This remarkably prescient observation opened the way for the investigation of the role of fatty acids in the establishment of insulin resistance ([115](#)). However, an enormous amount of new knowledge has accumulated since Randle's original observations.

Insulin resistance is characterized by decreased glucose uptake and altered lipid metabolism ([29](#), [43](#), [94](#), [152](#), [154](#)). It heralds the initial stages of type 2 diabetes, a metabolic disorder often associated with obesity, ectopic fat depots, and physical inactivity, and eventually evolves toward failure of the pancreatic  $\beta$ -cells. The relationship between insulin resistance and the accumulation of lipids in tissues suggests that these lipids are both markers and mediators of metabolic dysfunction, especially in skeletal muscle, which is the main site of insulin-stimulated glucose disposal ([26](#), [91](#), [93](#), [105](#), [116](#), [117](#), [122](#), [158](#), [191](#)).

One hypothesis, which has already been discussed for a long time, proposes that muscle insulin resistance results from decreased mitochondrial oxidation of fatty acids ([93](#), [116](#), [120](#), [158](#)). The unoxidized fatty acids are rerouted toward the synthesis of diacylglycerol and ceramide, which in turn stimulate stress-induced protein kinases that inhibit insulin signaling ([79](#), [120](#), [158](#)). Measurement of the concentrations of these lipids, of the mitochondrial oxidative capacity, and of the phosphorylation state of several components of the insulin-signaling pathway in hearts perfused with palmitate and in pathological samples from type 2 diabetic patients is in support of the hypothesis ([17](#), [26](#), [43](#), [93](#), [121](#), [124](#), [140](#), [163](#)).

However, more recent reports have seriously questioned the hypothesis because 1) induction of fatty acid oxidation with PPAR agonists does not correct insulin resistance ([35](#)), and 2) increasing these lipids by genetic manipulation or pharmacological agents does not induce insulin resistance ([7](#), [33](#), [119](#)). These observations led to an opposite hypothesis proposing that excessive rather than deficient fatty acid oxidation is the culprit ([122](#), [123](#)). In models of metabolic overload (unmatched by physical activity),

lipid-induced insulin resistance requires prior partial oxidation of fatty acids and accumulation of incompletely oxidized lipid intermediates, which one way or another downregulate insulin signaling ([97](#), [98](#)). In this model, excessive oxidation, unmatched by energy demand, induces insulin resistance.

These two opposite hypotheses may be reconciled by considering a continuum in the establishment of aberrant mitochondrial function that may evolve from a partial and discreet deficiency to a progressive failure of the oxidative mitochondrial capacities. The slowly progressing pathological process could be the consequence of a continuous overabundant diet enriched in both carbohydrate and lipid, unmatched by physical activity. In the mitochondria, the redox pressure from both substrates would provoke a continuous production of ROS, resulting first in minimal damage but deteriorating with time into more extensive and irreversible lesions. This interpretation is in agreement with recent data showing that mitochondrial alterations do not precede the onset of insulin resistance and result from increased ROS production in muscle in diet-induced diabetic mice ([15](#)). In addition, the importance of physical activity and energy utilization is fully taken into account in our interpretation, because they are expected to protect the mitochondria by decreasing ROS production. One may also wonder whether the beneficial effect of metformin, the most widely used drug for the treatment of type 2 diabetes, may be due to its capacity to decrease mitochondrial ROS production by inhibiting the reversed electron flow at the level of the complex 1 of the respiratory chain ([11](#), [103](#)).

## Conclusions and Outlook

The intricate interactions between glucose and fatty acid metabolism, originally described in the glucose-fatty acid cycle, are far more complex than originally proposed, as revealed by new molecular insights, including allosteric control, reversible phosphorylation, and expression of key enzymes. These mechanisms involve the control of 1) glucose uptake, glycolytic flux (PFK), and glucose oxidation (PDH), 2) fatty acid oxidation by malonyl-CoA (whose concentration depends on ACC, MCD, and AMPK), 3) fatty oxidation in the mitochondria by  $\Delta p$ , and 4) expression of key enzymes in the metabolic pathway of glucose and lipid metabolism by PPAR, SREBP-1c, and ChREBP. The elucidation of these interactions as well as of the importance of mitochondrial ROS production has led to a more refined understanding of the mechanisms leading to insulin resistance and type 2 diabetes. For the sake of completeness, another type of interaction not discussed in this review should still be mentioned. Here, the metabolic effects of certain amino acids, especially leucine and glutamine, on energy substrate metabolism deserve consideration ([65](#)). In the title of this article, we likened the Randle cycle to an “old hat.” From what has been said, it seems equally appropriate to liken the cycle to a book in which not all chapters have been written.

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## Footnotes

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<sup>1</sup>The words “regulation” and “control” are often used indifferently, because their meaning is somewhat overlapping. In this article, we have tried to restrict the use of regulation and control in keeping with their previous definition (39, 170). Regulation is related to homeostasis and defines the capacity of a system to respond to environmental changes, whereas metabolic control refers to the capacity of the mechanisms in the system to adapt. Thus, we say that regulation of blood glucose is achieved by hormonal control of metabolic pathways, in which control is distributed between several steps.

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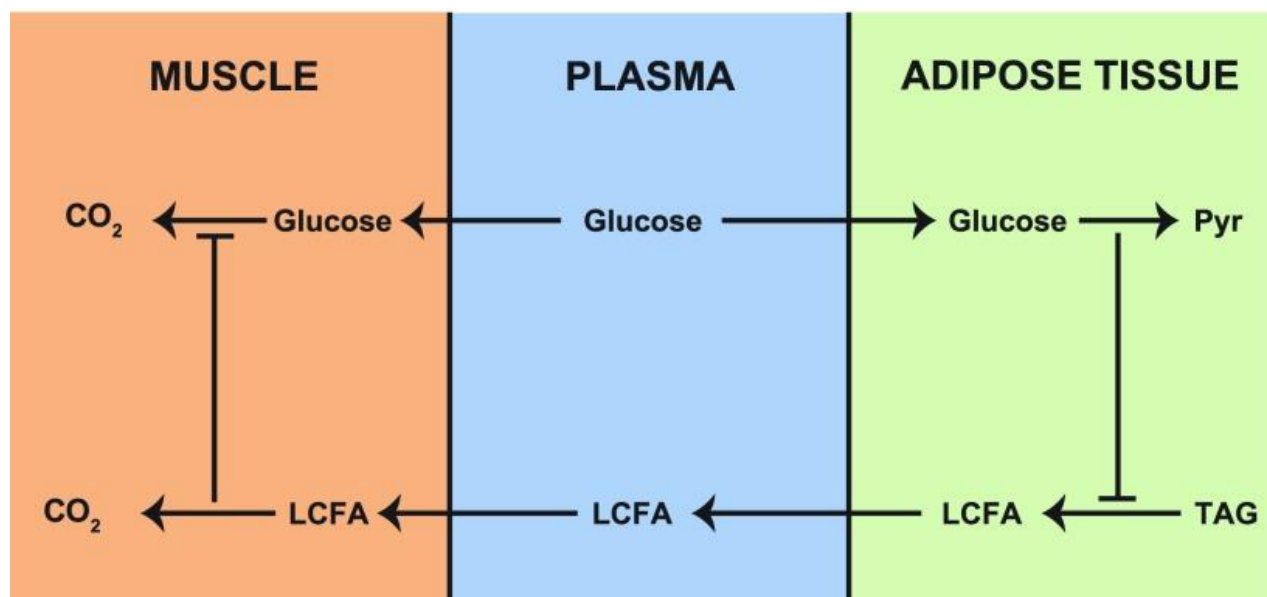


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**Figures and Tables**

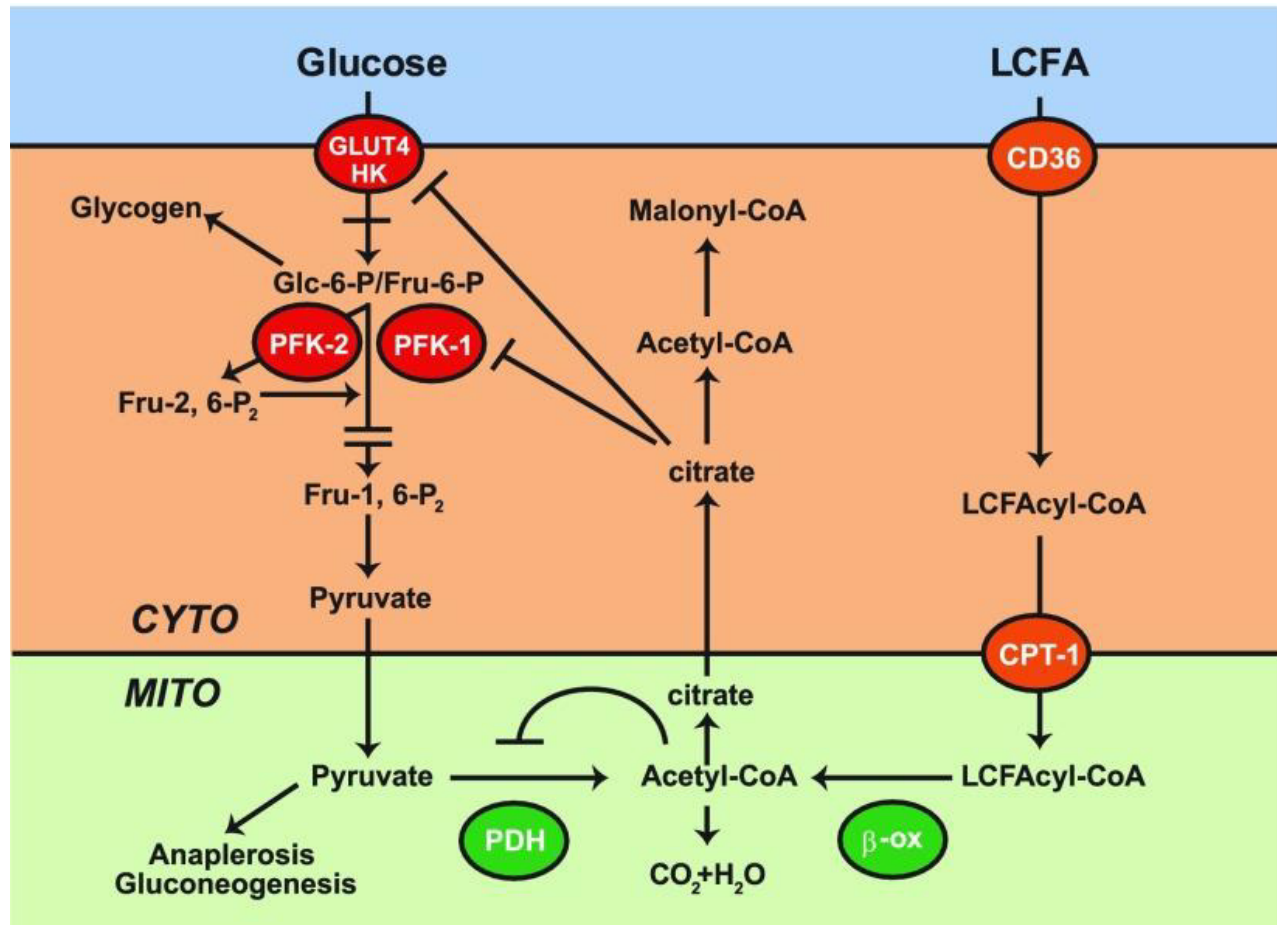
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**Fig. 1.**

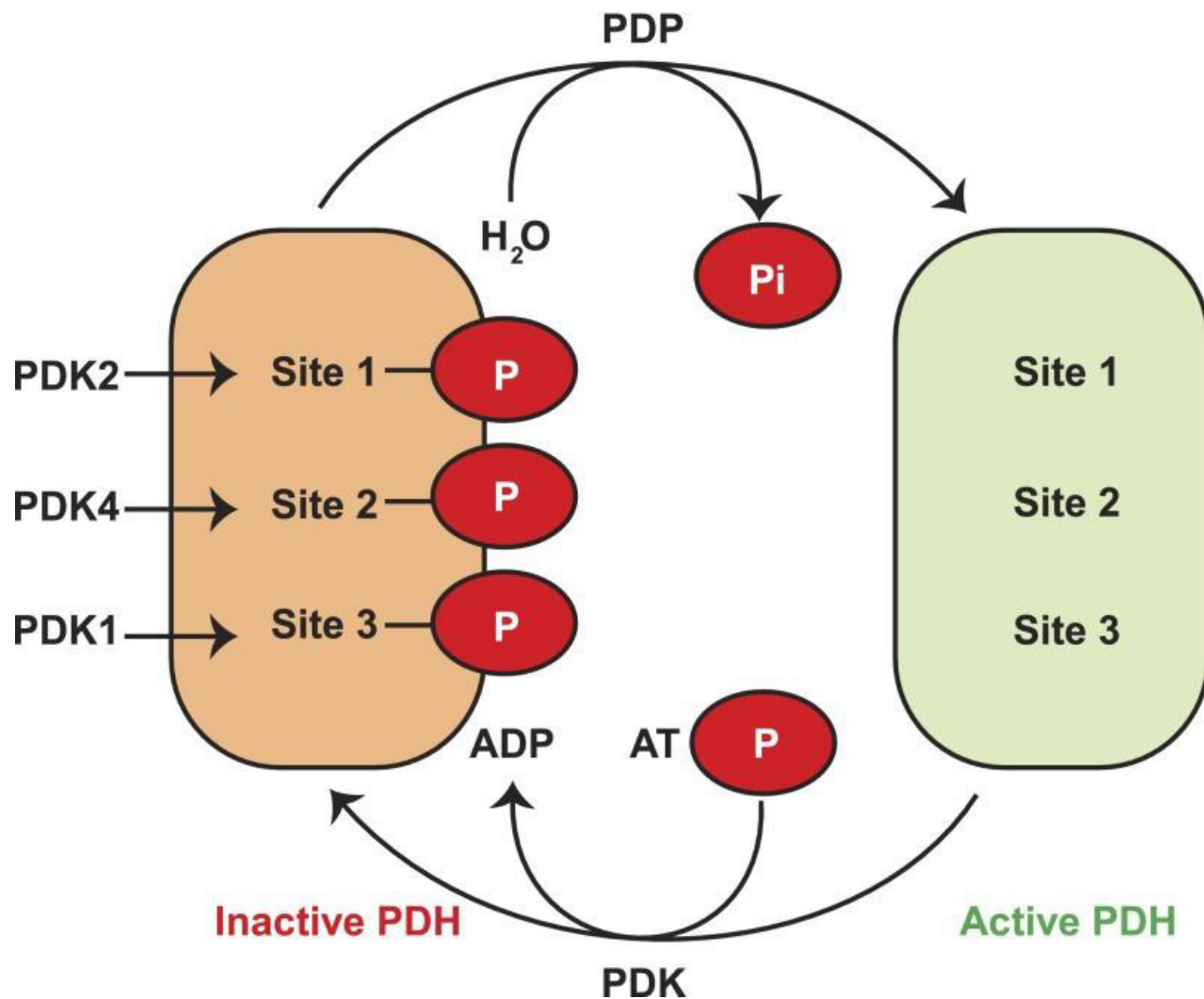
The “glucose-fatty acid cycle,” a homeostatic mechanism to control circulating concentrations of glucose and fatty acids (adapted from Ref. [142](#)). The term “cycle” is used here to describe a reciprocal control between glucose and fatty acid metabolism. The effect of glucose is mediated by insulin. LCFA, long-chain fatty acid; TAG, triacylglycerol; Pyr, pyruvate.

Fig. 2.



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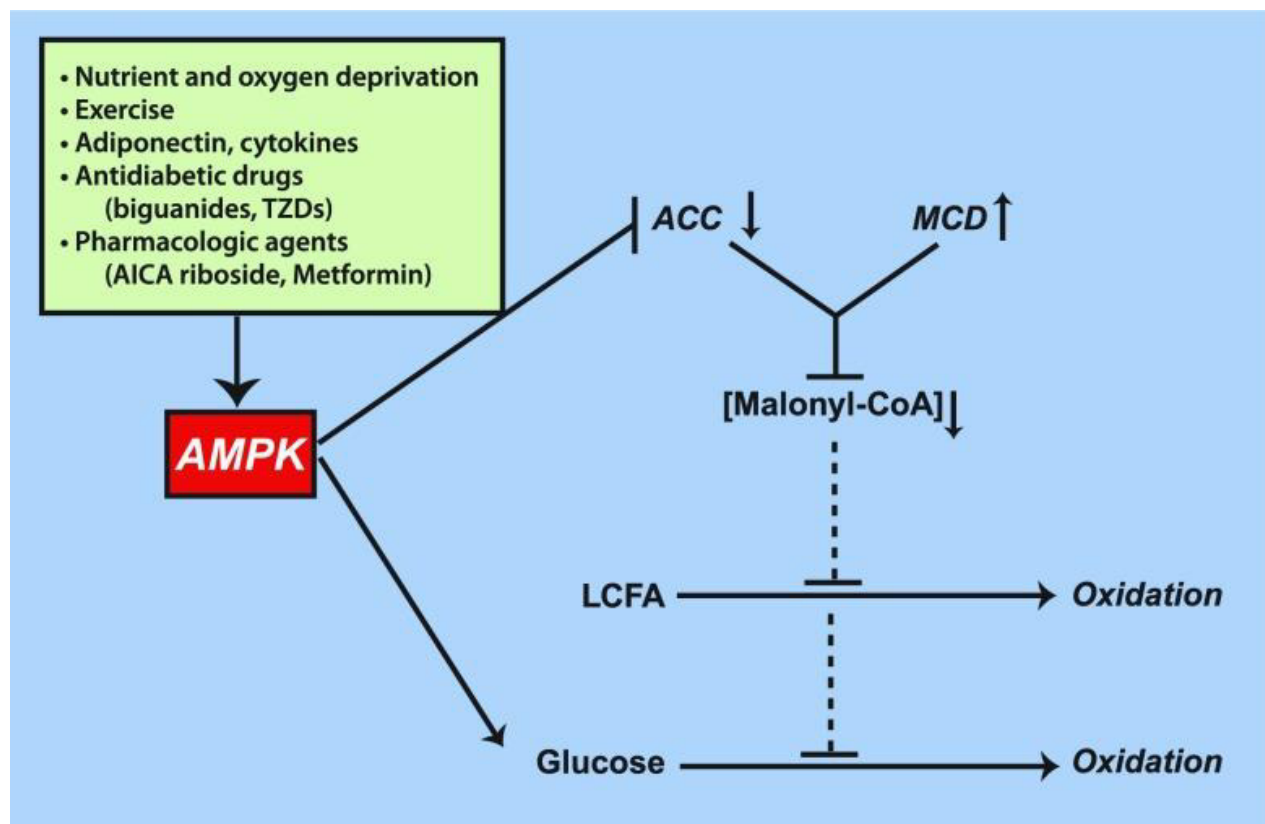
Mechanism of inhibition of glucose utilization by fatty acid oxidation. The extent of inhibition is graded and most severe at the level of pyruvate dehydrogenase (PDH) and less severe at the level of 6-phosphofructo-1-kinase (PFK) and glucose uptake. PDH inhibition is caused by acetyl-CoA and NADH accumulation resulting from fatty acid oxidation, whereas PFK inhibition results from citrate accumulation in the cytosol. The mechanism of inhibition of glucose uptake is not clear. These effects reroute glucose toward glycogen synthesis and pyruvate to anaplerosis and/or gluconeogenesis. See text for further details. CYTO, cytosol; MITO, mitochondria; GLUT4, glucose transporter 4; HK, hexokinase; Glc-6-P, glucose 6-phosphate; Fru-6-P, fructose 6-phosphate; CPT I, carnitine palmitoyltransferase I;  $\beta$ -ox,  $\beta$ -oxidation.

**Fig. 3.**

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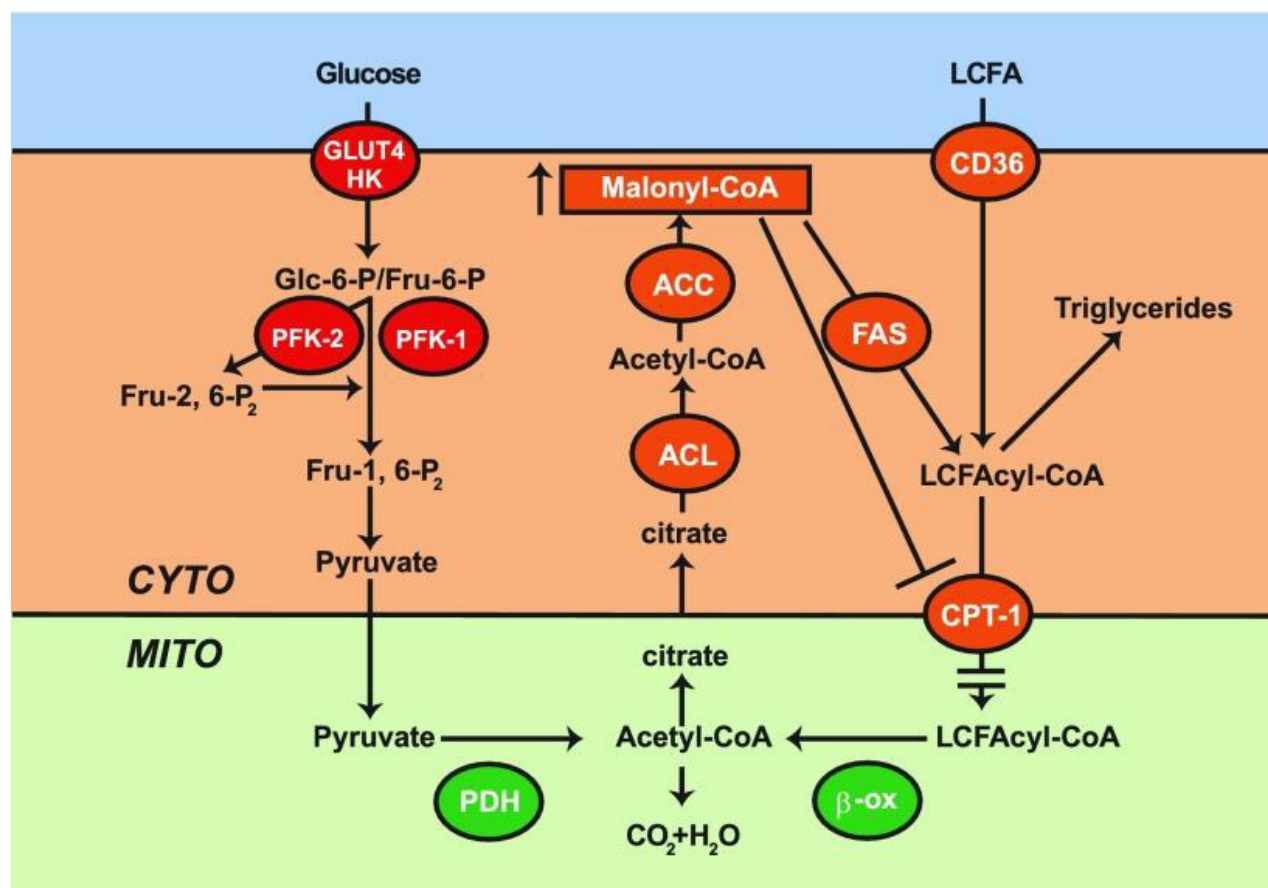
Control of PDH activity by covalent modification. Phosphorylation inactivates the enzyme, and dephosphorylation activates the enzyme. The 3 sites are located in the  $\alpha$ -subunit of E1 (pyruvate decarboxylase), 1 of the 3 components of the PDH complex. See text for further details. PDK, pyruvate dehydrogenase kinase; PDP, pyruvate dehydrogenase phosphatase; P, phosphate.



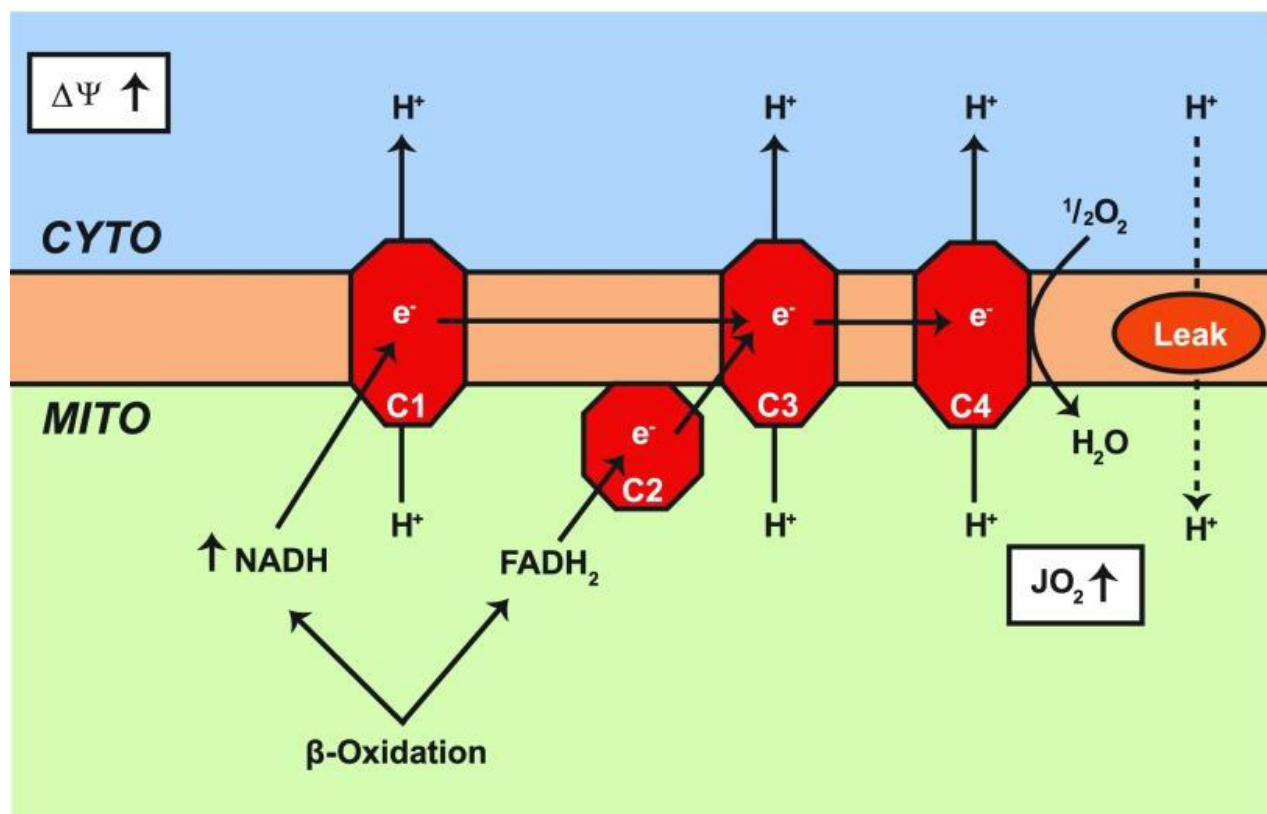
**Fig. 4.**

AMP-activated protein kinase (AMPK) stimulation of glucose and fatty acid utilization. Activation of AMPK leads to acetyl-CoA carboxylase (ACC) inactivation, possibly together with malonyl-CoA decarboxylase (MCD) activation, which decreases malonyl-CoA concentration and hence, favors fatty acid oxidation. AMPK also stimulates glucose uptake and glycolysis, and the inhibition of glucose uptake by fatty acid oxidation no longer prevails. TZDs, thiazolidinediones; AICA, 5-aminoimidazole-4-carboxamide.

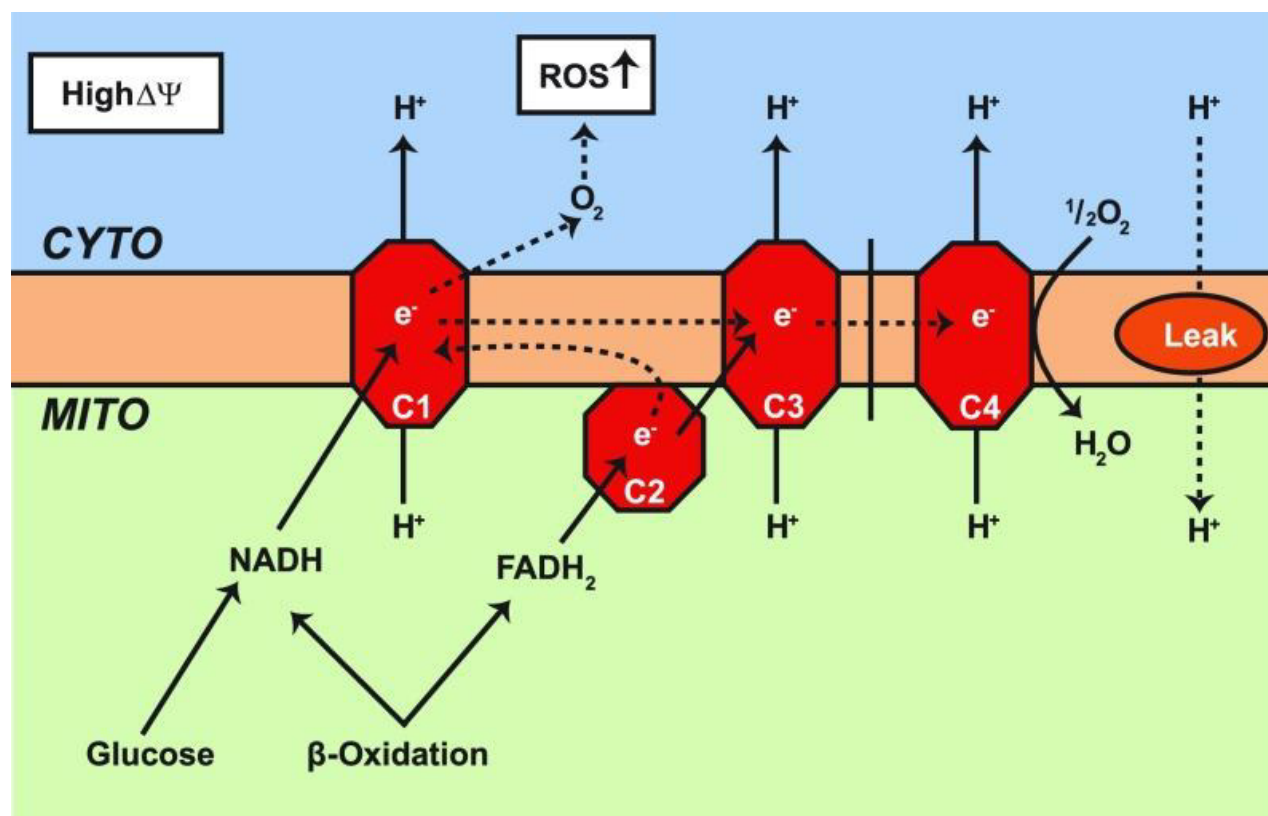
Fig. 5.



Mechanism of inhibition of fatty acid oxidation by glucose. This mechanism is mediated by malonyl-CoA, the concentration of which depends on ACC activity and which inhibits the entry of long-chain fatty acyl (LCFAcyl-CoA) moieties into mitochondria. This effect reroutes fatty acids toward esterification. In extrahepatic tissues, the effect of glucose is stimulated by insulin. See text for further details. ACL, ATP-citrate lyase; FAS, fatty acid synthase.

**Fig. 6.**

Stimulation of mitochondrial respiration by fatty acids.  $\beta$ -Oxidation of fatty acids stimulates mitochondrial oxygen consumption ( $JO_2$ ) and increases the  $NADH/NAD$  ratio and the mitochondrial membrane potential ( $\Delta\Psi$ ). Substrate oxidation provides the electron transfer chain with electrons, which are transferred to oxygen. The redox free energy ( $\Delta E$ ) span is used to synthesize ATP (not shown) by an energy transduction system involving the electrochemical gradient of protons (the proton motive force,  $\Delta p$ ) created by proton pumps located in the respiratory chain complexes 1, 3, and 4 and driven by  $\Delta E$ . Efficient coupling between ATP synthesis and oxygen consumption ( $ATP/O$ ) depends on 2 forces,  $\Delta E$  and  $\Delta\Psi$ . Proton leaks and inefficient coupling between electron and proton fluxes (redox slipping) decrease the system efficiency.

**Fig. 7.**

Proton leaks, reverse electron flow, and reactive oxygen species (ROS) production. High values of  $\Delta\Psi$  prevent electron flow, favor proton leaks, and lead to reverse electron flow and eventually enhanced production of ROS. This process is worsened by the concomitant oxidation of glucose and probably contributes to glucose toxicity. See text for further details.

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