

## MINIREVIEW

# Pharmacological Targeting of Adipocytes/Fat Metabolism for Treatment of Obesity and Diabetes

Paul F. Pilch and Nils Bergenhem

*Department of Biochemistry, Boston University School of Medicine, Boston, Massachusetts (P.F.P.); and AdipoGenix, Inc. Boston, Massachusetts (N.B.)*

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## ABSTRACT

Obesity is now recognized as a rapidly increasing worldwide threat to health, largely as a result of causing diabetes. Thus, considerable efforts are underway in the pharmaceutical industry to find drugs to treat this condition. Target validation in various academic and industrial laboratories has revealed a

number of potential molecular targets in fat cells or adipocytes. By definition, obesity is too much fat, and we here review efforts to treat obesity and, by proxy, diabetes by modulating the metabolic state of adipocytes.

The incidence of obesity is increasing dramatically to epidemic proportions in virtually all societies of the world (Flier, 2004), and with it come the major pathological consequences of type 2 diabetes and cardiovascular disease as well as other less common pathologies. From a thermodynamic perspective, obesity is a result of the imbalance between energy intake (feeding) and energy expenditure (thermal and physical activity, Fig. 1). Thus, in theory it can be dealt with by proper nutrition and adequate exercise, but most people are apparently unable to comply with these relatively simple measures. Consequently, the pathological sequelae of obesity are certain to present an enormous burden on worldwide medical care as well as have significant economic consequences for all societies.

The need for a pharmacologically viable intervention for obesity is therefore most pressing and well recognized by the pharmaceutical community. Potential sites of therapeutic intervention for treating obesity include the brain to alter neural signals regulating appetite, the gut to alter nutrient adsorption, and adipose tissue to alter fat storage and promote fat oxidation. Figure 1 lists the drugs currently in use for weight loss (left) and potential targets/processes for new

interventions regarding energy expenditure and metabolism (right). Possible targets in tissues other than adipocytes include uncoupling proteins 2 and 3, whose activation could potentially burn rather than store calories (thermogenesis), although evidence for a physiological uncoupling function for these proteins is not compelling (Crowley and Vidal-Puig, 2001). The metabolic sensor AMP-activated protein kinase is stimulated upon exercise and may augment lipid and glucose metabolism in muscle (Barnes and Zierath, 2005; Kahn et al., 2005), prompting interest in a small-molecule drug that can activate this protein; in effect, an exercise pill. Whether this is feasible remains to be determined. Thus, although this and other drug targets may prove attractive for obesity therapy, here we focus on adipocyte metabolism as a process most suitable for this end, based in large part on the phenotype of knockouts targeting important metabolic proteins in this tissue. First, we consider the status of existing obesity drugs.

There are presently two drugs approved by the United States Food and Drug Administration for the treatment of obesity; the neurotransmitter reuptake inhibitor sibutramine (Meridia) (Ryan, 2004) and the pancreatic lipase inhibitor tetrahydrolipstatin (Orlistat) (Hauner, 2004). The former acts in the brain to suppress appetite, and the latter works in the gut to limit free fatty acid formation and inhibit their adsorption. Neither is particularly effective and both

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**ABBREVIATIONS:** FA, fatty acid; PPAR $\gamma$ , peroxisome proliferation activating receptor  $\gamma$ ; RBP4, retinol binding protein 4; GW501516, (2-methyl-4-((4-methyl-2-(4-(trifluoromethyl)phenyl)-5-thiazolyl)methyl)thio)phenoxy)-acetic acid; SCD1, stearoyl-CoA desaturase-1; DGAT1, acyl CoA:diacylglycerol acyltransferase 1; 11 $\beta$ -HSD1, 11 $\beta$ -hydroxysteroid dehydrogenase type 1; PTP-1B, protein tyrosine phosphatase-1B.

have significant side effects that have limited their widespread use. In principle, an effective drug for appetite suppression has great appeal, as it would diminish the intake side of the thermodynamic equilibrium, which seems much easier to achieve than increasing the output (exercise) side for most people. The study of neuronal circuits that regulate appetite and energy expenditure is a robust activity of the basic research community, which may result in the revelation of new and/or better drug targets. Indeed, a cannabinoid receptor 1 antagonist, rimonabant (Acomplia) (Wadman, 2006), is a brain-acting appetite suppressant that shows promise in ongoing late-stage clinical trials; it is noteworthy that its mode of action may also involve direct effects on the adipocyte (Jbilo et al., 2005; Gary-Bobo et al., 2006). However, it remains to be seen how effective it will prove to be in long-term weight loss, considering possible mood altering actions of such a drug. Moreover, the blood-brain barrier remains an obstacle to any such central nervous system-directed therapeutic intervention, as does the cellular complexity of the brain. Despite these potential problems, it still

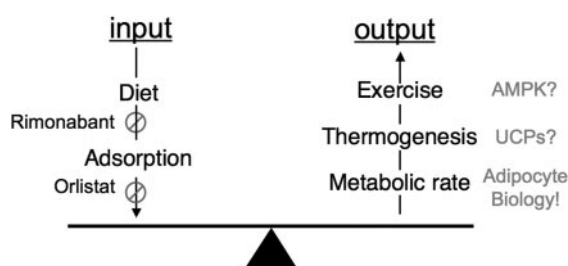
seems well justified to search for additional drugs and targets for this mode of action in the brain.

On the other hand, the inhibition of nutrient (fat) uptake seems a less likely effective means of weight control. Cells take up fatty acids (FA) primarily by simple diffusion (Hamilton and Kamp, 1999), although various membrane proteins, often called FA transporters, clearly play a role in the metabolism of FA and may enhance their uptake as a result. However, mouse knockout studies of CD36, the putative fatty acid transporter, shows a complex metabolic phenotype (Febbraio et al., 1999). These animals exhibit decreased muscle fatty acid oxidation in contrast to the adipocyte targets discussed below, where adipocyte mass is reduced and lipid oxidation in muscle is enhanced (Table 1 and text). Therefore, mechanisms other than inhibition of lipases (tetrahydrolipstatin) are unlikely to be effective in decreasing intestinal and/or cellular FA adsorption. Other than rimonabant, there are no antiobesity drugs in phase III clinical trials, although a selective serotonin receptor agonist, APD356 (Arena Pharmaceuticals, San Diego, CA), has recently been reported to produce meaningful weight loss in phase IIb trials (Melnikova and Wages, 2006). See Halford (2006) for another very recent review of early-stage antiobesity drugs directly targeting cells other than the adipocyte. We now turn our attention to fat cells (adipocytes) for which a significant number of mouse models exist in which the knocking out of enzymes involved in fat storage, and in related metabolic pathways, results in a leaner phenotype and enhanced FA oxidation. First we consider the physiology of the adipocyte with respect to organismal metabolic regulation.

## Adipocytes

Until just over 10 years ago, adipocytes or fat cells were generally considered to be a relatively inert tissue that merely responded to nutrient intake by storing fat (triglyc-

### Energy balance, thermodynamics



**Fig. 1.** The thermodynamics of energy balance. The effects or possible effects of existing and putative obesity drugs and their general mode of action are outlined.

**TABLE 1**  
Small molecule drugs/drug targets affecting adipocyte biology/metabolism

Target and Drug (candidate) or Knockout	Phenotype	Ref.
<b>PPAR<math>\gamma</math></b>		
Rosiglitazone & pioglitazone:	Increased insulin sensitivity with edema and weight gain as side-effects	Aronoff et al., 2000; Phillips et al., 2001; Hussein et al., 2004
Systemic knockout	-/-: lethal; impaired placental, cardiac, and adipose tissue development +/-: improved insulin sensitivity	Kubota et al., 1999; Miles et al., 2000; Yamauchi et al., 2001
<b>SCD1</b>		
Novartis/Xenon preclinical inhibitor	No published data	
Systemic knockout	-/-: decreased body fat mass, increased oxygen consumption, increased insulin sensitivity; abnormal skin, eyelid, and hair +/-: lower triglycerides, cholesterol ester, and wax ester levels in eye lids compared to +/+	Miyazaki et al., 2000; Ntambi et al., 2002
<b>DGAT1</b>		
Systemic knockout	-/-: resistance to diet induced obesity, increase metabolic rate; alopecia, impaired mammary gland development +/-: intermediary resistance to diet induced obesity	Smith et al., 2000; Chen et al., 2002; Chen, 2006
<b>11<math>\beta</math>-HSD</b>		
Amgen/Biovitrum: AMG 221, phase I	No published data	
Systemic knockout	-/-: resistance to diet induced obesity, increase metabolic rate +/-: no reported phenotype	Morton et al., 2004
<b>PTP-1B</b>		
IDD-3848, preclinical ISIS-113715, antisense (phase II)	Increased insulin sensitivity Reduction in HbA1c and fasting glucose	Abstracts only no published data
Systemic knockout	-/-: resistance to diet induced obesity, improved insulin sensitivity +/-: resistance to diet induced obesity, improved insulin sensitivity	Elchebly et al., 1999; Klaman et al., 2000

eride), and to the metabolic demands of fasting and exercise by releasing FA and glycerol. However, the discovery of the cytokine (now called an adipokine) leptin has motivated research that has revealed the adipocyte to be an endocrine cell at the center of metabolic regulation (Fig. 2). Leptin is made exclusively in adipocytes (Zhang et al., 1994), and its deficiency (*ob/ob* mice) or a deficiency of its receptor (*db/db* mice) causes massive obesity and diabetes (Friedman, 1998). Numerous studies have established that adipocytes secrete a variety of adipokines (Steppan et al., 2001; Berg et al., 2002; Fukuhara et al., 2005; Yang et al., 2005, 2006) that can affect adiposity and insulin resistance. In fact, it has been suggested that insulin resistance in adipocytes is the first metabolic manifestation leading to type 2 diabetes (Bergman, 1997), and this pathological condition is tightly linked to obesity. The phenotype of mouse leptin deficiency is recapitulated in the rare instances of the corresponding human mutations (Montague et al., 1997) (see *Leptin*). In humans, insulin resistance in adipocytes, paradoxically a condition in obesity in which insulin cannot promote normal fat storage, results in excess circulating FA that, in turn, promotes insulin resistance in muscle and consequently type 2 diabetes. Thus, pharmacological targeting of fat cells to correct this abnormality seems to be a very promising strategy. As noted above, a number of adipokines have now been identified that modulate metabolism; the most important of them are probably adiponectin (Berg et al., 2002) and retinol binding protein 4 (Yang et al., 2005) (Fig. 2). These also represent possible targets for treating obesity.

Thus, there are three somewhat independent target classes in adipocytes that may be suitable for therapeutic intervention in obesity and diabetes: 1) adipokines, 2) modulators of hormonal sensitivity, and 3) enzymes involved in fat storage. In fact, class 2 has already been validated as a major drug target by way of agonists of the peroxisome proliferation activating receptor,  $\gamma$  (PPAR $\gamma$ ) class of antidiabetic drugs [rosiglitazone (Avandia) and pioglitazone (Actos)] that enhance insulin sensitivity (Yki-Jarvinen, 2004). However, although these drugs are able to increase insulin sensitivity in all insulin-target tissues by first targeting adipocytes, they

cause an increase in adiposity and weight gain. Thus, the compensatory behavior of the organism needs to be considered in the actions of any of the above potential target classes, which we now consider in detail.

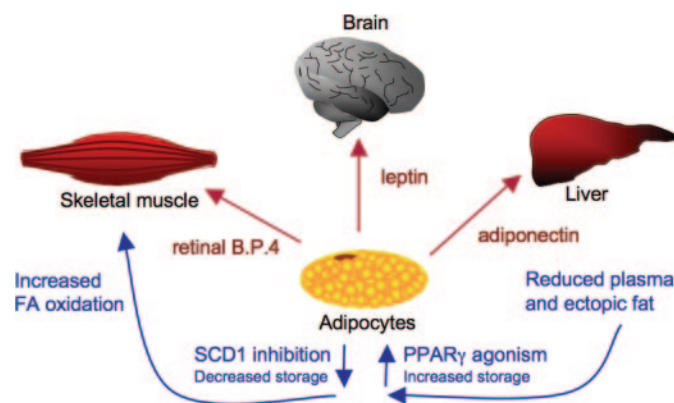
### Adipokines

**Leptin.** Leptin plays a major role in the regulation of food intake and metabolic rate (Friedman, 1998), and the amount of leptin in circulation is proportional to the fat mass (Maffei et al., 1995). Leptin is made primarily or exclusively in adipocytes and its principal target is the central nervous system, although peripheral actions have been reported (Bjorbaek and Kahn, 2004). Administration of leptin to rodents (Halaas et al., 1995; Pelleymounter et al., 1995) and humans (Farooqi et al., 2002) that have molecular defects in its expression is an effective therapy for their obesity. However, most obese patients already have high levels of circulating leptin and are resistant to the actions of this adipokine even when exogenously administered (Heymsfield et al., 1999). The mechanism of this resistance is not presently very well understood (Munzberg et al., 2005), but the bottom line is that leptin therapy may be useful only for rare leptin deficiencies and generalized lipodystrophy disorders (Javor et al., 2005), and it probably will not be useful for the vast majority of obese persons.

Additional considerations to the therapeutic use of leptin are the rather short half-life of the peptide in humans (25 min) (Klein et al., 1996), the high cost of production, and the need for injections, all facts that make the use of leptin in the clinic problematic for routine usage. These considerations also apply to adiponectin and retinol binding protein 4 (RBP4), the two adipokines currently being intensely studied for their possible role in regulating insulin sensitivity and possibly obesity.

**Adiponectin.** This adipokine was discovered in four laboratories, each of which gave it a different name: *adipoQ*, *adipose most abundant gene transcript* (*apM1*), *adipocyte complement-related protein of 30-kDa* (*Acrp30*), and *adiponectin* because it appeared to be a matrix protein (reviewed in Berg et al., 2002; Kadowaki and Yamauchi, 2005; Lihn et al., 2005). Adiponectin has now become the generally accepted and most widely used name for this adipokine. Circulating adiponectin levels correlate with insulin sensitivity in humans; interestingly, injection of adiponectin in mice has been shown to enhance oxidation of fatty acids in muscle as well as decrease hepatic glucose production and induce weight loss (Berg et al., 2001; Combs et al., 2001; Fruebis et al., 2001). However, adiponectin biochemistry is complex, and its endogenous levels in serum are quite high (Pajvani et al., 2004), thus mitigating enthusiasm for its direct therapeutic use. Moreover, from a drug discovery perspective, the effect of proteins such as adipokines have historically proven very difficult to mimic with small-molecule drugs, although it may be possible to transcriptionally modulate their expression (Yang et al., 2002).

**Other Adipokines.** Resistin is an adipokine that has an effect opposite that of adiponectin in that it causes insulin resistance in mice, as its name implies (Steppan et al., 2001). However, this effect may be species-specific and may not apply to humans (Arner, 2005). Retinol binding protein 4 (RBP4) is a recently discovered fat-derived serum protein the expression of which correlates with diabetes and obesity in



**Fig. 2.** Adipocytes at the center of metabolic regulation. Activation of PPAR $\gamma$  nuclear receptors leads to increased storage of fat in adipocyte. This results in reduced circulating lipids and ectopically stored fat, leading to increased insulin sensitivity. Reducing the activity of SCD1, for example, has the reverse effect of lowering of fat storage in adipocytes. This leads to increased fat oxidation in muscle, resulting in similarly improved insulin sensitivity. By secreting adipokines such as RBP-4, adiponectin and leptin, adipose tissue sends signals to skeletal muscle, liver and brain, which variously effect metabolism and energy balance.

humans and in animals (Yang et al., 2005). Although only one article has been published describing the possible role of this adipokine in diabetes, the fact that the synthetic retinoid fenretinide can normalize glycemia in diabetic mice has raised considerable interest in RBP4. Visfatin (Fukuhara et al., 2005) and omentin (Schaffler et al., 2005; Yang et al., 2006) are potential markers of specific fat depots of as yet uncertain physiological function as adipokines (Stephens and Vidal-Puig, 2006). A number of additional cytokines may also be considered adipokines and play a role in diabetes/obesity, as has been reviewed (Drevon, 2005).

### Modulators of Insulin Sensitivity

**PPAR $\gamma$ .** PPARs are a family of three ( $\alpha$ ,  $\beta/\delta$ , and  $\gamma$ ) nuclear receptors that affect the transcription and expression level of numerous target genes in adipocytes and other tissues/cells. They have been implicated in a variety of pathological states (Glass, 2006; Michalik and Wahli, 2006; Semple et al., 2006), and their properties have been extensively reviewed (Chinetti-Gbaguidi et al., 2005; Puigserver, 2005). In brief, they function by dimerizing with the retinoid X receptor, and their activity is controlled by the recruitment of a number of coactivators and corepressors. Although the natural ligands for PPARs are unknown, they are modulated by drugs of the fibrate family, in the case of PPAR $\alpha$  (Staels et al., 1998), which we will not discuss further, and by the thiazolidinedione class of insulin sensitizers in the case of PPAR $\gamma$ .

PPAR $\gamma$  is an intensively studied member of the PPAR family because its agonists have been used clinically and commercially for diabetes therapy for approximately 10 years. The first insulin sensitizer and PPAR $\gamma$  agonist used was troglitazone (Rezulin), which was taken off the market in 2000 because of liver toxicity, but now rosiglitazone and pioglitazone are used for this purpose, as previously noted. In addition to its role as a target for insulin sensitizers, PPAR $\gamma$  plays a major role (probably the major role) in the differentiation of preadipocytes to adipocytes (Spiegelman et al., 1997), the process of adipogenesis. Thus the drug regimen of PPAR $\gamma$  agonists rosiglitazone and pioglitazone results in enhanced differentiation of adipocytes, which unfortunately tends to cause weight gain in animals as well as humans (Evans et al., 2004; Lazar, 2005). It is noteworthy that whereas PPAR $\gamma$  homozygous deletions are embryonically lethal, heterozygous mice have an increased insulin sensitivity phenotype without weight gain (Miles et al., 2000; Yamauchi et al., 2001). PPAR $\gamma$  antagonists seem to have a similar effect on receptor heterozygosity (Rieusset et al., 2002), suggesting that inhibition of PPAR $\gamma$  could improve insulin resistance and, unlike the presently used full agonists of PPAR $\gamma$ , induce loss of body fat.

This rather counterintuitive result that increasing the activity as well as decreasing the amount of PPAR $\gamma$  leads to increased insulin sensitivity has produced an interest in the development of selective PPAR modulators (Berger et al., 2003), compounds that act as partial agonists, or antagonist to PPAR. Hence, the adipogenesis-promoting effects of PPAR $\gamma$  agonists seem unnecessary for the beneficial, insulin-sensitizing effects of such drugs. The idea behind the selective PPAR modulators is to develop agents that modulate PPAR $\gamma$  in such a way that the compounds improve insulin sensitivity without any promotion of weight gain. Another approach to try to overcome the increase in body weight seen

with full PPAR $\gamma$  agonists is to develop agonists that act on two or all three of the PPARs, the hypothesis being that stimulating PPAR $\alpha$  and/or PPAR $\delta$  will activate fatty acid oxidation and cancel out the adipogenic effects of PPAR $\gamma$  agonism (Farmer and Auwerx, 2004).

Serious side effects have been seen with several of the PPAR agonists, which raises some possible concerns about pharmacologically addressing this target. Hepatotoxic effects of the first member of the thiazolidinedione family marketed, troglitazone, resulted in its withdrawal from the market in 2000, as noted above. PPAR $\gamma$  agonists have been shown to promote colon cancer tumor growth in mice, although the effects on human colon cancer cell lines seem to be different (Evans et al., 2004). Increased growth of small intestine polyps in cancer-prone mice has also been reported with the PPAR agonist GW501516 (Evans et al., 2004). Several PPAR agonists have been terminated in late stage development because of the possibility of increased risk of cancer. The United States Food and Drug Administration's guidelines call for the completion of 2-year carcinogenicity studies before initiating any clinical studies of more than 6 months' duration with PPAR agonists (El-Hage, 2005).

Besides the stringent requirements to assess any carcinogenic effects of PPAR agonists in clinical development, recent phase 3 clinical studies with the dual PPAR $\alpha$ /PPAR $\gamma$  agonist muraglitazar showed an increase in major cardiovascular events (Nissen et al., 2005), which has raised the concern for this class of drugs. On the other hand, the impressive effects of another dual PPAR $\alpha$ /PPAR $\gamma$  agonist, tesaglitazar, in patients with prediabetes show this drug candidate to improve not only insulin resistance but also lipid and cholesterol profiles. These data suggest the possibility of preventing vascular complications as well as delaying or blocking the progression to diabetes with this drug (Fagerberg et al., 2005). Thus PPARs seem to be a type of classic drug target, albeit tricky to modulate because of their overlapping ligand preferences, complex tissue distribution, and mechanism of actions.

### Enzymes of Fat Metabolism

To treat obesity and its associated diabetes, an ideal approach would be to decrease fat storage and enhance its oxidation, and a number of mouse knockout models deficient in certain enzymes of fatty acid metabolism have just this phenotype. From a pharmacological standpoint, enzyme inhibitors, like receptor agonists and antagonists, are a classic type of drug. Thus, we consider this approach to be very promising, and we summarize the field in this regard.

**SCD1.** Stearoyl-CoA desaturase-1 (SCD1) catalyzes the desaturation of long-chain fatty acids to generate monounsaturated fatty acids, mainly oleic acid, for triglyceride and membrane lipid synthesis, and it is highly expressed in adipocytes as well as in liver (Ntambi et al., 1988). The disruption in the SCD1 gene in mice (Miyazaki et al., 2001; Ntambi et al., 2002), as well as a naturally occurring inactivating mutation in the SCD1 gene (asebia) (Zheng et al., 1999) results in mice that are resistant to diet-induced obesity and insulin resistance when fed a high-fat diet. Compared with wild-type mice, the mice with reduced SCD1 seem to have an increased metabolic rate. A complete lack of SCD1 leads to abnormal skin, eyelids, and hair as a result of deficiencies in triglycerides and cholesterol ester synthesis. On the other



hand, heterozygotes (Zheng et al., 1999) or mice treated with an SCD1 antisense oligonucleotide (Jiang et al., 2005) showed none these effects but retained resistance to diet-induced obesity (Jiang et al., 2005). These results suggest that partial inhibition of SCD1 by the appropriate small-molecule drug might have beneficial metabolic actions (Cohen and Friedman, 2004) without the deleterious side effects.

Mice deficient in other genes involved in lipid synthesis, such as Acetyl CoA carboxylase (*ACC*) 2 (Abu-Elheiga et al., 2001, 2003) and diacylglycerol acyl transferase (*DGAT*) 1 (Smith et al., 2000) (see *DGAT1*), also show an enhanced metabolic rate and resistance to obesity in mice. However, it is unclear whether inhibiting acetyl CoA carboxylase, the first enzyme in de novo fatty acid synthesis, in humans will have the same potential as it does in rodents (Harwood, 2004), because humans do very little de novo FA production. An additional point on the apparent generality of the phenotype resulting from inhibiting fat accumulation is that under these circumstances, the body does not break the first law of thermodynamics. The reaction to the reduced energy (fat) storage in adipocytes is an increased metabolic rate, and hence the law of energy conservation must apply. At least in the cases mentioned above, there seems to be no reason for concern in terms of dysregulation of fat metabolism resulting in ectopic fat storage, with the possible associated problems. The close coupling between energy intake, storage, and expenditure is preserved, and a decrease in storage capability seems to result in an increase in energy expenditure. This phenomenon makes targeting fat accumulation very attractive as an approach to treat obesity.

**DGAT1.** The enzyme microsomal acyl CoA:diacylglycerol acyltransferase 1 (*DGAT1*) catalyzes the final and committed step in the glycerol phosphate pathway. Knockout mice lacking *DGAT1* are resistant to diet-induced obesity and hepatic steatosis (Smith et al., 2000), seemingly as a result of an increase in energy expenditure and physical activity (Chen, 2006). As with the similar phenotype of the *SCD1* knockout mice, *DGAT1*-deficient mice also have an increased insulin and leptin sensitivity (Chen et al., 2002). It is noteworthy that obesity resistance and enhanced glucose metabolism were evident when white adipose tissue lacking *DGAT1* was transplanted to wild-type mice (Chen et al., 2003). This points to the existence of a factor being secreted from adipose tissue lacking *DGAT1* that affects adiposity and glucose disposal. This could be one of the previously noted adipokines, although this point has not been further studied. It should be noted that a total lack of *DGAT1* results in alopecia and impaired development of the mammary gland, but, as is the case for *SCD1*, the aim of any pharmacological intervention would be a partial inhibition of the enzyme.

**11 $\beta$ -HSD1.** The enzyme acyl CoA:diacylglycerol acyltransferase 1 (11 $\beta$ -HSD1) catalyzes the conversion of inactive cortisone to active cortisol in the liver and adipose tissue. Mice lacking a functional *11 $\beta$ -HSD* gene have been shown to be resistant to developing obesity and diabetes when put on a high-fat diet, even when consuming more calories than wild-type mice (Morton et al., 2004). High levels of cortisol are well known to cause insulin resistance (Friedman et al., 1996); in fact, increased expression of 11 $\beta$ -HSD I in adipocytes has been reported in acquired obesity. This phenomenon is related to accumulation of intra-abdominal and subcutaneous fat, as well as insulin resistance (Kannisto et al., 2004). These find-

ings have prompted interest in inhibition of 11-HSD1 as a drug target and candidate inhibitors are currently being developed (Table 1).

### Other Potential Targets

**PTP-1B.** The protein tyrosine phosphatase (PTP) 1B is one of the best biologically validated targets for both type 2 diabetes and obesity (Dube and Tremblay, 2005). This enzyme attenuates the signaling of insulin and leptin receptors by dephosphorylating the insulin receptor (Elchebly et al., 1999) and JAK2 in hypothalamus (Cheng et al., 2002; Zabolotny et al., 2002), consequently potentiating the strength and/or duration of the respective signals as determined in *PTP-1B* knockout mice. These animals are resistant to obesity and insulin resistance induced by a high-fat diet, and the mechanism underlying the physiological response may involve both insulin and leptin signaling. In the former case, an increase in skeletal muscle and possibly liver insulin sensitivity was noted (Elchebly et al., 1999), and a role for PTP 1B in adipose tissue was not observed in these studies even though PTP 1B is expressed in this cell, where it colocalizes with IRS1 (Calera et al., 2000). On the other hand, reducing PTP-1B expression in ob/ob mice by means of antisense RNA reduces adiposity, ameliorates diabetes, and augments insulin signaling in a somewhat complicated manner. These data nevertheless suggest that this phosphatase may play a significant role in adipose tissue as well (Rondinone et al., 2002; Zinker et al., 2002; Gum et al., 2003).

The effects on obesity and insulin resistance in mice lacking PTP 1B are quite impressive. Concerns of possible side effects have been raised because the enzyme has been shown to dephosphorylate a number of receptor and nonreceptor tyrosine kinases other than the insulin receptor (Johnson et al., 2002; Dube and Tremblay, 2005). However, the knockout animals are seemingly healthy, suggesting that a specific partial inhibition of this phosphatase would produce the desired effects, perhaps without any unwanted side effects.

The biological validation has led many pharmaceutical companies to attempt to develop PTP 1B inhibitors, but this has turned out to be a very difficult task. At this point, there are only a few reports on in vivo active PTP-1B inhibitors (Table 1). The metabolic effects are very similar to those observed with antisense oligonucleotides decreasing PTP-1B expression. In conclusion, inhibition of PTP-1B is one of the most interesting approaches for treatment of obesity and type 2 diabetes, and the future will tell whether the difficulties in developing small-molecule inhibitors for this enzyme can be overcome.

**C-cbl.** E3 ubiquitin ligases such as c-cbl regulate a variety of signaling pathways initiated by receptor tyrosine kinases such as the insulin receptor, usually in a negative fashion (Thien and Langdon, 2005). However, much interest was generated by the report that c-cbl served a positive role as an adaptor for insulin receptor signaling in adipocytes (Bauermann et al., 2000). More recently, evidence against this hypothesis has been generated in vitro, where small interfering RNA knockdown of c-cbl was without effect on insulin signaling (Mittra et al., 2004). Moreover, in vivo studies of c-cbl-deficient mice revealed them to have reduced adiposity and increased insulin sensitivity (Molero et al., 2004) and to be protected against diet induced obesity (Molero et al., 2006). Thus, a small molecule inhibitor of this ligase would be a

potential obesity/diabetes drug although more general efforts to develop E3 ligase inhibitors for other purposes have not been successful to date (Garber, 2005).

## Conclusions

There is no apparent shortage of potential drug targets for the treatment of obesity and diabetes. However, targeting metabolism to alter weight and energy balance has historically been very difficult because compensatory mechanisms come into play, and the body "stoutly" defends against weight loss. It perceives this as starvation and reduces energy expenditure accordingly. We expect that modern technology and our increasingly sophisticated understanding of the biology, as well as pharmaceutical chemistry, will nevertheless lead to effective treatments of obesity and diabetes.

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**Address correspondence to:** Paul F. Pilch, Department of Biochemistry, Boston University School of Medicine, 80 E. Concord St., Boston, MA 02118. E-mail: ppilch@bu.edu