invited review

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Recent advances in mechanisms regulating glucose oxidation at the level of the pyruvate dehydrogenase complex by PDKs

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Sugden, Mary C., and Mark J. Holness. Recent advances in mechanisms regulating glucose oxidation at the level of the pyruvate dehydrogenase complex by PDKs. *Am J Physiol Endocrinol Metab* 284: E855–E862, 2003; 10.1152/ajpendo.00526.2002.—The mitochondrial pyruvate dehydrogenase complex (PDC) catalyzes the oxidative decarboxylation of pyruvate, linking glycolysis to the tricarboxylic acid cycle and fatty acid (FA) synthesis. Knowledge of the mechanisms that regulate PDC activity is important, because PDC inactivation is crucial for glucose conservation when glucose is scarce, whereas adequate PDC activity is required to allow both ATP and FA production from glucose. The mechanisms that control mammalian PDC activity include its phosphorylation (inactivation) by a family of pyruvate dehydrogenase kinases (PDKs 1–4) and its dephosphorylation (activation, reactivation) by the pyruvate dehydrogenase phosphate phosphatases (PDPs 1 and 2). Isoform-specific differences in kinetic parameters, regulation, and phosphorylation site specificity of the PDKs introduce variations in the regulation of PDC activity in differing endocrine and metabolic states. In this review, we summarize recent significant advances in our knowledge of the mechanisms regulating PDC with emphasis on the PDKs, in particular PDK4, whose expression is linked with sustained changes in tissue lipid handling and which may represent an attractive target for pharmacological interventions aimed at modulating whole body glucose, lipid, and lactate homeostasis in disease states.

peroxisome proliferator-activated receptor-α; glucose; pyruvate; fatty acids

THE MITOCHONDRIAL PYRUVATE DEHYDROGENASE COMPLEX (PDC) catalyzes the oxidative decarboxylation of pyruvate. This reaction links glycolysis to the energetic and anabolic functions of the tricarboxylic acid (TCA) cycle (Fig. 1). As a consequence, adequate flux through PDC is particularly important in tissues with a high ATP requirement, including exercising muscle. Acetyl-CoA production via PDC is also important in tissues that are active in fatty acid (FA) synthesis (liver, lactating mammary gland, and adipose tissue), since mitochondrial acetyl-CoA, via citrate formation and efflux, provides the precursor of cytosolic acetyl-CoA, which is used for FA synthesis (Fig. 1). Because substrate competition exists potentially between glucose and FAs, PDC's role in facilitating production of the lipogenic intermediate malonyl-CoA under conditions where glucose is abundant (Fig. 1) means that a high PDC activity can limit mitochondrial FA uptake (and therefore oxidation) via inhibition of carnitine palmitoyltransferase I. Conversely, because no pathway exists for the conversion of acetyl-CoA to glucose in mammals, suppression of PDC activity is crucial for conservation of glucose (and facilitation of FA oxidation) when glucose is scarce. This review describes recent advances relating to the regulation of mammalian PDC activity by reversible phosphorylation, with emphasis placed on the acute and long-term modes of regulation of pyruvate dehydrogenase kinase (PDK), which phosphorylates and inactivates PDC.

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CHARACTERISTICS OF PHOSPHORYLATION AND DEPHOSPHORYLATION OF PDC

In addition to the three components that catalyze the conversion of pyruvate to acetyl-CoA [pyruvate dehydrogenase (E1), dihydrolipoamide acetyltransferase (E2), and dihydrolipoamide dehydrogenase (E3)], PDC contains two specific regulatory enzymes, PDK and pyruvate dehydrogenase phosphate phosphatase (PDP). PDK and PDP together catalyze a phosphorylation-dephosphorylation cycle involving specific serine residues on the α-subunit of E1 (Fig. 1). Importantly, because the phosphory-

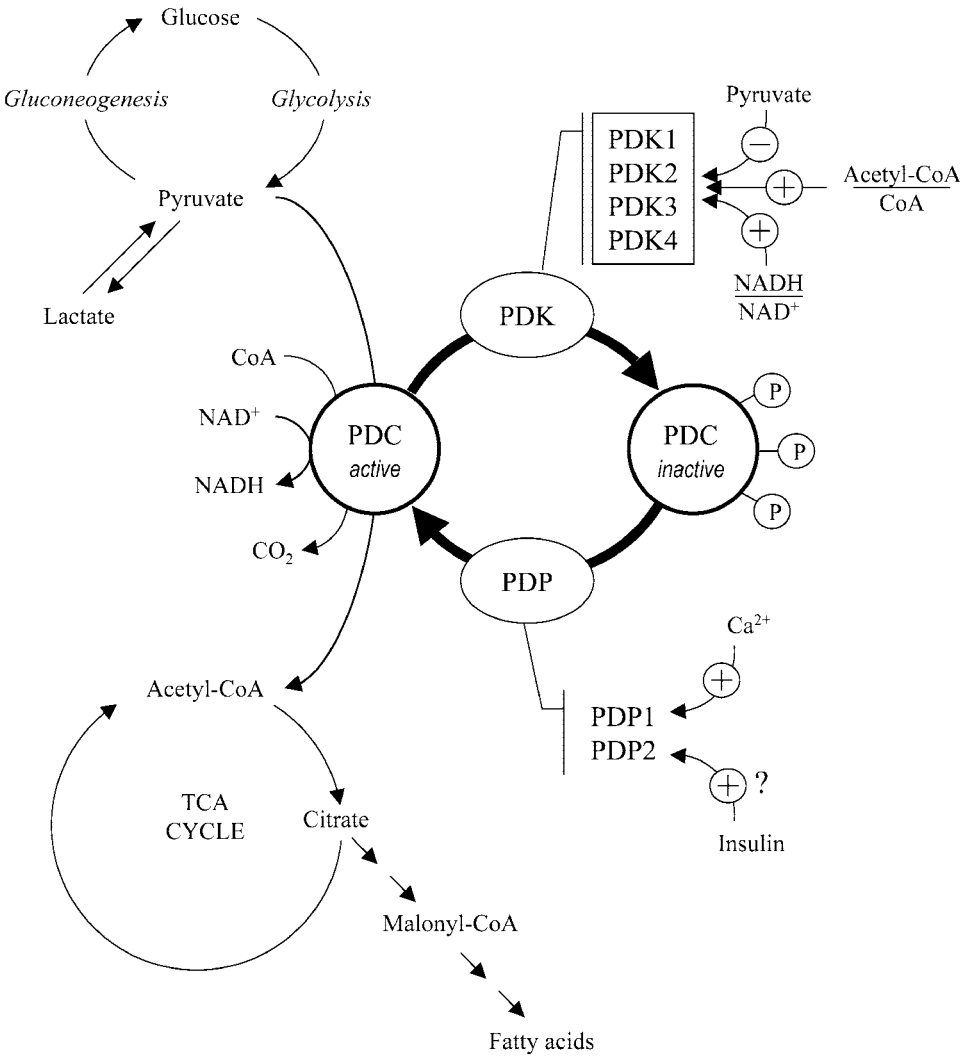

Fig. 1. Mechanisms regulating the pyruvate dehydrogenase complex (PDC) by phosphorylation-dephosphorylation, together with the reaction catalyzed by PDC and its links with other metabolic pathways. PDK, pyruvate dehydrogenase kinase; PDP, pyruvate dehydrogenase phosphate phosphatase; TCA, tricarboxylic acid cycle.

lation of the α-subunits of E1 renders PDC completely devoid of activity (31), the percentage of active PDC at any one time reflects the percentage of α-subunits of E1 that are phosphorylated. The percentage of active PDC thus reflects the activity of PDK (which catalyzes ATP-dependent E1 phosphorylation) (71) and PDP (which catalyzes E1 dephosphorylation) (56) (reviewed in Ref. 53).

Phosphorylation of E1 occurs at three specific serine residues (45, 57, 71), serine-264 (designated phosphorylation site 1), serine-271 (phosphorylation site 2) and serine-203 (phosphorylation site 3) (57). Half-of-the-site reactivity during phosphorylation of all three sites has been reported, which implies that a maximum of only three of the six potential phosphorylation sites (three potential sites for each E1α subunit) can be phosphorylated (26). Analysis of relative initial rates of phosphorylation of each site on E1α by use of rat heart complex demonstrated that site 1 phosphorylation is the most rapid and site 3 phosphorylation the least rapid (45). Construction of mutant human E1s with single functional phosphorylation sites has revealed that phosphorylation of each site alone can cause PDC inactivation (26). However, to reiterate the results obtained with purified mammalian PDC (45), phosphorylation of site 1 is 4.6-fold more rapid than that of site 2 and 16-fold more rapid than that of site 3 (26). Studies using recombinant proteins with mutations in the three phosphorylation sites have also revealed that dephosphorylation of sites 1, 2, and 3 occurs randomly (26). This implies that, in functional terms, phosphorylation of sites 2 and 3 could retard the rate of dephosphorylation of all three sites through site competition for PDP. Multisite phosphorylation of E1 leading to impaired reactivation by PDP has been proposed as one possible explanation for the delay in PDC reactivation that is found in liver, heart, and oxidative skeletal muscle on refeeding after starvation (15, 17, 52).

REGULATION OF PDP

Dephosphorylation of PDC is catalyzed by two PDP isoforms (PDP1 and PDP2), which are variably expressed in different tissues (11, 18, 40, 41, 44). PDP1, the dominant isoform in Ca^{2+}-sensitive tissues, requires Mg^{2+} and is stimulated by Ca^{2+} (18). Ca^{2+} stimulation of PDP1 arises in part because PDP1 binds

to E2 via an interaction that requires micromolar concentrations of Ca^{2+} (38) and in part because Ca^{2+} decreases the K_m of PDP1 for Mg^{2+} (61). PDP1 comprises a catalytic and a regulatory subunit (42, 56). The catalytic subunit (PDP1c) is in the phosphatase 2C class (28). The regulatory subunit (PDP1r) is a flavoprotein with a bound flavin adenine dinucleotide that influences the Mg^{2+} concentration that is required for PDP1c activity (29, 69). The second PDP isoform, PDP2, is found in liver and adipose tissue (18). Rat PDP2 shares 55% sequence identity with rat PDP1c but is not activated by Ca^{2+} (18). In adipose tissue, insulin reduces the concentration dependence of PDP(2) activity for Mg^{2+} (60).

REGULATION OF PDK

The activity of PDK is also highly regulated (see Fig. 1). Short-term mechanisms of PDK regulation by metabolites include its inhibition by the E1 substrate pyruvate (generated via glycolysis or from circulating lactate) and its activation by acetyl-CoA and NADH, products of both the PDC reaction and FA β-oxidation (22). PDK consists of two dissimilar subunits (α and β). Kinase activity resides in the α-subunit, as its selective proteolytic cleavage results in loss of activity. The β-subunit is a regulatory subunit.

Isolation of a cDNA encoding a 48-kDa form of PDK, later termed PDK1, from a rat heart cDNA library allowed determination of the primary structure of PDK (41). Analysis of the deduced amino acid sequences demonstrated that the PDKs lack the signature sequence motifs found in other eukaryotic serine/threonine protein kinases but contain highly conserved regions in the COOH terminus resembling motifs conserved in prokaryotic histidine protein kinases (41). In addition, molecular modeling has suggested that the PDKs are folded into a three-dimensional structure resembling that of prokaryotic histidine protein kinases (3). It has thus been suggested that the PDKs belong to the ATPase/kinase superfamily (composed of bacterial histidine protein kinases, DNA gyrases, and molecular chaperone Hsp90) (2, 3, 47). To date, four PDK isoenzymes have been identified in humans and rodents. These have been designated PDK1, PDK2, PDK3, and PDK4 (3, 39). Two PDK isoforms are found in plants (58, 59), one in nematodes (5), and one in *Drosophila melanogaster* (21). The primary structures of the four PDK isoforms are extremely conserved, with 66–74% identity: PDK3 and PDK4 are the most distinct and PDK1 and PDK2 the most conserved (with 70% identity between PDK1 and PDK2) (40). There is also very high sequence identity for the same PDK isoform between species, and PDK1 and PDK2 are >95% identical between rat and human. The amino acid sequences of the human precursor PDKs vary, with 436 residues for PDK1, 411 for PDK4, 407 for PDK2, and 406 for PDK3 (44). Similarly, the molecular masses of the PDKs vary such that mature PDK1 corresponds to a 48-kDa subunit, whereas mature PDK2, PDK3, and PDK4 correspond to a 45-kDa subunit.

Mammalian PDKs exhibit tissue-specific expression (3). PDK1 has been detected in heart (3, 55, 68), the pancreatic islet (48), and skeletal muscle (36). PDK2 is ubiquitously expressed in the fed state, with particularly high expression in heart, liver, and kidney (3). PDK3 has a relatively limited tissue distribution (testis, kidney, and brain) (3, 18). PDK4 is expressed at high levels in heart (3, 55, 68), skeletal muscle (3, 14, 36, 54, 66), liver (3, 50, 51, 65), kidney (3, 49, 51, 65), and the pancreatic islet (48).

Isoform-specific differences in kinetic parameters, regulation, and phosphorylation site specificity introduce variations in the regulation of PDC activity in differing endocrine and metabolic states. Although all four PDK isoenzymes can phosphorylate and inactivate PDC in vitro, the relative catalytic activity of recombinant isoenzymes toward wild-type E1 varies (PDK2 < PDK4 < PDK1 < PDK3) (3). In addition, individual recombinant PDK isoenzymes differ in their acute regulation by metabolites (3). Recombinant (r)PDK2 is the most sensitive (K_i = 0.2 mM) to inhibition by the pyruvate analog dichloroacetate (DCA) (3) (Fig. 2). In contrast, rPDK4 is relatively insensitive to suppression by DCA (3) but more responsive to an increased NADH-to-NAD^+ concentration ratio than rPDK2 (3) (Fig. 2). However, further addition of acetyl-CoA activates rPDK2, but rPDK4 does not show activation above that seen with NADH alone (3) (Fig. 2).

The specificity of the four mammalian PDKs toward the three phosphorylation sites of E1 has been investigated using recombinant E1 mutant proteins with only one functional phosphorylation site (25, 27). All four PDKs phosphorylate sites 1 and 2; site 3 is phosphorylated only by PDK1 (25, 27) (Fig. 2). Although PDK is activated by binding to E2 (70), all four PDKs can phosphorylate sites 1 and 2, and PDK1 can phosphorylate site 3 in the absence of E2-E3 binding protein (27). All four PDKs exhibit higher activity toward site 1 of free E1 compared with the other two phosphorylation sites, PDK2 exhibiting the highest activity and PDK3 the lowest activity toward site 1 (27). In contrast, in the free form, PDK4 exhibits a much higher activity toward site 2 compared with PDK1, PDK2, and PDK3 (27).

LONG-TERM REGULATION OF MAMMALIAN PDK EXPRESSION

PDK activity in several oxidative tissues is increased in response to nutritional and endocrine manipulations that increase lipid supply and utilization. Culture of hepatocytes (9), cardiac myocytes (32, 35), and soleus strips (46) with FAs increases PDK activity. PDK is present in limited amounts in PDC (1–2 molecules per complex), and, in the intact animal, the protein expression of one specific PDK isoenzyme, PDK4, is modified when there is a sustained change in tissue lipid delivery and/or handling. PDK4 protein expression in heart, skeletal muscle, and liver increases with starvation

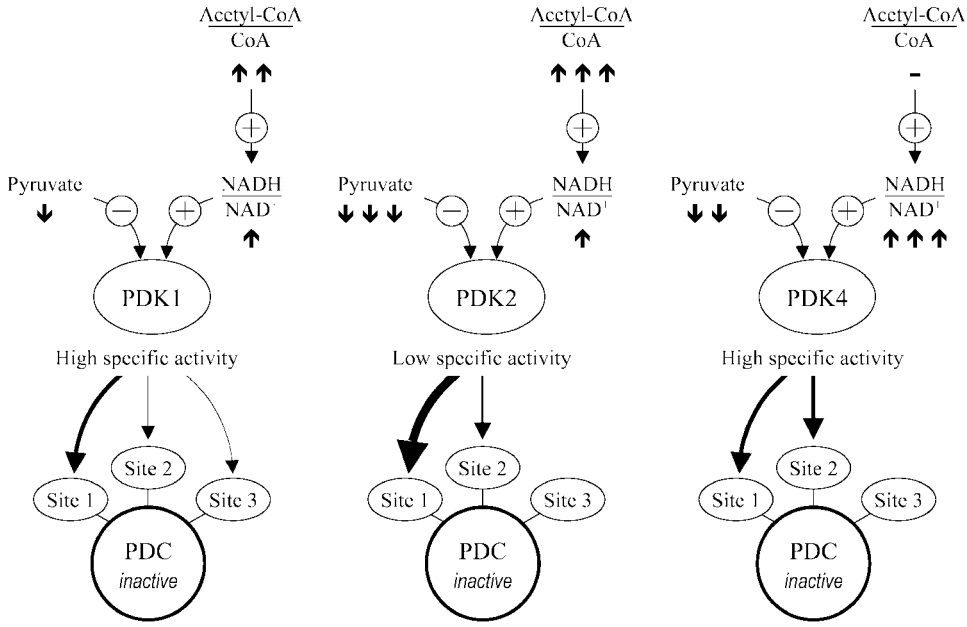

Fig. 2. Comparison of the kinetic parameters of PDK1, PDK2, and PDK4. Data are taken from Refs. 3, 25, and 27. Thicknesses of the lines indicate the relative activities of individual PDK isoforms toward the phosphorylation sites on the pyruvate dehydrogenase α-subunit (E1α) of PDC.

(13, 16, 50, 65, 68), insulin resistance induced by high-fat feeding (14, 37, 55), streptozotocin diabetes (68), and hyperthyroidism (16, 55). Hence, one long-term mechanism of PDK regulation involves changes in the relative expression of individual PDK isoforms. PDK2 activity may account for short-term inhibition of PDC through phosphorylation of site 1. In contrast, the longer-term increase in PDK4 protein observed in response to a sustained increase in lipid delivery/oxidation may be more important for phosphorylating site 2. It would be predicted that, in the absence of increased site 2 phosphorylation, PDC would be more rapidly dephosphorylated and reactivated. In support of this scenario, reactivation of PDC in liver, heart, and skeletal muscle is much slower when PDK4 expression is enhanced by prolonged starvation than after acute starvation (15, 17, 52). Similarly, because PDK1 alone is capable of phosphorylating site 3, phosphorylation of all three sites must be limited to tissues containing PDK1. From this, it follows that multisite phosphorylation of E1 in tissues expressing PDK1 would be greater than in tissues expressing only PDK2, PDK3, and/or PDK4, leading to even greater retardation of dephosphorylation and reactivation. This is demonstrated by greatly retarded reactivation of PDC in heart, which expresses PDK1, PDK2, and PDK4, compared with that in liver, which expresses only PDK2 and PDK4 (15, 52). Insulin suppresses hepatoma PDK2 mRNA expression but is less effective at lowering hepatoma PDK4 mRNA expression (19). Differential sensitivity of PDK2 and PDK4 to suppression by insulin may possibly be extrapolated to other tissues. Thus starvation increases only PDK4 in slow-twitch muscle (54) but increases both PDK2 and PDK4 protein in fast-twitch skeletal muscle (54), which is relatively less insulin sensitive than slow-twitch skeletal muscle (20).

Regulation of PDK expression may occur at the levels of both mRNA and protein expression. The half-life of the PDK4 mRNA in Morris hepatoma cells is relatively short (~1.5 h) compared with that of PDK2 ($t_{½}$ > 6 h) (19). Increases in PDK2 mRNA and protein expression evoked by prolonged starvation on PDK isoform expression in liver and kidney are relatively similar (~2-fold) in magnitude, suggesting that regulation of PDK2 expression occurs primarily at the level of transcription (65). Conversely, the relative increases in hepatic and renal PDK4 mRNA expression evoked by prolonged starvation (3.0- and 8.9-fold, respectively) are much higher than the corresponding increases in PDK4 protein expression (1.9- and 3.8-fold, respectively) (65). Hence, both transcriptional and translational mechanisms are likely to participate in the long-term regulation of PDK4 expression in liver and kidney (65). Interestingly, starvation increases PDK4 mRNA expression in brain and white adipose tissue without any corresponding increase in PDK4 protein expression, suggesting dominant regulation of PDK4 protein expression in these tissues at the level of translation.

FUNCTIONAL SIGNIFICANCE OF PDK ISOFORM SHIFTS

We have previously developed the hypothesis that PDK4 is a "lipid status"-responsive PDK isoform, facilitating FA oxidation by "sparing" pyruvate for oxaloacetate formation (51). In heart and skeletal muscle, increased anaplerotic entry of pyruvate into the TCA cycle as oxaloacetate facilitates entry of acetyl-CoA derived from FA β-oxidation into the TCA cycle through increased citrate formation. In turn, citrate formation acts as a signal of FA abundance to suppress glucose uptake and glycolysis. Furthermore, by maintaining acyl-CoA removal by β-oxidation, upregulation of PDK4 would be predicted to allow continued uptake

of long-chain fatty acyl-CoA into the mitochondria for oxidation, preventing long-chain fatty acyl-CoA accumulation in the cytoplasm, where it would be predicted to exert deleterious effects on function. We have demonstrated in skeletal muscle that enhanced PDK4 protein expression after prolonged starvation is associated with a rightward shift in the sensitivity curve for suppression of PDK activity by pyruvate and attenuation of the maximal response of PDK to suppression by pyruvate (54). A similar shift in sensitivity of PDK activity to suppression by pyruvate is observed in response to prolonged starvation in the heart (43). Thus the relative insensitivity of PDK to suppression by pyruvate in heart and skeletal muscle evoked by prolonged starvation (43, 54) correlates with selective increases in PDK4 protein expression (16, 68). Insulin resistance induced by prolonged high-fat feeding also leads to a reduction in the sensitivity of skeletal muscle PDK to inhibition by pyruvate (14). Thus it appears that PDK isoform switching toward increased PDK4 expression can be associated with altered regulatory characteristics of PDK in vivo, as would be predicted from studies with the recombinant PDK4 protein (3). Within the physiological context of intermittent feeding, loss of sensitivity of skeletal muscle PDK to suppression by pyruvate as a consequence of PDK4 upregulation may be geared to facilitate direction of glycolytically derived pyruvate toward lactate output rather than oxidation, with subsequent use for glucose synthesis. Within the pathological context of prolonged starvation, trauma, and sepsis, a further functional consequence of altered muscle PDK4 expression may relate to the fact that skeletal muscle protein, particularly fast-twitch muscle protein, is relatively expendable to generate carbon skeletons of amino acids to act as additional gluconeogenic precursors. Skeletal muscle amino acids are transaminated with pyruvate to produce alanine, which is then released into the circulation. Increased expression of PDK4, which is less pyruvate sensitive (Fig. 2), may permit the maintenance of adequately high pyruvate levels to ensure the removal of amine nitrogen from muscle in states of negative nitrogen balance. Finally, diversion of pyruvate from oxidation toward lactate or alanine output by skeletal muscle may fuel excessive rates of endogenous glucose production and ultimately the development of hyperglycemia in insulin-resistant states. Thus pharmacological suppression of skeletal muscle PDK4 expression/activity may represent a potential strategy to oppose the development of hyperglycemia associated with insulin resistance.

In liver and kidney, PDK4 upregulation during starvation (49, 50, 65, 67) may again participate in directing available pyruvate toward oxaloacetate formation, but in this case for entry into the gluconeogenic pathway and glucose synthesis. Concomitant upregulation of PDK2 may couple suppression of pyruvate oxidation with stimulation of pyruvate carboxylation via the common effector acetyl-CoA. Conversely, impaired upregulation of PDK4 protein expression, resulting in an inappropriately high PDK2-to-PDK4 activity ratio, could result in increased flux via PDC at the expense of entry of pyruvate into gluconeogenesis. Support for this possibility comes from studies of peroxisome proliferator-activated receptor-α (PPARα)-null mice where pharmacological inhibition of mitochondrial FA oxidation results in severe hypoglycemia (7). Upregulation of PDK2 protein expression, in addition to that of PDK4, in liver after prolonged starvation may subserve a further function in that it could permit activation of PDC should pyruvate accumulate. Such circumstances might include vigorous exercise (where lactate efflux from fast-twitch muscle contributes to a greatly enhanced hepatic lactate supply) or suppression of FA oxidation.

REGULATION OF MAMMALIAN PDK4 EXPRESSION BY PPARS

PPARs are ligand-activated transcription factors that have hypolipidemic actions (reviewed in Ref. 23). PPARγ, the predominant molecular target for the insulin-sensitizing thiazolidinediones, is most abundantly expressed in adipose tissue, where it induces adipocyte genes that increase FA delivery (e.g., lipoprotein lipase) or uptake and sequestration (e.g., fatty acid transporter 1) (reviewed in Ref. 23). Through its action to facilitate lipid trapping in adipose tissue, lipid delivery to tissues other than adipose tissue, including those that express PDK4 at relatively high levels, is reduced. Use of PCR differential mRNA display, DNA microarrays, and related techniques has shown that skeletal muscle PDK4 gene expression is suppressed by treatment of insulin-resistant rats with PPARγ agonists (64). This observation supports a direct inverse relationship between lipid entrapment in adipose tissue and tissue PDK4 expression.

PPARα is the molecular target for the fibrate class of lipid-modulating drugs (reviewed in Ref. 23). Like PPARγ, PPARα has a hypolipidemic action. However, in this case, the lipid-lowering effect results from enhanced FA uptake, activation, and oxidation by tissues other than white adipose tissue (4, 6, 7, 12, 33, 62, 63). Because of the clear correlation between altered lipid homeostasis and tissue PDK4 protein expression and the resulting impact that this might have on rates of glucose oxidation, much current interest has been focused on the potential regulation of PDK4 expression by PPARα.

PPARα is expressed at high levels in the liver and kidney (8). PPARα-deficient mice exhibit an impaired ability to upregulate hepatic FA oxidation in response to fasting, despite suppression of insulin levels and increases in FA supply (24, 30). Activation of PPARα by WY-14643 in vivo enhances hepatic and renal PDK4 protein expression in the fed state (19, 51). Furthermore, the upregulation of hepatic and renal PDK4 protein expression normally evoked in response to prolonged starvation is markedly impaired in PPARα-deficient mice (49, 50, 67). Incubation of Morris hepatoma 7800C1 cells with WY-14643 or an FA (palmitate or oleate) increases PDK4 mRNA and protein (19). Thus there is compelling evidence that FAs, acting at

least in part via PPARα, are important factors in the regulation of hepatic and renal PDK4 expression.

Cardiac PDK4 mRNA and protein expression are enhanced in response to dietary administration of WY-14643 for 3 days in wild-type mice but not in PPARα-deficient mice (67). Cardiac-specific overexpression of PPARα also results in enhanced cardiac PDK4 mRNA expression, which is further augmented when the PPARα-overexpressing transgenic mice are chronically treated with WY-14643 as a component of the diet (10). Conversely, cardiac PDK4 mRNA expression is suppressed in pressure overload cardiac hypertrophy (72), where cardiac PPARα expression and activity are suppressed (1). These data indicate that modulation of PPARα expression can influence PDK4 expression. Nevertheless, the enhancement of cardiac PDK4 protein expression elicited by starvation is only modestly attenuated by PPARα deficiency in PPARα-null mice (16, 34, 67). Thus mechanisms in addition to signaling via PPARα contribute to the regulation of cardiac PDK4 expression in starvation. Within this context, both prolonged starvation and experimental diabetes, conditions associated with increased cardiac FA utilization, have been reported to suppress cardiac PPARα expression (72). A comparison of the responses of cardiac PDK isoform protein expression to PPARα activation by WY-14643 in fed and starved rats over a timescale comparable to that over which effects of starvation can be observed (24 h) failed to demonstrate an effect of PPARα activation on cardiac PDK4 protein expression (16). The apparent lack of impact of acute (24 h) WY-14643 treatment on cardiac PDK4 protein expression (16) compared with the increased cardiac PDK4 mRNA expression observed after longer periods of treatment with WY-14643 (67) probably reflects the fact that the adult rat heart is a relatively poor target for PPARα activators compared with other tissues, in particular liver. It should be appreciated that, in PPARα-null mice, FA oxidation is not completely suppressed; rather, the ability to increase the required rate of FA oxidation sufficiently to avoid tissue accumulation of lipid is impaired (24, 30). PPARα-null mice fed ad libitum on a standard high-carbohydrate, low-fat rodent diet do not exhibit any obvious cardiac abnormalities (24, 30).

Oxidative skeletal muscle is a major site of FA catabolism in mammals, for example during starvation and exercise, when circulating lipid delivery increases. However, most evidence suggests that signaling via PPARα may be more important for the regulation of PDK4 expression in fast-twitch muscle, which does not oxidize FA as avidly as slow oxidative muscle. Although dietary administration of WY-14643 for 3 days selectively upregulates PDK4 in gastrocnemius muscle (a fast glycolytic skeletal muscle) (66) and activation of PPARα with WY-14643 in vivo for 24 h increases PDK4 protein expression in anterior tibialis (a predominantly fast oxidative-glycolytic skeletal muscle), PPARα activation does not significantly increase PDK4 protein expression in soleus (a slow oxidative skeletal muscle) (13). Conversely, the response of PDC activity to pharmacological inhibition of PDK with DCA in vivo is less in fast-twitch than in slow-twitch muscle, suggesting a higher functional PDK activity in slow-twitch muscle in the fed state (13). Activation of PPARα by WY-14643 during prolonged starvation does not further enhance upregulation of PDK4 protein expression in either fast oxidative glycolytic or slow oxidative skeletal muscle (13), and the effect of 24-h starvation to increase PDK4 mRNA and protein expression in skeletal muscle is intact in PPARα-null mice (13, 34). These data demonstrate that there is no obligatory participation of signaling via PPARα. Ablation of PPARα results in abnormally high accumulation of neutral lipid in heart and liver in response to physiological or pharmacological interventions that influence FA metabolism (6, 7). In contrast, starvation of PPARα-null mice leads to only minor abnormalities of skeletal muscle FA metabolism and no accumulation of neutral lipid (34). These observations have been attributed to a relatively low level of PPARα expression in mouse skeletal muscle, where PPARδ is the major PPAR subtype expressed (8) and may substitute for PPARα (34). Activation of either PPARα or PPARδ leads to marked increases in PDK4 mRNA expression in both primary human skeletal muscle cultures and L6 myotubes (34).

CONCLUDING REMARKS

In this review, we have presented strong evidence that the mechanisms regulating PDK4 protein expression differ significantly among tissues in a manner that may reflect individual tissue responses to altered lipid supply and/or oxidation. Further studies in this area will refine and expand our knowledge of the mechanistic impact of chronic changes in expression of specific regulatory kinases, such as PDK, with a view to potential therapeutic uses in the correction of hyperglycemia and metabolic acidosis as well as metabolic disorders in which tissue ATP generation from glucose is inadequate.

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