

Dichotomous roles of leptin and adiponectin as enforcers against lipotoxicity during feast and famine

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ABSTRACT Science is marked by the death of dogmas; the discovery that adipocytes are more than just lipid-storing cells but rather produce potent hormones is one such example that caught physiologists by surprise and reshaped our views of metabolism. While we once considered the adipocyte as a passive storage organ for efficient storage of long-term energy reserves in the form of triglyceride, we now appreciate the general idea (once a radical one) that adipocytes are sophisticated enough to have potent endocrine functions. Over the past two decades, the discoveries of these adipose-derived factors (“adipokines”) and their mechanistic actions have left us marveling at and struggling to understand the role these factors serve in physiology and the pathophysiology of obesity and diabetes. These hormones may serve an integral role in protecting nonadipose tissues from lipid-induced damage during nutrient-deprived or replete states. As such, adipocytes deliver not only potentially cytotoxic free fatty acids but, along with these lipids, antilipotoxic adipokines such as leptin, adiponectin, and fibroblast growth factor 21 that potentially eliminate excessive local accumulation of these lipids or their conversion to unfavorable sphingolipid intermediates.

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INTRODUCTION

Understanding the mechanisms of adipose-derived hormones is a major challenge. Notably, the specific manner in which leptin (the first adipokine to be described) was discovered posed a serious teleological conundrum. Leptin was found by positional cloning in *ob/ob* mice, which are leptin-deficient and in which obesity is reversed by pharmacological replacement with leptin (Halaas *et al.*, 1995). Thus it appeared that the role of leptin was to prevent obesity. This appealing hypothesis was rendered untenable by subsequent studies showing that diet-induced obesity in animals (Frederich *et al.*, 1995) and in humans (Considine *et al.*, 1996) is invariably accompanied by a progressive increase in plasma leptin levels. This not only

ended the hope for an anti-obesity hormone, but it left unexplained the true function of this fascinating adipocyte product. Meanwhile, leptin was demonstrated to have multiple actions on multiple targets, but one action, the stimulation of β -oxidation of fatty acids by activating AMP-dependent kinase (AMPK) and increasing the expression of UCP-1 and UCP-2, seems particularly important (Minokoshi *et al.*, 2002).

While the work on leptin was ongoing, adiponectin, a second important adipokine, was described (Scherer *et al.*, 1995). In culture, its actions on fatty acids appear similar to those of leptin: it increases fatty acid oxidation in muscle (Yamauchi *et al.*, 2001). More recent evidence suggests that adiponectin may additionally oppose lipotoxicity by enhancing deacylation of ceramide (Holland *et al.*, 2011), a lipid metabolite heavily implicated in the lipid-induced dysfunction of numerous cell types. Thus both leptin and adiponectin appear to oppose lipotoxicity, the impaired function or survival of a cell due to excess accumulation of lipid and lipid-derived intermediates.

LEPTIN AND ADIPONECTIN PRODUCTION

Although leptin and adiponectin have similar lipo-oxidative actions, they differ strikingly in terms of the perturbations that elicit increases

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Abbreviations used: FGF21, fibroblast growth factor 21; PPAR, peroxisome proliferator-activated receptor.

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in their secretion. Leptin secretion rises acutely during feeding or in response to overnutrition as adipocytes expand in size and number (Unger, 2002). The associated hypoxia caused by undervascularization of the expanding adipose tissue prompts hypoxia-inducible factor (HIF1 α) to increase the production of leptin (Sun *et al.*, 2013). Adiponectin secretion is increased during undernutrition and exercise, when adipocytes tend to diminish in size because lipolysis is most active (Miyazaki *et al.*, 2010). These effects are evident even in the diurnal variation of these factors, which displays an interesting dichotomy (R. S. Ahima and P. E. Scherer, personal communication). Leptin levels are highest in the postprandial state at 2 a.m. for rodents and wane prior to consumption of a meal at the onset of the dark cycle. Leptin rises with postprandial increases in circulating fatty acids. By contrast, adiponectin levels are highest in the fasted state; at 2 p.m., adiponectin levels are significantly higher than at the nadir of 12 a.m. Such variations can also be evoked during fasting–feeding experiments, as leptin falls and adiponectin rises when food is withdrawn—a phenomenon reversible by refeeding. (Asterholm and Scherer, 2010). The “yin and yang” of these two adipokines, which are oppositely regulated under essentially all conditions, suggests coordinate regulation, and they may offer complementary approaches to managing lipid flux during feast or famine.

Fibroblast growth factor 21 (FGF21) has recently emerged as a likely modulator of this coordinate regulation of adipokines. Although FGF21 is produced in adipose tissue at significant levels, it was first noted for its abundant production in liver (Nishimura *et al.*, 2000), where fasting or ketogenic diets drive its production in a peroxisome proliferator-activated receptor α (PPAR α)-dependent manner (Badman *et al.*, 2007; Inagaki *et al.*, 2007). The 21st member of this FGF superfamily was first reported by Nobuyuki Itoh at Kyoto University (Nishimura *et al.*, 2000) and has received exponential attention since the discovery of its antidiabetic properties in 2005 (Kharitonov *et al.*, 2005). This factor is also produced within the adipocyte in response to PPAR γ activation and appears to be a critical player in conveying nutritional cues through its adipose-specific actions (Adams *et al.*, 2012; Ding *et al.*, 2012). Notably, both FGF21 (Dutchak *et al.*, 2012; Lin *et al.*, 2013) and adiponectin (Kubota *et al.*, 2006; Nawrocki *et al.*, 2006) appear to play important and intertwining roles in mediating the antidiabetic effects of PPAR γ agonists. While adiponectin and FGF21 appear to be key players in the antidiabetic effects of PPAR γ agonist, improvements in glucose homeostasis can occur independently of these secreted factors, especially in the presence of suprapharmacological doses of thiazolidine diones (TZDs).

A series of recent reports has established FGF21 as a critical regulator of circulating leptin and adiponectin (Coskun *et al.*, 2008; Adams *et al.*, 2012; Ding *et al.*, 2012). FGF21 rapidly promotes adiponectin secretion (Holland *et al.*, 2013; Lin *et al.*, 2013) and diminishes circulating leptin (Coskun *et al.*, 2008). By enhancing expression of leptin receptors, FGF21 may simultaneously enhance leptin sensitivity in tissues such as liver. Notably, these studies have determined a critical role for leptin on FGF21-induced weight loss (Veniant *et al.*, 2012; Holland *et al.*, 2013), while adiponectin is important for the insulin-sensitizing and glucose-lowering properties of FGF21 (Holland *et al.*, 2013; Lin *et al.*, 2013). Consistent with adiponectin's effect as an antilipotoxic agent, FGF21 lowers ceramides in liver and serum in an adiponectin-dependent manner (Holland *et al.*, 2013).

OPPOSING LIPOTOXICITY

The foregoing facts suggest to the teleologist an interesting survival advantage provided by the evolution of these adipokines. The likely

reason for the evolution of adipocytes is that nonadipocyte cells in the system lack the lipid-storing capacity or tolerance to support their own caloric needs during times of limited nutrient availability. This implies that most of our highly specialized cells, such as pancreatic β cells and cardiomyocytes, have a relatively limited storage capacity for fuel or a relatively high sensitivity to lipotoxic molecules. If there were no endogenous fuel storage capability, even relatively brief periods of caloric limitation would be detrimental. Adipocytes not only solved the problem of storing calories in times of nutrient availability, but solved the problem of damage to lipid-intolerant tissues from either dietary fat during overnutrition or endogenous fatty acids discharged from adipocytes during lipolysis. This suggests that these remarkable lipid-storing cells, exquisite sensors of caloric balance, have arranged to protect vital tissues from accumulation of unutilized lipids, whether derived from food or from the cells' own lipid stores, by burning away the surplus or promoting the degradation of lipotoxic intermediates.

If lipid influx into a cell exceeds the oxidative or storage capacity of the cell, then lipotoxic lipid intermediates are likely to accumulate (Figure 1). On entry into the cell, lipids receive a CoA charge and are shunted into one of several competing pathways: 1) they can be oxidized in the mitochondria to produce energy equivalents; 2) they can be acylated onto a glycerol backbone to form diacylglycerols, can be stored as triglycerides, or can form membrane phospholipids; or 3) they can be acylated onto a serine backbone, giving rise to the sphingolipid ceramide and its complex derivatives. As each of these pathways competes for substrate, impairments in lipid oxidation promote the enhanced formation of glycerolipid and sphingolipid. While both diacylglycerols and ceramides from these pathways have been implicated in insulin resistance (Savage *et al.*, 2007; Holland and Summers, 2008), ceramide has additionally been invoked as a mediator of cell death, with most reports suggesting proapoptotic mechanisms at play with this intermediate. The unsurpassed storage capacity of adipocytes prevents excess fatty acids from forming lipotoxic intermediates in adipocytes, with excess lipids efficiently forming triglyceride-enriched lipid droplets.

Leptin has potent protective effects on cardiomyocytes. Loss-of-function experiments from leptin-deficient (Mazumder *et al.*, 2004) or leptin receptor-defective rodents show enhanced lipid accumulation and impaired contractile function. By engineering mice with cardiomyocyte-specific overexpression of acyl-CoA synthetase (ACS; Chiu *et al.*, 2001) or GPI-anchored lipoprotein lipase (GPI^{LPL}; Yagyu *et al.*, 2003), researchers have described independent models of lipid-induced heart failure. Both models accumulate aberrant ceramides and die prematurely of dilated cardiomyopathy (Chiu *et al.*, 2001; Park *et al.*, 2008). Pharmacologic inhibition of de novo ceramide synthesis using the fungal toxin myriocin prevents the lipid-induced cardiac hypertrophy and contractile dysfunction while extending lifespan in GPI^{LPL} transgenic mice (Park *et al.*, 2008). Similarly, overexpressing leptin in ACS transgenic mice diminishes lipid accumulation, prevents cardiac hypertrophy, and restores cardiac function (Lee *et al.*, 2004). Acute treatment of cultured cardiomyocytes with leptin indicates enhanced rates of lipid oxidation likely contribute to the protective mechanisms of the adipokine (Palanivel *et al.*, 2006), and leptin appears to require Janus kinase 2 (Jak2) and p38 mitogen-activated protein (MAP) kinase to induce lipid oxidation (Akasaka *et al.*, 2010).

Adiponectin also has potent cardioprotective effects. Walsh and colleagues have demonstrated in a series of publications that adiponectin ablation exacerbates pressure-overload hypertrophy and ischemia–reperfusion injury, while adenoviral overexpression prevents cardiomyocyte death via mechanisms involving AMPK and

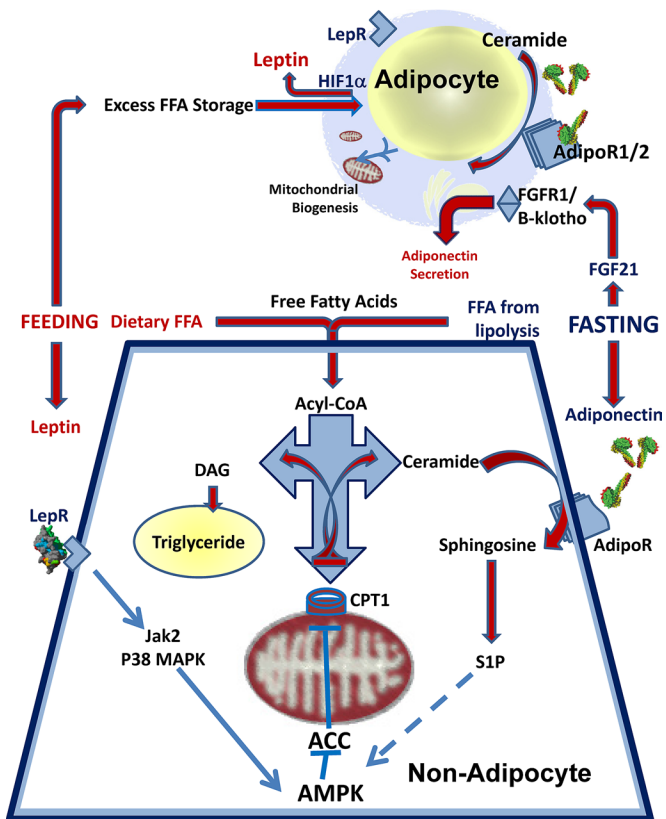


FIGURE 1: Schematic diagram of factors influencing ectopic lipotoxin accumulation. Mitochondrial lipid oxidation is gated by carnitine palmitoyltransferase 1 (CPT1) via acetyl-CoA carboxylase (ACC). When the abundance of CoA-charged lipids exceeds the capacity to oxidize them, lipids are forced into diacylglycerol or ceramide biosynthetic pathways. Leptin, excreted by adipocytes during feeding and driven by HIF1 α , promotes lipid oxidation in adipose and nonadipose tissues to alleviate lipid burden. Adiponectin, with enhanced secretion induced by FGF21 during fasting, directly targets ceramide degradation in target tissues. Adiponectin receptors facilitate the deacylation of ceramide into sphingosine to alleviate toxic effects of ceramide and may also promote lipid oxidation via S1P-induced activation of AMP kinase. Functional adipose tissue protects nonadipocytes from excess lipid by storing excess lipid, limiting lipolysis to times of need, and secreting protective adipokines. Leptin and adiponectin promote mitochondrial biogenesis in adipose, allowing adipose greater capacity to eliminate lipids through energy production.

cytochrome c oxidase subunit II (COX2) activation (Shibata *et al.*, 2004, 2005). Adiponectin-induced AMPK activation is associated with enhanced lipid oxidation and maintains cardiac output in isolated working-heart models (Fang *et al.*, 2010). During ischemic damage, ceramide is regenerated from sphingomyelin. This alternative source of ceramides offers a remarkable parallel between lipotoxic ceramide production (from de novo synthesis) and ischemic insults (ceramides are regenerated from the most abundant cellular sphingolipid—sphingomyelin). Recent work suggests that adiponectin promotes the deacylation of ceramide via a receptor-dependent mechanism, which represents the most upstream signal evoked by adiponectin (Holland *et al.*, 2011). This finding opened the door to the concept that adiponectin may directly oppose lipotoxicity by targeting the degradation of ceramide—the lipid metabolite most commonly implicated as a mediator of lipotoxic cell

death. Even on chow diets, ceramide accumulation is elevated in both the heart and the serum of adiponectin-null mice, while adiponectin-overexpressing transgenic mice display lower levels of the sphingolipid. In “Heart-ATTAC mice,” a model of inducible caspase-8-mediated cardiomyocyte apoptosis, the gene dosage of adiponectin strongly promotes survival of the cardiomyocytes in cell culture or live animals in vivo. Addition of endogenous or exogenous ceramide to cultured neonatal myocytes from these mice revealed a facilitative role for ceramide in promoting caspase-8-dependent apoptosis, as blocking de novo ceramide synthesis with myriocin protected both cardiomyocytes and Heart-ATTAC mice from death. The by-product of the ceramide degradation induced by adiponectin is a cytoprotective sphingolipid base termed sphingosine-1-phosphate (S1P), which is generated in a two-step reaction requiring ceramidase and sphingosine kinase. Delivery of S1P to cardiomyocytes or Heart-ATTAC mice offered essentially complete protection against death. Interestingly, this S1P-dependent protective mechanism evoked by adiponectin parallels previous work showing a reliance on sphingosine kinase-induced S1P formation for adiponectin to promote the COX-2 formation involved in cardiomyocyte protection (Ikeda *et al.*, 2008). Though unclear, protective mechanisms of S1P include activation of several kinases known to promote survival, including AMPK, protein kinase B (Akt), and extracellular signal-related kinase (ERK; Holland *et al.*, 2011).

Adiponectin and leptin both protect against β -cell failure. The Zucker diabetic fatty rat, with mutant alleles encoding the long form of the leptin receptor, develops spontaneous β -cell failure during progression to diabetes. Pancreata from these rats become triglyceride laden, and isolated islets display an enhanced propensity to shunt incoming lipids into sphingolipid synthetic pathways due to overexpression of serine palmitoyltransferase (which catalyzes the first and rate-limiting step in sphingolipid synthesis; Shimabukuro *et al.*, 1997, 1998). These lipid-overloaded islets subsequently die from sphingolipid-dependent lipoapoptosis. Similar lines of work by Poitout and colleagues have also implicated ceramide as an inhibitor of insulin expression in wild-type islets exposed to elevated lipid and glucose, resulting from enhanced ERK, Per-Arnt-Sim kinase, and impaired glucose-stimulated musculo aponeurotic fibrosarcoma oncogene homology A (MafA) expression, as well as nuclear exclusion of pancreatic and duodenal homeobox 1 (PDX-1; Hagman *et al.*, 2005; Fontes *et al.*, 2009). Thus sphingolipid accrual in islets can promote either lipotoxic destruction or a glucolipotoxic dysfunction involving impaired insulin transcription, depending on the predisposition of the islet. In leptin-defective rodents, adiponectin overexpression, restoration of leptin action, or targeted inhibition of ceramide synthesis prevents the onset of diabetes and maintains functional islet mass. Adiponectin and its resulting lipid by-product, S1P, potentially protect cultured INS-1 β cells from lipid/cytokine-evoked apoptosis by direct addition of ceramide analogues (Holland *et al.*, 2011). Notably, S1P is sufficient to promote AMPK activation in this cell type, while inhibiting ceramidase activity prevents adiponectin from activating AMPK. In vivo, Pan-ATTAC mice, which allow for inducible activation of caspase-8 and result in inducible apoptosis in the mature β cell, are much more susceptible to cell death in the absence of adiponectin and are protected by adiponectin overexpression. In summary, leptin and adiponectin help to maintain functional β -cell mass by diminishing sphingolipid accumulation.

Direct effects of leptin and adiponectin on white adipocytes themselves should not be overlooked when evaluating adipokine effects on ectopic lipid deposition. Leptin, adiponectin, and FGF21 all enhance mitochondrial proliferation in white adipose tissue and

whole-body energy expenditure associated with the lipid burning in beige adipocytes (Park *et al.*, 2006; Kim *et al.*, 2007; Fisher *et al.*, 2012). It has been shown in multiple models that adiponectin-mediated enhancements in adipose expansion are highly effective at limiting lipid spillover to other tissues and diminishing formation of lipotoxic metabolites in nonadipose tissues. Thus these adipokines also prevent lipid exposure to cardiomyocytes and β cells by making adipose a more effective storage organ with enhanced lipid-oxidative characteristics.

Could ectopic lipids be the real targets for adipokines? As summarized here, both leptin and adiponectin are capable of increasing fatty acid oxidation and of protecting cells from aberrant ceramide accumulation. This raises the possibility that these adipokines are an integral tool for the lipid-tolerant adipocytes to protect lipid-intolerant nonadipocytes from the lipotoxic consequences of fatty acid spillover. The fact that serum lipids rise as adipocytes expand in size and number as a consequence of overnutrition suggests that leptin's assigned role is the burning of fatty acid overflow, thereby blocking free fatty acid (FFA) entry into lipotoxic pathways, such as those resulting in ceramide formation or the generation of reactive oxygen species. We propose that, in addition to storage of surplus fuel, adipocytes offer nonadipose tissues additional protection against lipotoxicity by secreting a subset of adipokines with antilipotoxic functions. These in turn prompt excess unneeded exogenous or endogenous fatty acids to be oxidized before they can damage the cells in which they are less effectively stored. Thus adipocytes protect nonadipocytes from fatty acid-induced damage by oxidizing surplus lipids unable to be esterified to triglycerides. As such, the adipocyte delivers its toxic cargo (FFAs) along with the antidote (leptin, adiponectin, and FGF21, each made under specific physiological conditions) (Figure 1).

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