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MINIREVIEWS

Emerging role of protein kinase C in energy homeostasis: A brief overview

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Abstract

Protein kinase C-β (PKCβ), a member of the lipid-activated serine/threonine PKC family, has been implicated in a wide range of important cellular processes. Very recently, the novel role of PKCβ in the regulation of triglyceride homeostasis *via* regulating mitochondrial function has been explored. In this review, I aim to provide an overview of PKCβ regarding regulation by lipids and recently gained knowledge on its role in energy homeostasis. Alterations in adipose PKCβ expression have been shown to be crucial for diet-induced obesity and related metabolic abnormalities. High-fat diet is shown to induce PKCβ expression in white adipose tissue in an isoform- and tissue-specific manner. Genetically manipulated mice devoid of PKCβ are lean with increased oxygen consumption and are resistant to high-fat diet-induced obesity and hepatic steatosis with improved insulin sensitivity. Available data support the model in which PKCβ functions as a "diet-sensitive" metabolic sensor whose induction in adipose tissue by high-fat diet is among the initiating event disrupting mitochondrial homeostasis *via* intersecting with $p66^{Shc}$ signaling to amplify adipose dysfunction and have systemic consequences. Alterations in PKCβ expression and/or function may have important implications in health and disease and warrants a detailed investigation into the downstream target genes and the underlying mechanisms involved. Development of drugs that target the PKCβ pathway and identification of miRs specifically controlling PKCβ expression may lead to novel therapeutic options for treating age-related metabolic disease including fatty liver, obesity and type 2 diabetes.

Key words: High-fat diet; Signal transduction; Obesity; Mitochondrial function; Insulin resistance

Core tip: Nutrition has important long-term consequences for health. It is one of the lifestyle factors that contribute to the development and progression of obesity (increased fat accumulation), diabetes, and cardiovascular diseases. In fact, obesity rates are increasing dramatically worldwide and obesity amplifies the risk of developing various age-related chronic diseases, such as type 2 diabetes and cardiovascular disease. The prevention or management of chronic diseases is a global priority since they constitute a serious strain on health care systems and account for more than half of the deaths worldwide. Although correct lifestyle remains the mainstream solution to this problem, pharmacological strategies are also being actively seeked. Current antiobesity strategies have not controlled increasing epidemic of obesity and obesity-related disorders. We hope that a better knowledge of the molecular players and biochemical mechanism linking dietary fat to fat accumulation and development of glucose intolerance are critically needed. This review examines a way of metabolizing dietary fat into heat instead of storing them as fat, and the possibility that the "browning" of white fat is regulated by a diet-inducible kinase Protein kinase C-β (PKCβ) may help us explore new translational approaches to combat obesity, improve insulin sensitivity and potentially increase longevity. Finally, attenuation of inflammation in fat by PKCβ inhibition

could have profound clinical consequences because of the large size of the fat organ and its central metabolic role.

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INTRODUCTION

Protein kinase C (PKC) family is the largest serine/threonine-specific kinase family known to comprise approximately 2% of the human kinome[1]. PKCs are broadly conserved in eukaryotes, ranging in complexity from a single isoform in budding yeast (Saccharomyces cerevisiae) to 5 isoforms in Drosophila melanogaste and 12 in mammals[2,3]. Three distinct subfamilies can be identified according to their dependency on three combinations of activators: conventional (α, βⅠ, βⅡ, γ) require phosphatidylserine, diacylglycerol, and Ca^{2+}; novel (δ, ε, η, θ) need phosphatidylserine (PS) and DAG but not Ca^{2+}; atypical PKCs (λ/ι, ζ) are insensitive to both DAG and Ca^{2+}. PKC isoforms differ in primary structure, tissue distribution, subcellular localization, *in vitro* mode of action, response to extracellular signals, and substrate specificity. The role of individual PKC isoform is thought to be determined through sub isoform-specific activation processes or isoform-specific substrates in the region downstream of the PKC pathway[4]. Specific role of each isoform is beginning to be understood using isoform-specific transgenic and knockout mouse models. PKCs have been extensively discussed in the literature, and the aim of this review is to focus on the functions of PKCβ in the context of obesity and related metabolic syndromes.

REGULATION OF PKCβ ACTIVITY AND EXPRESSION BY LIPIDS

PKCβ is unique among all PKC isoforms in that a single gene locus encodes two proteins, PKCβⅠ and PKCβⅡ, which are generated by alternative splicing of C-terminal exons and are shown to be physiologically relevant[5]. The difference between these two isoforms resides in the C-terminal V5 domains, which still exhibit a moderate homology (45%) at their amino acid sequences[6,7]. PKCβ is highly expressed in the brain and adipose tissue, and widely expressed at a lower level in multiple tissues including liver, kidney, and skeletal muscle. Analysis of the primary structure of PKCβ reveals the presence of four domains conserved across PKC isoforms (C1-C4) and five variable domains that are divergent (V1-V5). Two functional domains have been described: an amino terminal regulatory domain and a carboxyl terminal catalytic domain. The regulatory domain (V1-V3) contains the so-called pseudosubstrate site which is thought to interact

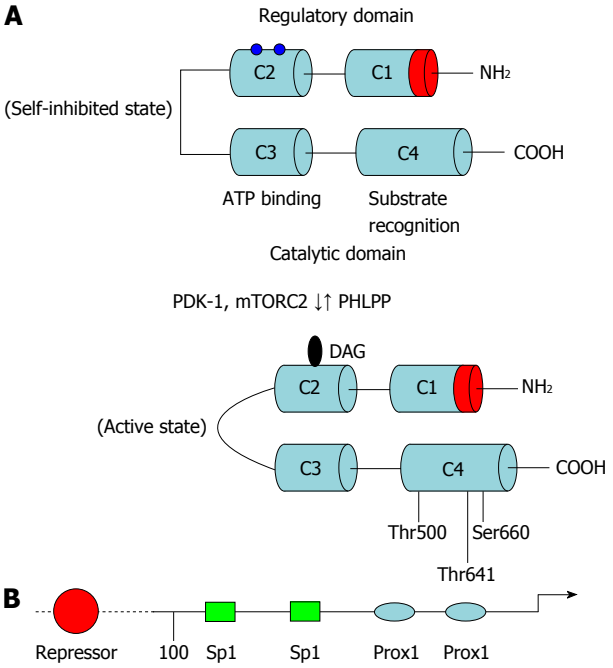

Figure 1 Domain composition of protein kinase C-β and its regulation at the transcriptional and posttranscriptional levels. A: Membrane-targeting modules (C1 and C2), pleckstrin homology domain, the pseudosubstrate region, the kinase core and the C-terminal tail; B: Schematic representation of promoter structure of protein kinase C-β gene. Approximate locations of known regulatory regions are indicated. ATP: Adenosine-5'-triphosphate; PHLPP: PH domain and leucine rich repeat protein phosphatases; PDK-1: 3-phosphoinositide-dependent protein kinase 1.

with the catalytic domain to retain PKCβ in an inactive conformation. The regulatory domain also contains sites for the interaction of PKC with PS, DAG/phorbol ester, and Ca^{2+}. The Ca^{2+} dependency is mediated by the C2 region, while phorbol-ester binding requires the presence of two cysteine-rich zinc finger regions within the C1 domain. The catalytic domain contains two conserved regions, C3 and C4, which are essential for the kinase activity and the binding of adenosine-5'-triphosphate (ATP)/substrate (Figure 1).

In addition to the above specific inputs, other regulatory processes influence the function of PKCβ, including phosphorylation and interaction with specific binding partners. PKCβ is processed by three distinct phosphorylation events before it is competent to respond to the coactivators and is phosphorylated at three conserved serine/threonine residues in the C-terminal domain[8]. Phosphorylation at the activation loop (Thr^{500}) is generally proposed to be first and to be followed by two ordered phosphorylations at the C-terminal tail, the turn motif (Thr^{641} in PKCβⅡ) and then the hydrophobic motif (Ser^{660} in PKCβⅡ). The phosphorylation of the turn motif depends on the mTORC2 complex; this phosphorylation triggers autophosphorylation of the hydrophobic motif[9,10]. The fully-phosphorylated "mature" PKCβ is in a closed conformation in which the pseudosubstrate occupies the substrate-binding cavity, thus autoinhibiting the kinase. Signals that cause hydrolysis of phosphatidylinositol-4,5-bisphosphate result in trans-

location of PKCβ to the membrane by a low-affinity interaction where it binds DAG *via* the C1 domain. Engaging both the C1 and C2 domains on the membrane results in a high-affinity membrane interaction that results in release of the pseudosubstrate, allowing downstream signaling. The membrane-bound conformation is highly phosphatase-sensitive, so that prolonged membrane binding results in dephosphorylation of PKCβ by pleckstrin homology domain Leucine-rich repeat protein phosphatase and PP2A, and subsequent degradation[11]. Binding of Hsp70 to the dephosphorylated turn motif on the C-terminus stabilizes PKCβ, allowing it to become rephosphorylated and reenter the pool of signaling-competent PKC. PKCβ that is not rescued by hsp70 is ubiquitinated by E3 ligases such as the recently discovered RINCK and degraded[12].

PKCβ is also responsive to oxidative stress[13-15]. Why is PKCβ sensitive to oxidative stress? In the PKCβ structure, two pairs of zinc fingers are found within the regulatory domain. They are sites of DAG and phorbol ester binding. Each zinc finger is formed by a structure that is composed of six cysteine residues and two zinc atoms. The high level of cysteine residues renders the regulatory domain susceptible to redox regulation[16,17]. The oxidant destroys the zinc finger conformation, and the autoinhibition is relieved, resulting in a PKCβ form that is catalytically active in the absence of Ca^{2+} or phospholipids[18].

Besides the lipid activation at the post-transcriptional level, PKCβ expression also fluctuates in response to high-fat diet intake. It is shown that feeding high-fat diet (HFD) for 12 wk induces adipose PKCβ expression in an isoform and tissue-specific manner[19]. The molecular mechanism(s) underlying transcription induction have yet to be elucidated but previous studies have cloned and sequenced PKCβ promoter[20-22]. A putative 5'-promoter region for PKCβ is identified and suggested that there is heterogeneity in the active promoter region dependent upon the cellular context. Analysis of the 5'-promoter of PRKCB revealed that a region between -110 bp and -48 bp contains two Sp1 binding sites which are important for basal expression of *PKCβ* gene. In addition two PROX1 sites are also present 3' to Sp1 sites and are involved in inhibiting Sp1-mediated basal transcription of PKCβ promoter[23]. In fact, an inverse relationship between PROX1 and PKCβ levels exist in colon cancer cell lines. It was also found that treatment with a demethylating agent, 5-aza-2'-deoxycytidine, restored PKCβ mRNA expression in PROX1-expressing cells, suggesting that the 5'-promoter of PKCβ is methylated in these cells[23]. Actually, a CpG island in this region, in particular a CpG site within the distal Sp1 site is identified in this study, leading to downregulation of PKCβ transcription. Hypermethylation of PROX1 sites inhibits direct Sp1 binding to this region in PROX1 overexpressing cells. Finally, previous studies have also identified a repressor region located upstream of -110 bp in the PKCβ promoter and the identity of the nuclear factor(s) binding to this region has not been characterized.

NOVEL ROLE OF PKCβ IN LIPID HOMEOSTASIS

A significant conceptual advance in our understanding of the importance of PKCβ signaling in obesity has come from realization that mice deficient in PKCβ express higher levels of genes that regulate fatty acid oxidation and proteins involved in energy dissipation, highlighting its role as a corepressor and in controlling the balance between energy consumption and energy expenditure[24]. On the contrary, genes involved in FA synthesis and gluconeogenesis seem to be downregulated in the absence of PKCβ[25,26]. As a consequence, PKCβ mice are lean, with a significant reduction of body fat and body weight compared to WT mice and are resistant to HFD-induced obesity and hepatic steatosis so that these mice maintain their insulin sensitivity[19]. Moreover, PKCβ levels are shown to be elevated in adipose tissue of leptin-deficient (ob/ob) mice and deletion of PKCβ in ob/ob mice attenuates obesity syndrome of these mice[26]. An important mechanistic insight is the revelation that in PKCβ-deficient mice white adipose tissue (WAT) express genes characteristic of BAT including peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1α), fatty acid transporter carnitine palmitoyltransferase, and uncoupling protein-1 (UCP-1). Targeted disruption in mice of several genes directly involved in energy metabolism and fat accumulation also leads to lean phenotype with a marked increase in UCP-1 expression in adipocytes, particularly in white fat depots[27-29]. Thus total energy consumption is increased significantly in PKCβ-null mice, presumably as a consequence of energy dissipation in WAT resulting from the expression of UCP-1 and increased mitochondrial activity. The ability of white and brown adipocytes in each depot to reversibly switch into one another has been reported, but the extent to which this occurs and the precise mechanisms involved are not fully understood. The search for regulators that could mediate conversion of white adipocytes (energy storing) into brown adipocytes (energy consuming) has led to the identification of PGC-1α, FOXC2 and positive regulatory domain-containing 16 as transcriptional regulators that have been found to promote a brown fat genetic program, while retinoblastoma protein and RIP140 have been described to favor a white adipose phenotype[27-30]. Another important aspect of these studies relates to possible connection between PKCβ and β-adrenergic receptor levels in WAT. Results presented argue strongly in favor of an inverse relationship between PKCβ and β3-adrenergic receptor expression[26]. The proposed relationship is consistent with earlier reports showing that sustained PKC activation suppressed β-ARs expression at the transcriptional level[31-33]. The net consequence of PKCβ-mediated adipose dysfunction could have profound clinical consequences because of the large size of the fat organ and its central metabolic role. Interestingly, in agreement with the above animal studies, adipose

PKCβ activation is subsequently linked to obese side effects of antipsychotic drugs in humans[34]. Moreover, in agreement with its role in energy homeostasis, PKCβ is shown to be required for adipocyte differentiation[35], PKCβ inhibition promotes insulin signaling in adipocytes[36,37], and PKCβ promoter polymorphism is associated with insulin resistance in humans[38].

The role of PKCβ in obesity is further supported by its potential involvement in angiogenesis. To ensure a sufficient supply of nutrients and oxygen and to transport fatty acids and adipokines, an extended microvasculature is mandatory for adipose tissue. Adipogenesis and angiogenesis are two closely related processes during adipose tissue enlargement, as shown in animal studies and *in vitro* models[39,40]. As adipocyte hypertrophy endures, local adipose tissue hypoxia may occur due to hypoperfusion since the diameter of fat cells overgrows the diffusion limit of oxygen. As a result, hypoxia-inducible transcription factors are expressed triggering the expression of angiogenic factors [vasuclar endothelial growth factor (VEGF), hepatocyte growth factor, plasminogen activator inhibitor-1]. In view of role of PKCβ/HuR in regulating VEGF expression at the post-transcriptional level, simultaneous induction of PKCβ is expected to promote VEGF expression[41,42].

Finally, specific overexpression of a constitutively active PKCβ Ⅱ mutant in mouse skeletal muscle demonstrated that this splice variant of PKCβ not only induces insulin resistance, but also affects the levels of several genes involved in lipid metabolism[43]. Thus impairment in the expression of PGC-1α, acyl CoA oxidase and hormone-sensitive lipase, but enhanced expression of the lipogenic transcription factor sterol response element-binding protein 1c in skeletal muscle, were associated with decreased lipid oxidation and increased intra-myocellular lipid deposition. In addition to these direct effects in muscle, these animals showed defects in insulin action in the liver and brain, as well as hepatic lipid accumulation similar to that seen in fat-fed animals.

POTENTIAL ROLE OF PKCβ IN MITOCHONDRIAL FUNCTION

Several studies have emphasized the association between enhanced mitochondria-derived H_2O_2 and insulin resistance, particularly in the context of excessive nutrient intake that results in metabolic imbalance[44-47]. Oxidative stress has also been described clinically, as well as in WAT of many additional mouse models of obesity, such as the KKAy and db/db mice. Systemic markers of oxidative stress increase with adiposity, consistent with the role of reactive oxygen species (ROS) in the development of obesity-induced insulin resistance. Available data suggest that an increase in ROS significantly affects WAT biology and leads to deregulated expression of inflammatory cytokines such as tumor necrosis factor-α, interleukin-6, and macrophage chemoattractant protein-1, and insulin resistance, which could contribute to obesity-associated diabetes and cardiovascular diseases[47]. Moreover, oxidative stress induced by ROS stimulates fat tissue development both *in vitro* and *in vivo*. H_2O_2-induced oxidative stress is shown to facilitate the differentiation of preadipocytes into adipocytes by accelerating mitotic clonal expansion[48]. Antioxidants such as flavonoids and N-acetylcysteine inhibit both adipogenic transcription factors C/EBP-β and PPAR-γ expression, as well as adipogenic differentiation in 3T3-L1 preadipocytes[49,50]. N-acetyl cysteine (NAC) was also shown to reduce ROS levels and fat accumulation in a concentration-dependent manner[50]. Moreover, animals on a HFD with the antioxidant NAC exhibited lower visceral fat and body weight[51]. Finally, ROS scavenging is associated with fat reduction in obese Zucker rats[52].

Recent studies have highlighted a novel, unexpected signaling pathway bridging the oxidative challenge of a cell to the activation of PKCβ/$p66^{Shc}$-controlled mitochondrial lifespan[53,54]. PKCβ activated by oxidative stress is shown to be required for phosphorylation of the Ser36 of $p66^{Shc}$ and the effect of PKCβ overexpression on mitochondrial Ca^{2+} signaling was not observed in $p66^{Shc-/-}$ cells. Importantly, the mitochondrial consequences of hydrogen peroxide are blocked by hispidine, a specific PKCβ inhibitor. The pathway emerging from these studies is the following: during oxidative stress PKCβ is activated and induces $p66^{Shc}$ phosphorylation, thus allowing $p66^{Shc}$ to be recognized by Pin1, isomerised and imported into mitochondria after dephosphorylation by type 2 protein serine/threonine phosphatase. The $p66^{Shc}$ protein translocated into the appropriate cell domain, can exert the oxidoreductase activity, generating H_2O_2 and inducing the opening of MPTP. This event in turn perturbs mitochondria structure and function. Identification of a novel signaling mechanism, which is operative in the pathophysiological condition of oxidative stress, may open new possibilities for pharmacologically addressing the process of organ deterioration during aging. The above studies are among the first to dissect the downstream target genes and regulatory properties of the PKCβ protein, and therefore make an important contribution to our understanding of the molecular basis to the lean phenotype exhibited by $PKCβ^{-/-}$ mice. Based on a very recent demonstration that PKCβ/$p66^{Shc}$ mitochondrial axis inhibits autophagy[55] and the evolving role of autophagy in energy homeostasis[56-61], it is possible that a combination of adipose PKCβ activation, mitochondrial dysfunction and insufficient autophagy may contribute to the development of diet-induced obesity. In addition to mitochondrial effects, PKCβ is an upstream regulator of NOX but this signaling axis actively produces superoxide across the membranes of neutrophils and phagosomes[62-65]. Accumulating data so far implicates mitochondria as the main source for regulation of autophagy by ROS production in adipocytes[66], whereas NOX contributes to activation of selective, bacterial autophagy[67] (Figure 2).

Although biological function of PKCβ in energy

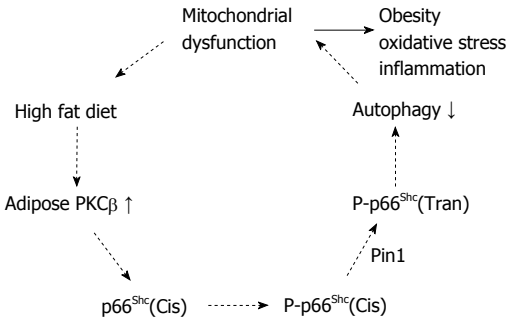

Figure 2 Proapoptotic signals, including reactive oxygen species, activate protein kinase C-β, which in turn phosphorylates p66^{Shc} at serine 36. Phosphorylated p66^{Shc} translocates to the inner mitochondrial membrane and acts as a redox enzyme to amplify oxidative stress by generating H_2O_2. Increased H_2O_2, in turn, causes opening of the mitochondrial permeability transition pore and apoptosis. Protein kinase C-β (PKCβ) activated by reactive oxygen species further induces p66^{Shc} phosphorylation. This event in turn perturbs mitochondria structure and function.

homeostasis appears to be mostly linked with events occurring at the mitochondria, however, increasing evidence has implied a role for this kinase in nuclear functions, suggesting this may be a pathway to communicate signals generated at the plasma membrane to the nucleus. For example, Goss *et al*[68] first showed that PKCβ translocates to the nucleus at G2/M, concomitant with the phosphorylation of lamin B1. Subsequently, a considerable number of nuclear proteins have been identified which are *in vivo* and/or *in vitro* substrates for PKCβ. These proteins include: histone H3, DNA topoisomerase I and Ⅱa, DNA polymerase α and β, cyclic AMP-response element-binding protein, retinoblastoma protein, and vitamin D receptor[69-73]. It has even been shown that PKCβ I co-localizes with androgen receptor and lysine-specific demethylase 1 on target gene promoters and phosphorylation of histone H3 at threonine 6 by PKCβ I is the key event that prevents lysine-specific demethylase 1 from demethylating histone H3 lysine 4[69]. Finally, activated PKCβ indirectly can affect other signaling cascades, including PI3-kinase/Akt pathway, extracellular signal-regulated kinase, and p38 pathway which can impact nuclear events[74-79]. It is thus clear that characterization of PKCβ downstream signaling in the nucleus and its relevance to energy homeostasis is another facets that requires in-depth investigation.

The above findings are applicable to the pathogenesis of obesity and type 2 diabetes since mitochondrial loss in WAT correlates with the development of obesity and type 2 diabetes[80,81]. Indeed, mitochondrial DNA copy number, mitochondrial mass, and mitochondrial activity are all decreased in the white adipose tissue of mouse models of obesity, such as ob/ob and db/db mice[82,83]. Similarly in patients with insulin resistance, type 2 diabetes, and severe obesity, the abundance of mitochondria and the expression of key genes pertinent to mitochondrial function are significantly reduced in white adipose tissue, in concert with decreased adipocyte oxygen consumption rates and ATP production[84,85]. The mitochondrial dysfunction, which could impair substrate oxidation in adipose tissue, is thought to participate in metabolic impairment capacity, thereby accentuating the development of obesity and associated pathologies, such as type 2 diabete. As a result, WAT mitochondria are emerging as highly attractive organelles for therapeutic interventions with the potential to impact upon systemic metabolism. Interestingly, the insulin-sensitizing effects of thiazolidinediones are closely matched by robust increases in adipose tissue mitochondrial biogenesis[86].

CONCLUSION

We have reviewed recent advances pertaining to the potential role of PKCβ in regulating energy homeostasis and contribution to the development of metabolic syndrome. Evidence gathered recently point to an essential role for PKCβ in diet-induced obesity. As a signaling pathway, PKCβ is highly sensitive to changes in environment and fluctuations in lipid supply activate adipose PKCβ, which in turn appears to promote fat accumulation *via* modulating mitochondrial function. A positive loop between oxidative stress and PKCβ/p66^{Shc} is promising and may be the major mechanism underlying contribution of PKCβ activation in generating oxidative stress observed in the obese state. The main gap in our understanding today lies in the specific, molecular and chemical mechanisms of PKCβ-mediated energy homeostasis. What are the mitochondrial and nuclear targets of PKCβ physiologically relevant to energy homeostasis? How is the dietary lipid signals transmitted to the PKCβ promoter? Is PKCβ regulatory signaling network dysregulated in metabolic disease states? Can PKCβ inhibition be adopted to prevent human obesity? These important questions should be the target of future studies. The manipulation of PKCβ levels, activity, or signaling might represent a therapeutic approach to combat obesity and associated metabolic disorders.

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