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From PDE3B to the regulation of energy homeostasis

Eva Degerman[1], **Faiyaz Ahmad**[2], **Youn Wook Chung**[2], **Emilia Guirguis**[2], **Bilal Omar**[1], **Lena Stenson**[1], and **Vincent Manganiello**[2]

[1]Department of Experimental Medical Science, Division for Diabetes, Metabolism and Endocrinology, Lund University, Lund, Sweden

[2]Cardiovascular Pulmonary Branch, National Heart, Lung and Blood Institute, Bethesda

Abstract

The incidence of obesity in the developed world is increasing at an alarming rate. Concurrent with the increase in the incidence of obesity is an increase in the incidence of type 2 diabetes. Cyclic AMP (cAMP) and cGMP are key second messengers in all cells; for example, when it comes to processes of relevance for the regulation of energy metabolism, cAMP is a key mediator in the regulation of lipolysis, glycogenolysis, gluconeogenesis and pancreatic β cell insulin secretion. PDE3B, one of several enzymes which hydrolyze cAMP and cGMP, is expressed in cells of importance for the regulation of energy homeostasis, including adipocytes, hepatocytes, hypothalamic cells, and β cells. It has been shown, using PDE3 inhibitors and gene targeting approaches in cells and animals, that altered levels of PDE3B result in a number of changes in the regulation of glucose and lipid metabolism and in overall energy homeostasis. This article highlights the complexity involved in the regulation of PDE3B by hormones, and in the regulation of downstream metabolic effects by PDE3B in several interacting tissues.

Introduction

The incidence of obesity in the developed world is increasing at an alarming rate. Concurrent with the increase in the incidence of obesity is an increase in the incidence of type 2 diabetes (T2D) [e.g. 1]. It has been reported that over 80% of adults diagnosed with T2D are obese. The connection between obesity and the development of T2D has been the focus of intense research in recent years. It has been demonstrated that low-grade, systemic inflammation originating from adipose tissue is a factor associated with systemic insulin resistance [e.g. 2]. Adipose tissue secretes numerous adipokines which affect whole body insulin sensitivity and dysregulation of production and secretion of these factors could contribute to the development of insulin resistance in obesity [e.g. 2, 3]. Also, excess fatty acids released from the adipocytes of obese persons contribute to ectopic fat storage in non-adipose tissues like liver and muscle, thereby exacerbating their insulin resistance [e.g. 4].

The composition of cAMP-signalling networks, which play key roles in target tissues of relevance for energy homeostasis, are growing in complexity [5, 6]. Cyclic nucleotide PDEs (phosphodiesterases) are important actors in this context. The PDE superfamily contains eleven structurally related, but functionally distinct, gene families (PDE1–11), which differ in primary structures, affinities for cAMP and cGMP, responses to specific effectors,

sensitivities to specific inhibitors, and mechanisms of regulation [e.g. 7]. By virtue of their distinct intrinsic characteristics and their intracellular targeting to different subcellular locations, different PDEs integrate multiple cellular inputs and modulate the amplitude, duration, termination, and specificity of cyclic nucleotide signals and actions [6]. The PDE3 family contains two subfamilies, PDE3A and PDE3B [8, 9], which are encoded by distinct but related genes and exhibit distinct, but overlapping, patterns of expression. For example, PDE3A is more highly expressed in the cardiovascular system and PDE3B is more highly expressed in cells of importance for the regulation of glucose and lipid metabolism. This article highlights some key aspects of the role of PDE3B in normal and dysfunctional regulation of energy homeostasis.

Mechanisms for regulation of PDE3B and related signalling networks

When it comes to the overall regulation of PDE3B functions and the intracellular signalling networks involved in PDE3B regulation and action, the intracellular localization of the enzyme, phosphorylation events, as well as the formation of unique protein complexes containing PDE3B have critical roles.

Some molecular characteristics of relevance for the regulation and action of PDE3B

The structural organization of PDE3B (Fig. 1), which is identical to that of PDE3A, includes a catalytic domain conserved among all PDEs in the C-terminal portion of the enzymes, followed by a hydrophilic C-terminal region [8, 9]. The kinetic properties of PDE3 catalytic domains show high affinities for both cAMP and cGMP with Km values in the range of 0.1 to 0.8 μM, and velocity for cAMP hydrolysis being 4–10 fold higher than that for cGMP [8, 9]. Also, the catalytic domains of PDEs are the target for family and subfamily selective inhibitors [9, 10]. Such inhibitors have been very useful in dissecting specific functions for selected PDEs, including PDE3s, and are also used in the clinic or are being developed for the treatment of various diseases. The regulatory N-terminal portions of PDE3s contain large hydrophobic regions that are implicated in membrane targeting of these enzymes [8, 9, 11, 12]. Downstream of the hydrophobic regions lies serine residues that are subjected to reversible phosphorylation in intact cells. The importance of intracellular localization as well as reversible protein phosphorylation events for PDE3B function will be discussed below.

Intracellular localization

PDE3B is predominantly associated with membranes in adipocytes, hepatocytes, and pancreatic β cells. In adipocytes and hepatocytes, PDE3B is localized to detergent resistant parts of the plasma membrane, including lipid rafts and caveolae, and to the endoplasmic reticulum [8, 9, 13, 14]. Caveolae are special forms of lipid rafts observed as small flask-shaped 50–100 nm invaginations of the plasma membrane [15]. Although caveolae are observed in many cell types they are particularly abundant in adipocytes. Caveolae have a high content of cholesterol and sphingolipids and are stabilized by one or more isoforms of caveolin. They are believed to be important in the organization of intracellular signalling events. Thus, caveolae localization of PDE3B and a potential interaction between caveolin and PDE3B is interesting in the context of signalling. In pancreatic β cells, PDE3B appears to be localized to the insulin granules and the plasma membrane, a location believed to be critical for a role of PDE3B in the regulation of exocytosis [16].

Hormone-induced phosphorylation, activation and complex formation

PDE3B enzymes are phosphorylated and activated in hepatocytes and adipocytes in response to stimulation by insulin and/or agents that increase cAMP, and are implicated in cAMP-mediated metabolic effects in those cells [8, 9]. In β cells, PDE3B regulates glucose-

stimulated insulin secretion as well as cAMP-potentiation of glucose-stimulated insulin secretion, and is involved in regulation of both the acute first phase and the second sustained phase of insulin secretion [17–21] (Fig. 2). PDE3B is activated in cell models in response to a number of stimuli relevant to β cell function such as glucose, insulin, IGF-1, leptin, high K^+, and cAMP-elevating agents [21–23]. Activation of PDE3B in response to glucose is associated with reduced phosphorylation of PDE3B whereas activation induced by insulin, forskolin and the phosphatase inhibitor okadaic acid is associated with increased phosphorylation [21]. In β cells the precise physiological role of PDE3B activation, identity of the phosphorylation sites and the particular kinases and phosphatases that are involved in its regulation remain to be elucidated.

Most studies on mechanisms of regulation of PDE3B and PDE3B-associated signalling networks have utilized the adipocyte as a model. Insulin-induced phosphorylation and activation of PDE3B, partially mediated via PKB (protein kinase B), is a key event in the anti-lipolytic effect of insulin [8, 9] (Fig. 3). PDE3B is also involved in the regulation of insulin-induced glucose uptake and lipogenesis [24, 25]. cAMP activation of PKA (cAMP-dependent protein kinase) induces phosphorylation and activation of PDE3B, an effect that is important in negative feedback regulation of cAMP. The interplay between insulin and cAMP-mediated regulation of PDE3B also appears to involve cAMP/PKA-mediated activation of PKB [26] and PDE3B appears to have a role in the regulation of AMPK (AMP-activated protein kinase) [27, 28]. A number of serine residues have been identified as targets for insulin and cAMP-increasing hormones in adipocytes as well as in hepatocytes [e.g. 8, 9, 29–31]. It is likely that kinases other than PKB and PKA also contribute to the regulation of PDE3B. An additional level of complexity regarding regulatory mechanisms of PDE3B relates to the fact that insulin and cAMP increasing agents induce phosphorylation and activation of PDE3B at different intracellular locations, involving unique protein complexes. Thus, insulin preferentially phosphorylates and activates endoplasmic reticulum-associated PDE3B, whereas increases in cAMP preferentially lead to phosphorylation and activation of plasma membrane-associated PDE3B [30, 31]. The protein complexes present in insulin-stimulated cells contain tyrosine-phosphorylated insulin receptor substrate 1 and its downstream signalling proteins, whereas cAMP-induced complexes contain β_3-adrenergic receptor, the PKA regulatory subunit II and hormone sensitive lipase. PDE3A and PDE4 are other examples of PDEs as components of signalling complexes, signalosomes, in other cells and contexts [32, 33].

Implications for PDE3B in normal physiology and development of obesity and type 2 diabetes

PDE3B plays a key role in the regulation of insulin secretion

In agreement with results from studies using insulin-secreting cell lines and isolated pancreatic islets as models to modulate PDE3B expression and activity [17, 18] (Fig. 2), mice that specifically over-express PDE3B in β cells show a PDE3B protein dose-dependent decrease in glucose-induced insulin secretion as well as a decrease in the ability of GLP-1 to potentiate glucose-mediated insulin secretion [19, 20]. Furthermore, the seemingly moderate dysregulation of cAMP in pancreatic β cells negatively influences insulin secretion to the extent that it affects glucose homeostasis. Targeted PDE3B over-expression also sensitizes mice to high-fat feeding so as to precipitate the diabetes-like symptoms, which suggests that cAMP is important in preventing or delaying the development of fatty diet-induced insulin resistance. These results are in agreement with findings in PDE3B KO mice [34] and with findings using PDE3 inhibitors in vivo [e.g. 35, for more references see 8, 9]

Reduced PDE3B levels in vivo result in multiple alterations in the regulation of energy homeostasis

PDE3B knock-out (KO) mice [34] demonstrate a number of alterations in the regulation of energy homeostasis, both beneficial and non-beneficial, including signs of insulin resistance as well as reduced amounts of white adipose tissue and increased lean mass. Reduced ability of insulin to lower glucose output from the liver, shown using hyperinsulinemic-euglycemic clamps, as well as increased ability of catecholamines to induce lipolysis along with reduced ability of insulin to lower circulating fatty acid levels represent physiological alterations that contribute to the generation of systemic insulin resistance in PDE3B KO mice. Furthermore, liver triglycerides, cAMP content, expression of key gluconeogenic enzymes and several other insulin signalling-, inflammation-, and stress-related components are altered in PDE3B KO mice [14, 34]. Despite those non beneficial effects, these mice do not develop frank diabetes which could be explained by a potentiation of insulin secretion and some protective long term changes in adipose tissue. Islets from PDE3B KO mice show a potentiation of glucose-, as well as GLP-1- mediated insulin secretion, which is in agreement with other studies on cells and islets as discussed above.

With regard to the generation of a potential long term protective effect in adipose tissue which lacks PDE3B, PDE3B KO mice show reduced fat mass, smaller adipocytes, and reduced weight gain than control mice when maintained on a high fat diet. Unpublished studies indicate increased fatty acid oxidation and increased energy dissipation in isolated epididymal PDE3B KO adipocytes as well as increased oxygen consumption in intact PDE3B KO mice in response to intraperitoneal administration of a β_3-adrenoreceptor agonist. In addition, mRNA levels of macrophage-related proteins were decreased in PDE3B KO adipose tissue, suggesting reduction in macrophage accumulation (unpublished results). Macrophage infiltration of adipose tissue is considered to be part of the chronic inflammation involved in development of insulin resistance and obesity [e.g. 2].

Consistent with our findings in PDE3B KO mice, administration of milrinone, a PDE3 inhibitor, to intact rats increases lipolysis and insulin secretionand blocks insulin-induced suppression of endogenous glucose production [e.g. 35, for more references see 8, 9].

PDE3B plays a role in the regulation of food intake and body weight

Leptin, a hormone primarily secreted from adipocytes, is required for normal food intake and body weight homeostasis via its actions in the hypothalamus [36, 37]. Leptin signalling activates PDE3B in the hypothalamus, and the PDE3 inhibitor, cilostamide, reverses anorexia and reduction in body weight produced by leptin [38–40]. Furthermore, the PDE3B pathway is responsible for the activation of proopiomelanocortin and neurotensin neurons, which play a critical role in energy homeostasis [39]. Thus, while central injection of leptin significantly increased both proopiomelanocortin and neurotensin mRNA levels in the medial basal hypothalamus, cilostamide completely reversed this effect of leptin. These results suggest that the PDE3B pathway plays an important role in mediating leptin signalling in the hypothalamus and thereby hypothalamic effects on energy homeostasis.

PDE3B expression in adipose tissue from patients with obesity and diabetes

Early studies on adipocytes from patients with diabetes demonstrated reduced PDE activity in adipose tissue [41]. Also, an important role of PDE3B in the regulation of lipolyis in humans has been demonstrated using a microdialysis approach [e.g. 42, for other references see 43]. Recently, PDE activities have been investigated with respect to differences in obesity and between different adipose tissue depots, considering the fact that the visceral depot is the metabolically toxic one as compared to the subcutaneous depot [44]. Results show that, in obese patients, total cAMP-hydrolyzing PDE, PDE3 and PDE4 activities were

significantly reduced in both omental and subcutaneous adipose tissue depots compared to non-obese patients. Furthermore, there were inverse correlations between body mass index and total cAMP hydrolyzing PDE activity and PDE3 activities in adipocytes isolated from omental adipose tissue. Further studies are necessary to connect the altered activity profile of PDEs to different biological functions and to determine if and how they play a role in the development of adipose tissue insulin resistance. In obese subjects the antilipolytic effect of insulin is diminished [45], and PDE3B is the central enzyme controlling the antilipolytic effect of insulin. Thus, decreased PDE3B activity with increasing obesity may be a contributing factor to the diminished antilipolytic effect of insulin seen in obese patients. One possible mechanism whereby PDE3B is downregulated is via TNF-α, a cytokine known to be increased in obesity and known to be associated with insulin resistance in cell and animal models as well as in obese humans [46, 47]. Thus, in 3T3-L1 and human adipocytes, downregulation of PDE3B by TNF-α contributes to TNF-α - and ceramide-induced lipolysis, an effect that could be reversed by treating 3T3-L1 adipocytes with troglitazone [48–50]. Excess production of TNF-α has been shown to enhance the rate of adipose tissue lipolysis, hence increasing the concentration of circulating fatty acids and contributing to TNF-α-induced systemic insulin resistance.

Conclusion

PDE3B is an important actor in the regulation of energy metabolism. However, with regard to PDE3B as a possible target for drugs in the context of treatment for obesity and T2D, one has to keep in mind the dynamic interplay among multiple tissues expressing PDE3B. Indeed, the final outcome of PDE3 inhibitors in the context of dyregulated energy homeostasis is difficult to predict (Fig. 4). Tissue-specific delivery systems appear to be necessary since the effects of PDE3B inhibition on hepatocytes, adipocytes and hypothalamus may result in worsening of glucose disposal and glucotoxicity, in the development of fatty acid-induced insulin resistance and even in weight gain. On the other hand, specific delivery to pancreatic β cells might indeed be beneficial by potentiating the effects of incretins such as GLP-1 on insulin secretion. Also, the induction of energy dissipation and reduced inflammation in adipose tissue would be beneficial. Thus, due to the different responses in different tissues, it is a challenge to target PDE3Bs to prevent and treat dysregulated metabolic states. To this end one must raise the question as to whether the PDE3B gene could function as a susceptibility or modifier gene for the development of specific types of diabetes.

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*of special interest

**of outstanding interest

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Highlights

1. Acute hormonal regulation of PDE3B involves reversible protein phosphorylation and protein complex formation at different subcellular locations
2. PDE3B plays a key role in the regulation of adipocyte lipolysis
3. PDE3B plays a key role in the regulation of insulin secretion
4. PDE3B plays an important role in overall energy homeostasis
5. PDE3B is down regulated in adipose tissue in human obesity

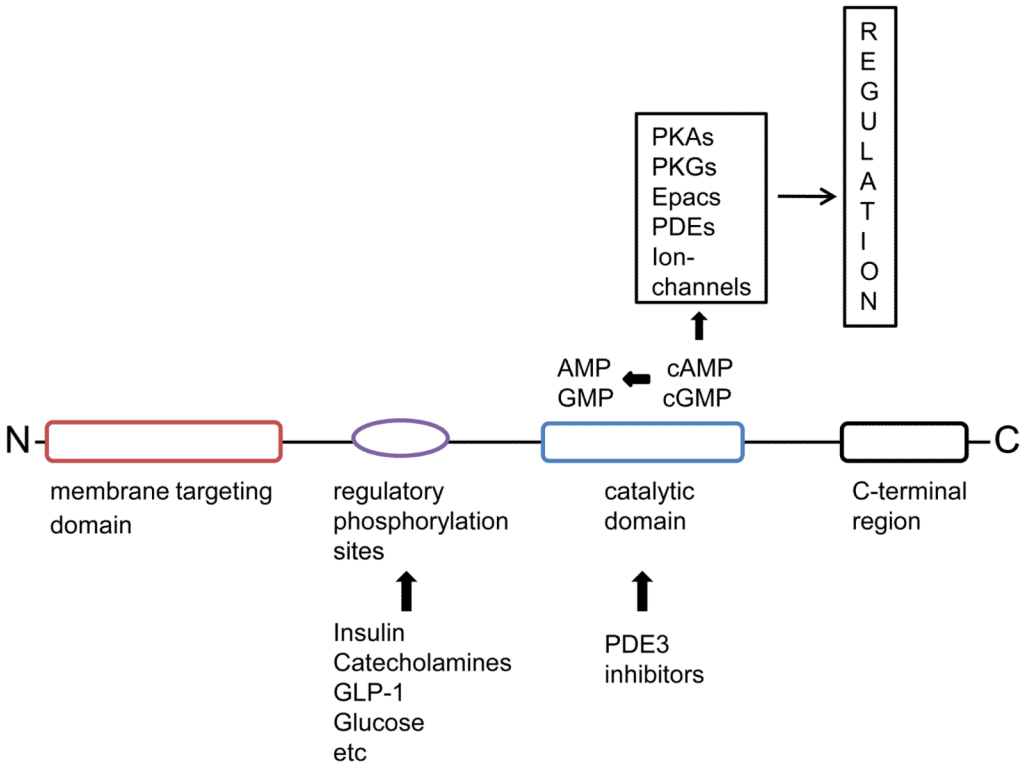

Figure 1. Structural organization of PDE3B

The structural organization of PDE3B involves the catalytic domain conserved among all PDEs in the C-terminal portion of the enzymes followed by a hydrophilic C-terminal region. The catalytic domain hydrolyzes both cAMP and cGMP and is the target for PDE3 inhibitors. The regulatory N-terminal portion contains large hydrophobic regions with predicted transmembrane helical segments. Downstream of the hydrophobic regions lies regulatory serine residues that are phosphorylated in intact cells. Signalling induced by cAMP and cGMP primarily involves their activation of cAMP- and cGMP-activated protein kinases (PKA and PKG), with subsequent phosphorylation of critical effectors. However, direct interactions of cyclic nucleotides with binding proteins are now recognized as alternative mechanisms for transduction of their signals. These binding proteins include cAMP-activated guanine nucleotide exchange factors (GEFs) also called Epacs (exchange proteins activated by cAMP or cAMP GEF) which regulate Rap1, cyclic nucleotide-gated channels and several PDEs, which contain allosteric, non-catalytic cyclic nucleotide-binding sites located in GAF domains (the GAF domain is named after some of the proteins it is found in: c**G**MP-specific phosphodiesterases, **a**denylyl cyclases and **F**hlA).

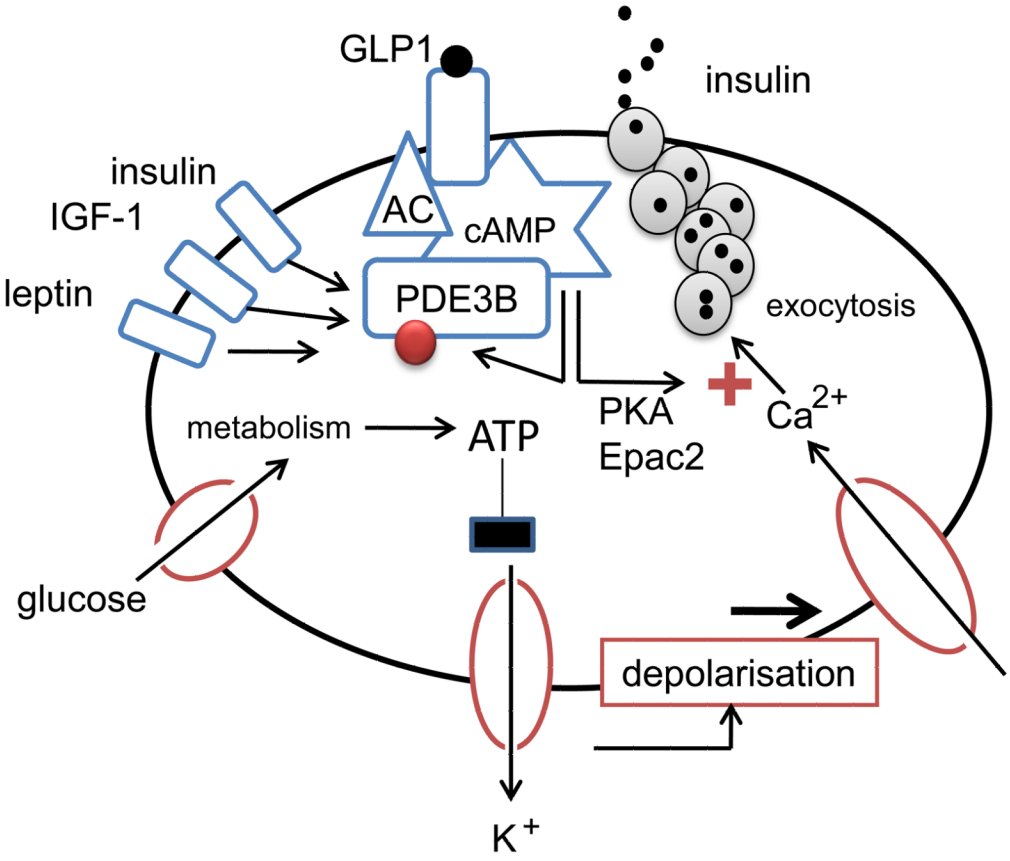

Figure 2. Role of PDE3B in the regulation of insulin secretion

The main stimulator of insulin secretion is glucose, which is metabolized inside the β cell. The subsequent increase in ATP/ADP ratio causes closure of K_{ATP}-dependent ion channels, resulting in depolarization of the plasma membrane. In consequence, L-type Ca^{2+} channels are opened, leading to influx of Ca^{2+}. The increased intracellular concentration of Ca^{2+} stimulates exocytosis of insulin. cAMP initiates processes to enhance insulin secretion, including activation of PKA and binding to Epac2. Exocytosis of insulin is then stimulated through multiple pathways, only a few of which have been established so far. Glucagon-like peptide (GLP)-1 is an insulinoptropic gut hormone, which acts through a G-protein-coupled receptor to activate adenylate cyclase (AC) and thereby trigger an increase in cAMP. PDE3B in turn has been shown to negatively regulate insulin secretion through its cAMP-hydrolyzing activity. Other hormones known to activate β cell PDE3B are insulin, IGF-1 and leptin. The red ball indicates phosphorylation-sites.

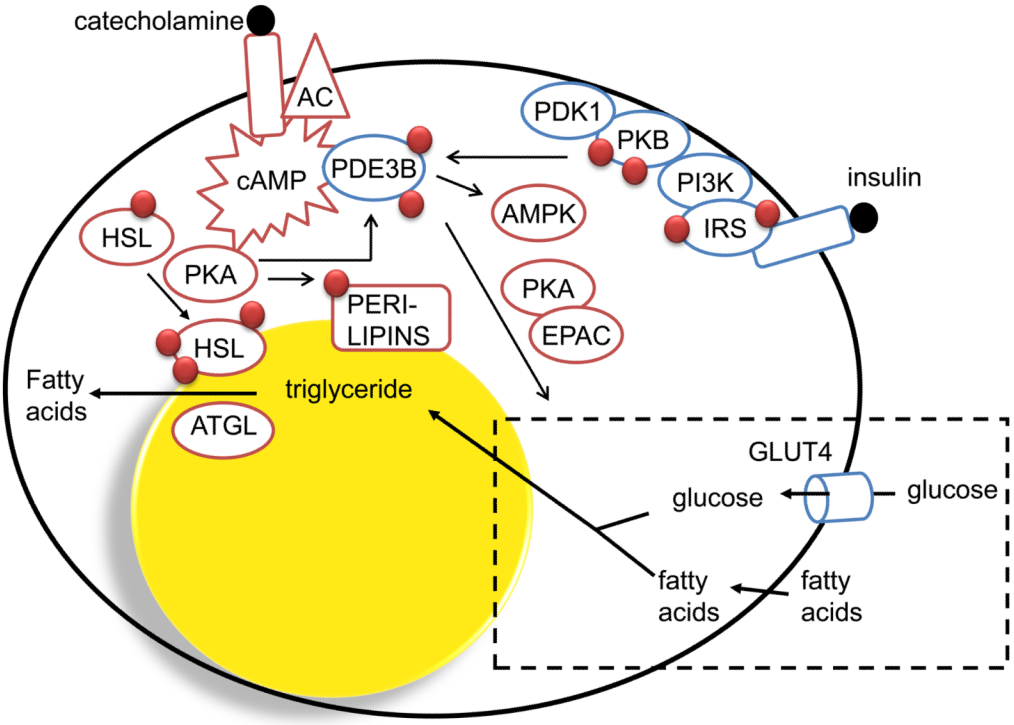

Figure 3. Role of PDE3B in hormone-mediated regulation of adipocyte functions

Activation of PDE3B leads to increased hydrolysis of cAMP and thereby inhibition of catecholamine-induced lipolysis, a process which involves PKA-dependent phosphorylation of hormone-sensitive lipase (HSL) and perilipin. Insulin-mediated phosphorylation and activation of PDE3B involves tyrosine phosphorylation of insulin receptor substrates (IRS) catalyzed by the activated insulin receptor tyrosine kinase (IRTK), activation of PI3K and increased production of phosphatidyl inositol 3,4/3,4,5 phosphates. This is followed by the activation of PKB which is believed to be one important kinase that phosphorylates and activates PDE3B. Phosphorylation and activation of PDE3B by cAMP-increasing hormones are thought to be important in feedback-regulation of cAMP and cAMP-mediated responses. PDE3B is also important in insulin-induced regulation of glucose uptake and lipogenesis which involves PKA as well as Epac proteins. Finally, PDE3B as well as PDE4 seem to regulate cAMP pools that affect the activation/phosphorylation state of AMPK. ATGL (adipose triglyceride lipase).

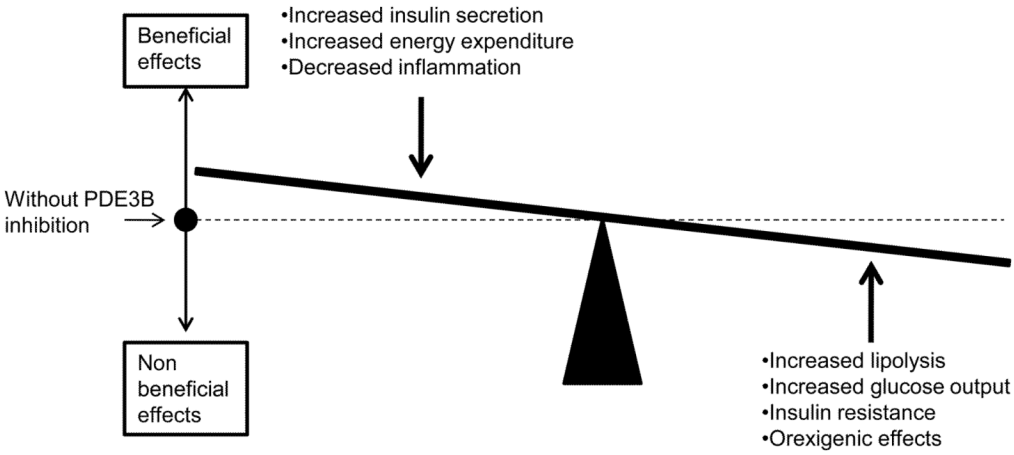

Figure 4.
Multiple effects of PDE3 inhibitors. It is a challenge to target PDE3Bs to prevent and treat dysregulated metabolic states due to the different responses in different tissues.