Role of malonyl-CoA in heart disease and the hypothalamic control of obesity

Clifford D.L. Folmes, Gary D. Lopaschuk *

Cardiovascular Research Group, University of Alberta, Edmonton, Alberta, Canada

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Abstract

Obesity is an important contributor to the risk of developing insulin resistance, diabetes, and heart disease. Alterations in tissue levels of malonyl-CoA have the potential to impact on the severity of a number of these disorders. This review will focus on the emerging role of malonyl-CoA as a key “metabolic effector” of both obesity and cardiac fatty acid oxidation. In addition to being a substrate for fatty acid biosynthesis, malonyl-CoA is a potent inhibitor of mitochondrial carnitine palmitoyltransferase (CPT) 1, a key enzyme involved in mitochondrial fatty acid uptake. A decrease in myocardial malonyl-CoA levels and an increase in CPT1 activity contribute to an increase in cardiac fatty acid oxidation. An increase in malonyl-CoA degradation due to increased malonyl-CoA decarboxylase (MCD) activity may be one mechanism responsible for this decrease in malonyl-CoA. Another mechanism involves the inhibition of acetyl-CoA carboxylase (ACC) synthesis of malonyl-CoA, due to AMP-activated protein kinase (AMPK) phosphorylation of ACC. Recent studies have demonstrated a role of malonyl-CoA in the hypothalamus as a regulator of food intake. Increases in hypothalamic malonyl-CoA and inhibition of CPT1 are associated with a decrease in food intake in mice and rats, while a decrease in hypothalamic malonyl-CoA increases food intake and weight gain. The exact mechanism(s) responsible for these effects of malonyl-CoA are not clear, but have been proposed to be due to an increase in the levels of long chain acyl CoA, which occurs as a result of malonyl-CoA inhibition of CPT1. Both hypothalamic and cardiac studies have demonstrated that control of malonyl-CoA levels has an important impact on obesity and heart disease. Targeting enzymes that control malonyl-CoA levels may be an important therapeutic approach to treating heart disease and obesity.

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1. Introduction

Diabetes mellitus is a major health concern, with the incidence growing at a rate of 6% annually [1]. A dramatic rise in the incidence and severity of obesity is a major reason for this rise in diabetes prevalence [1]. This increase in obesity and diabetes is disconcerting, since these conditions are associated with a high incidence of morbidity and mortality, with heart diseases being a major cause of death in diabetics [2–4]. The high risk for heart disease is due both to a high incidence of coronary artery disease and hypertension in the diabetic, as well as the development of cardiomyopathies that occur independent of these risk factors [5,6]. The prevalence of diastolic dysfunction even in young normotensive diabetic patients is also alarming high [7,8]. The exact cause for cardiac dysfunction during disease is not completely understood. One contributing factor is alteration in cardiac fatty acid metabolism, which contributes to abnormal cardiac function in the diabetic, as well as to the degree of muscle injury during and following myocardial ischemia.

Despite that fact that there are numerous contributing factors to the severity of obesity and abnormal cardiac fatty acid metabolism, of interest for this review is that alterations
in the control of tissue levels of malonyl-CoA has emerged as an important contributor to both obesity and heart disease. Malonyl-CoA has long been recognized as an important precursor of fatty acid biosynthesis in lipogenic tissues such as the liver and has an important role in regulating fatty acid oxidation in heart and skeletal muscle. Malonyl-CoA has also recently emerged as an important regulator of food intake and energy balance. This review will focus on the role of malonyl-CoA as a regulator of cardiac fatty acid oxidation and its role in regulating food intake and energy balance.

2. Regulation of cardiac energy metabolism by malonyl-CoA

Malonyl-CoA is a key regulator of fatty acid oxidation in the heart. It is a potent inhibitor of carnitine palmitoyltransferase (CPT1), a key enzyme involved in the mitochondrial uptake of fatty acids (Fig. 1). As a result, a rise in cardiac malonyl-CoA levels results in a decrease in mitochondrial fatty acid uptake and oxidation, while a decrease in malonyl-CoA results in an increase in fatty acid oxidation [9–16]. Because of these important metabolic effects, malonyl-CoA levels in the heart are highly regulated. Malonyl-CoA is synthesized by the carboxylation of acetyl-CoA by acetyl-CoA carboxylase (ACC) [9–12] and degraded to acetyl-CoA and carbon dioxide by malonyl-CoA decarboxylase (MCD) (Fig. 1) [13–16]. The synthesis and degradation of malonyl-CoA is important in the control of its steady state level, as its half-life is only 1.25 min [17].

ACC activity is dependent on the supply of its substrate, acetyl-CoA and its phosphorylation status at ser79 or ser219 for the ACC265 and ACC280 isoforms, respectively. Our laboratory has shown that in isolated working rat hearts, not only does ACC co-purify with the α2 catalytic subunit of AMP-activated protein kinase (AMPK), but AMPK can phosphorylate and inactivate both isoforms of ACC, resulting in an almost complete loss of activity [18,19]. Thus, an activation of AMPK results in a decrease in cytosolic malonyl-CoA concentrations and an acceleration of fatty acid oxidation (see Ref. [20] for a review).

MCD catalyzes the decarboxylation of malonyl-CoA, and thus has been proposed to play an important role in the regulation of myocardial fatty acid oxidation. Generally in situations where MCD activity is elevated, malonyl-CoA content is low, which results in elevated rates of fatty acid oxidation [9–16]. While MCD is found in many compartments, including mitochondria, peroxisomes and cytosol [21] it appears that MCD plays an important role in the regulation of cytoplasmic malonyl CoA levels, and therefore fatty acid oxidation, and patients with MCD deficiencies have phenotypes consistent with alterations in fatty acid oxidation [22,23].

2.1. Modulation of cardiac energy metabolism by malonyl-CoA

In order to meet the high energy demands of contraction and ionic homeostasis, the heart must produce a constant and abundant supply of ATP by metabolizing a variety of carbon substrates including carbohydrates (glucose, lactate, and pyruvate), fatty acids and ketone bodies [24,25]. Fatty acids are normally the primary energy substrate of the heart, and are supplied to the heart either as free fatty acids bound to albumin or as fatty acids within triacylglycerols (TG) present within chylomicrons or VLDL [26]. The amount of fatty acids utilized by the heart depends on a number of factors, including the supply of fatty acids to the heart and subcellular alterations in the control of fatty acid metabolism. For instance, an increase in plasma fatty acids, such as can occur in diabetes, increases the contribution of fatty acids to overall energy metabolism, with a reciprocal decrease in glycolysis and glucose oxidation in the heart. Malonyl-CoA control of mitochondrial uptake of fatty acids at the level of CPT1 is another key site of regulation [27,28]. The role of malonyl-CoA in controlling fatty acid oxidation in diabetic patients will be discussed later in this review. Also of relevance is the role of malonyl-CoA in controlling fatty acid oxidation during and following myocardial ischemia.

2.2. Regulation of cardiac fatty acid oxidation during ischemia and reperfusion

Inadequate supply of oxygen during myocardial ischemia results in a reduction in the oxidative metabolism of both carbohydrates and fatty acids, and an impairment of ATP production [25]. As glucose oxidation is inhibited, pyruvate normally metabolized in the mitochondria is converted to
lactate to preserve enough oxidized NAD$^+$ to sustain flux through glycolysis. This uncoupling of glycolysis from glucose oxidation is associated with an increase in cytosolic protons, resulting in intracellular acidosis [29–31].

When reperfusion of reversibly injured myocardium occurs, a rapid recovery of oxygen consumption and TCA cycle activity leads to a replenishment of the supply of ATP [30,32,33]. During this reperfusion period, fatty acids can provide over 90% of the myocardium’s energy requirement [33,34]. This excessive use of fatty acids is due, in part, to an increase in the levels of circulating fatty acids and to a decrease in the cytosolic malonyl-CoA levels. The decrease in malonyl-CoA is associated with an increase in mitochondrial fatty acid uptake and oxidation [11,32,33,35]. The reduction in malonyl-CoA is due to the ischemia-induced activation of AMPK [36]. AMPK can phosphorylate the heart isoform of ACC on Ser227, resulting in an inactivation of the enzyme [19]. As MCD activity is preserved during reperfusion, there is a reduction in malonyl-CoA levels, a stimulation of fatty acid oxidation and impairment in the recovery of glucose oxidation.

The net consequence of ischemic-induced decreases in malonyl-CoA levels is an increase in the contribution of fatty acid oxidation to overall mitochondrial oxidative metabolism, with a resultant decrease in glucose oxidation. The resultant uncoupling of glycolysis from glucose oxidation results in the production of protons that can lead to the accumulation of sodium and calcium [37]. This can lead to a decrease cardiac efficiency, as well as an increase cell injury and death. It should be noted, however, that not all studies have shown that fatty acid oxidation is accelerated during reperfusion following ischemia. Measurements of fatty acid oxidation in both regionally ischemic hearts [38], in isolated hearts [39,40] and patients [41] have shown that rates can either be unchanged or actually decreased. However, whether this occurred secondary to a decrease in contractile function is not clear. A study by Van de Velde et al. demonstrated in chronically instrumented dogs raising plasma fatty acid levels following LAD coronary artery occlusion could actually improve systolic wall thickening fraction compared to baseline and that this effect was blocked with oxefencine, a partial fatty acid oxidation blocker however direct measurement of fatty acid oxidation was not performed in this study. This observation is at odds with a large literature which suggests that inhibiting fatty acid oxidation, and hence stimulating glucose oxidation (by the Randle Cycle) is beneficial to the recovery of mechanical function following an ischemic bout (see Ref. [42] for review). This discrepancy may be accounted for by the time frame which the fatty acid levels are modified, as it is typically considered that the most critical time for reperfusion is the first few minutes, thus supplying the heart with more fatty acid 15 min following reperfusion would supply the heart with additional substrate.

Because of the negative consequences of a decrease in cardiac malonyl-CoA levels and increases in fatty acid oxidation during and following ischemia as well as the literature that suggests that partial inhibition of fatty acid oxidation is beneficial, a potential therapeutic approach to treating ischemia is to increase cardiac malonyl-CoA levels. One approach to doing this is to inhibit malonyl-CoA degradation at the level of MCD. Recently, potent MCD inhibitors (CBM-300864 and CBM-301940) have been developed and used to directly determine the role of malonyl-CoA in the metabolic modifications that occur during ischemia and reperfusion [13]. Addition of these inhibitors to aerobically perfused rat hearts resulted in a 7-fold increase in malonyl-CoA levels, which is associated with a partial inhibition of fatty acid oxidation, acceleration of glucose oxidation and maintained glycolytic rates [13]. As predicted based upon the above discussion, MCD inhibition was shown to be beneficial in a number of ischemia/reperfusion models. In isolated working rat hearts subjected to 30 min of global no-flow ischemia and 60 min of reperfusion, MCD inhibition significantly improved cardiac function, associated with a significant increase in glucose oxidation during reperfusion [13]. Post-ischemic cardiac function was improved whether the inhibitors were added prior to ischemia or at the beginning of reperfusion, suggesting that the majority of the benefit of MCD inhibition occurred during reperfusion. Inhibition of MCD also plays an important role during ischemia as observed in an in vivo porcine model of demand-induced ischemia.[13] In this model left anterior descending flow was decreased by 20% followed by a dobutamine stimulation of heart rate and contractility without a change in myocardial oxygen consumption. Inhibition of MCD resulted in a significant increase in malonyl-CoA levels, a doubling of glucose oxidation rates and a significant decrease in lactate production. As a result, cardiac function was improved in treated hearts. These observations were similar in an isolated working rat heart model of mild ischemia, where coronary flow was reduced by 35% of aerobic values for 30 min. Inhibition of MCD shifts residual oxidative metabolism from fatty acid oxidation to glucose oxidation, implying the importance of malonyl-CoA in substrate selection (unpublished data). This shift in oxidative metabolism improves the coupling of glucose metabolism and hence reduced the proton production in the inhibitor treated hearts.

Studies showing ischemic cardioprotection using MCD inhibitors have been confirmed using MCD null mice. If isolated working hearts from mice in which MCD is deleted are subjected to ischemia, a marked cardioprotection is observed [43]. Taken together, these studies suggest that MCD is an important regulator of cardiac fatty acid oxidation in the heart and that pharmacological inhibition of MCD may be beneficial in the treatment of ischemic heart disease. Despite the many studies looking at malonyl-CoA in acute ischemic heart disease; there is little knowledge about the role of malonyl-CoA in chronic ischemic heart disease, and the transition to heart failure.

2.3. Modulation of cardiac fatty acid metabolism in diabetes and obesity

In uncontrolled diabetics, myocardial glucose use is reduced and fatty acid oxidation accounts for most of the
catabolic myocardial oxygen consumption. This is due in part to a decrease in the number and transport of GLUT 4 to the sarcolemmal membrane. However, a major reason for the decrease in glucose metabolism is the elevated levels of plasma fatty acids seen in the diabetic. Use of fatty acids for mitochondrial oxidative metabolism decreases the activity of pyruvate dehydrogenase and phosphofructokinase 1, key enzymes in glucose oxidation and glycolysis, respectively. 

While high circulating levels of fatty acids in the diabetic decrease glucose metabolism, it is clear that other metabolic changes in the heart are also responsible for low rates of glucose metabolism. This is supported by the observation that glucose oxidation rates are significantly lower in diabetic rat hearts compared to control hearts, even if hearts are exposed to similar concentrations of fatty acids. Therefore, it is the combination of high levels of circulating fatty acids and direct alterations in insulin control of fatty acid and glucose oxidation that result in the diabetic heart becoming almost entirely dependent on fatty acid oxidation for its energy requirements. We have shown that AMPK activation in streptozotocin diabetic rat hearts is an important mechanism responsible for the increase in fatty acid oxidation rates. In addition during diabetes, an increased activity and expression of MCD contributes to the high rates of fatty acid oxidation.

Exposure of the heart to high levels of fatty acids also has the potential to result in the accumulation of fatty acids within the myocardium. This accumulation of lipids, has been termed “cardiac lipotoxicity.” Excessive accumulation of lipids within non-adipose tissue increases the intracellular pool of long chain fatty acyl CoA, thereby providing fatty acid substrate for non-oxidative processes, including triacylglycerol and diacylglycerol synthesis. This can lead to cell dysfunction, insulin-resistance and potentially cell death through apoptosis. The potential for lipotoxicity in obesity and insulin-resistance has also recently been described. A marked accumulation of triacylglycerol occurs within the myocardium of obese and insulin-resistant rats, which is associated with the development of contractile dysfunction. We have also shown that insulin-resistant rat hearts have elevated levels of triacylglycerol, which is associated with a decrease in glucose uptake and glycolysis. However, presently there is a confusion as to the relative importance of an increase in fatty acid supply versus a decrease in fatty acid oxidative capacity as the major contributor to lipotoxicity. Several studies have implicated a suppression of fatty oxidation as the contributing factor for the accumulation of triacylglycerol and overall lipotoxicity in obesity, insulin resistance and diabetes. In obesity, Roger Unger’s group has implicated a downregulation of PPARα and an underexpression of fatty acid oxidative enzymes as contributing to lipotoxic heart disease. Several studies have implicated that an impairment of myocardial fatty acid oxidation during obesity, insulin-resistance and diabetes may also accelerate contractile dysfunction, due in part to a decrease in PPARα responsiveness. In support of this, Oakes et al. showed using in vivo tracers methods that the average level of cardiac fatty acid oxidation is comparable in ob/ob mice and normal animals. Using 123I-heptadecanoic acid Turpeinen et al. observed that patients with non-insulin dependent diabetes had lowered fatty acid uptake and oxidation, while patients with insulin-dependent diabetes has similar fatty acid kinetics to normal subjects. However recent experimental and clinical studies have shown that fatty acid oxidation is increased in obesity and insulin-resistance. Using positron emission tomography (PET) and 11C-palmitate imaging, elegant studies by Linda Peterson and Robert Gropler have shown that obese women and type 2 diabetics have an increased uptake and oxidation of fatty acids. Studies using isolated working hearts from obese insulin resistant ob/ob and db/db mice have shown that fatty acid oxidation rates are also elevated. This increase in fatty acid oxidation is paralleled by a decrease in glucose oxidation and glycolysis, as well as a decrease in cardiac efficiency. These recent studies in mice, parallel studies we performed in obese insulin-resistant JCR/LA rats, in which an increase in fatty acid oxidation contribution to energy production was observed. We have also shown that in mice fed a high fat diet, fatty acid oxidation rates increase in the heart. This is associated with a decrease in insulin-sensitive glucose oxidation. In these high fat fed mice, a significant decrease in cardiac malonyl-CoA levels is observed, which appears to be related to an increase in MCD expression (unpublished data).

Combined, studies to date suggest that there is controversy over whether cardiac fatty acid oxidation rates are increased, or decreased, in obesity, insulin-resistance and type 2 diabetes. Data does suggest, however, that a decrease in malonyl-CoA control of fatty acid oxidation contributes to the observed high fatty acid oxidation rates.

2.4. Ischemic tolerance of the diabetic heart

Epidemiological data and clinical studies have convincingly demonstrated that diabetic patients have increased susceptibility to ischemic injury, as diabetics have increased incidence of atherosclerosis but there are additional important nonvascular components. For example, complications of acute myocardial infarction are greater in the diabetic despite having the same size or even smaller infarcts. Despite this evidence there has been less consensus in experimental studies as to whether changes in the diabetic heart can modify the severity of ischemic damage. In vitro studies in diabetic rat hearts have shown that when subjected to anoxia or low flow ischemia, these hearts are more sensitive to ischemic injury when compared to control hearts. In contrast, a number of studies have shown that diabetic rat hearts will recover to the same degree or even better when subjected to a severe degree of ischemia (no-flow or very low flow). Other studies have shown that diabetic rat hearts can have suppressed function following severe ischemia. It appears that the increased sensitivity...
of the diabetic heart during hypoxia or mild ischemia is due to a decrease in glucose uptake and metabolism, while the diabetic heart is less sensitive to severe ischemia due to a decrease in the accumulation of glycolytic byproducts and changes in the control of intracellular pH (see Refs. [82,83] for reviews).

3. Regulation of food intake and obesity by hypothalamic malonyl-CoA

3.1. Metabolic signaling in the hypothalamic control of energy balance in obesity and insulin-resistance

Hypothalamic control of energy balance plays a central role in the development of obesity [84–86]. This has resulted in a major research effort to understand how hypothalamic neuronal signaling controls both food intake and peripheral energy expenditure (see Refs. [84–86] for reviews). The involvement of anorexigenic and orexigenic signaling pathways in the arcuate nucleus (AN) and paraventricular nucleus (PVN) of the hypothalamus have been well defined. The involvement of several anoxerigenic hormones (leptin, adiponectin, insulin, glucagon-like peptide 1 (GLP-1), glucose, fatty acids, lactate, pyruvate, amino acids, histamine, melanocyte stimulating hormone, and α-lipoic acid) and oxerigenic hormones on these pathways have also been shown (ghrelin, cannabinoids) [86–91]. These diverse and complex signals converge on neurons in the AN, including neuropeptide Y (NPY)/agouti-related protein (AGRP) neurons and proopiomelanocortin (POMC)/cocaine-ampthetamine-related transcript (CART) neurons [86,91].

The hypothalamus not only plays an important role in regulating food intake, but also an important function in central control of peripheral energy expenditure, body fat content, and hepatic glucose production. For example, insulin can act at the level of the hypothalamus to decrease hepatic glucose production [86,92,93]. Glucose sensing neurons in the hypothalamus can also detect hypoglycemia and result in an increase in hepatic glucose production. It is also apparent that a number of anoxerigenic peptides and substances, such as leptin, adiponectin and α-lipoic acid can increase peripheral energy expenditure [93–95]. This involves CNS sympathetic neuronal control of muscle, liver and adipose tissue function, as well as central mediated alterations in muscle metabolic enzymes (i.e. such as mitochondrial uncoupling proteins in muscle) [93–95].

3.2. Regulation of energy balance by hypothalamic AMPK

Recently, it has become evident that enzymes and metabolites that have important roles in regulating muscle energy metabolism, may also have an important function in controlling hypothalamic function. For instance, the well established anorexigenic effects of leptin have recently been shown by a number of groups to involve inhibition of hypothalamic AMPK, while the orexigenic actions of ghrelin are accompanied by activation of hypothalamic AMPK (Fig. 2) [91,94,96–98]. In support of this, icv injection of either AMPK agonists or adenovirus containing constitutively active AMPK in mice promotes food intake [91,97,98]. In addition, the orexigenic actions of endocannabinoids such as Δ⁹-tetrahydrocannabinol have recently been shown to be accompanied by an increase in hypothalamic AMPK activity (Fig. 2) [99]. It has been proposed that decreased AMPK activity enhances the suppression of AN NPY/AGRP signaling neurons, resulting in an enhancement of melanocortin receptor (MC4R) inhibition of AMPK in the PVN [91]. The mechanism by which AMPK achieves this is not clear, but one possibility is via inhibition of acetyl-CoA carboxylase (ACC), resulting in a decrease in hypothalamic malonyl-CoA. The role of hypothalamic AMPK in regulating food intake fits with the concept of AMPK being a “fuel gauge”, with activation of AMPK in times of metabolic stress promoting food intake.

Nutrient sensing in food intake regulation may also involve AMPK. Nutrients such as glucose, amino acids, fatty acids, and pyruvate can signal the hypothalamus to decrease food intake [100,101]. This involves complex signaling pathways involving NPY/AGRP and POMC/CART neurons in the AN. A recent study by Lee et al. [101] showed that inhibition of hypothalamic glucose utilization with 2-deoxyglucose results in an activation of AMPK, while administration of pyruvate decreases AMPK activity. These authors proposed that low α-lipoic acid have also been shown to inhibit hypothalamic AMPK, while the orexigenic actions of ghrelin are accompanied by activation of hypothalamic AMPK (Fig. 2) [91,94,96–98].
neuronal cell ATP levels can trigger a cascade of events via AMPK-mediated events to increase food intake. Low hypothalamic ATP also negatively correlates with the expression of AGRP. As a result, hypothalamic neuronal cell energy status may activate AMPK, which then modulates NPY and AGRP expression and subsequent food intake.

AMPK may also be involved in hypothalamic control of peripheral glucose metabolism. The ventromedial hypothalamus (VMH) appears to play a critical role in hypoglycemia sensing [98,100,101]. Specialized glucose-sensing neurons that can be stimulated by glucose have been localized to the VMH. A role of hypothalamic AMPK in hypoglycemia sensing has recently been proposed by McCrimmon et al. [98].

Insulin and insulin-signaling pathways also have a central role in hypothalamic mediated regulation of energy balance [86]. Insulin functions as a “catabolic adiposity negative feedback signal” to provide a central signal to mediate food intake. Insulin administration via the icv route reduces food intake and decreases hepatic glucose production [102]. This involves the insulin signaling pathway that acts through phosphatidylinositol 3-kinase (PI3K) to modify the JAK/STAT signaling pathway, and involves the release of melanocyte-stimulating hormone, increases in POMC expression, and activation of downstream melanocyte “target” neurons [103]. The role of insulin in regulating food intake is supported by studies showing that downregulation of hypothalamic insulin receptors in rats [93] or insulin receptor substrate 2 in mice [92] causes hyperphagia and insulin resistance. Although not previously examined in hypothalamic insulin receptors in rats [93] or insulin receptor substrate 2 in mice [92]

3.3. Regulation of energy balance by hypothalamic malonyl-CoA

Alterations in hypothalamic malonyl-CoA have also recently been implicated in the control of food intake. Inhibition of hypothalamic fatty acid synthase (FAS) increases malonyl-CoA levels and decreases food intake in mice [96,110–116]. Fasting also decreases hypothalamic malonyl-CoA, supporting the important role of malonyl-CoA in controlling food intake.

Support for a role of malonyl-CoA in the control of food intake also arises from studies examining the hypothalamic localization of FAS. FAS is expressed in a number of brain regions, including the AN and PVH [111]. Kim et al. also showed that FAS is co-localized with NPY in neurons of the AN [111]. Treatment of mice with the FAS inhibitor, C75, decreased NPY immunoreactivity in the axon terminals that innervate the PVH and the lateral hypothalamus. It was concluded that increasing malonyl-CoA levels may alter food intake via interactions within the AN-PVN pathway mediated by NPY.

Recent studies by Luciano Rossetti’s group have provided a potential mechanism by which hypothalamic malonyl-CoA may play a central role in nutrient sensing of food intake [117–119]. At the level of the hypothalamus, both glucose and fatty acids decrease food intake, decrease hepatic glucose production, and increase peripheral energy expenditure [117–119]. Glucose, pyruvate, or lactate can increase the supply of acetyl-CoA for ACC malonyl-CoA synthesis, which then results in a malonyl-CoA-induced inhibition of hypothalamic CPT1, thereby increasing long chain acyl CoA (LCAC) levels. Increased fatty levels will also increase hypothalamic LCAC [87,119]. The increase in LCAC then activates K\textsubscript{ATP} channels, resulting in neuronal stimulation that modifies food intake, peripheral energy expenditure and hepatic glucose production (see Ref. [118] for review).

Since alterations in hypothalamic AMPK can modulate energy balance, it is possible that these effects of AMPK may involve alterations in malonyl-CoA. However, this has yet to be established. The study by Minokoshi et al. demonstrating hypothalamic AMPK inhibition by icv injection of leptin proposed that leptin inhibition of AMPK was “consistent with increased hypothalamic malonyl-CoA levels” [91] (Fig. 3). Andersson et al. showed that leptin inhibition of hypothalamic AMPK was accompanied by a decrease in ACC phosphorylation, which normally increases ACC activity [97]. Ghrelin activation of AMPK is accompanied by an increase in ACC phosphorylation.

To date, studies on modulation of hypothalamic malonyl-CoA have concentrated on modifying FAS activity, which uses malonyl-CoA for fatty acid biosynthesis. However, another potential fate of malonyl-CoA is via decarboxylation to acetyl-CoA by MCD. The identification of hypothalamic malonyl-CoA as a mediator of food intake raises the intriguing possibility that the hypothalamus also contains MCD activity that could degrade malonyl-CoA. The hypothalamus does contain MCD activity. In support of this, Kim et al. recently performed RNA in situ hybridization and localization studies in mice hypothalamus, and showed that MCD in the hypothalamus co-localized with FAS and NPY [111]. ACC was also found to co-localize with FAS and NPY [111]. Colocalization of FAS and NPY also occurs in human hypothalamus [111]. This raises the intriguing possibility that hypothalamic MCD, which regulates malonyl-CoA levels, may also regulate energy balance. In support of this, increasing MCD expression in the arcuate nucleus (using adenoviral delivered MCD) results in an increase food intake and weight gain in mice and rats, and prevented leptin-induced inhibition of food intake [120]. This effect of MCD expression was accompanied by a decrease in hypothalamic long chain acyl CoA in rat hypothalamus, which would be expected if malonyl-CoA inhibition was prevented.

3.4. Mechanisms by which malonyl-CoA regulates food intake

Despite compelling evidence that increases in hypothalamic malonyl-CoA decrease food intake and body weight, the mechanism by which this occurs has not been
established. It is likely that malonyl-CoA inhibition of CPT1 is also involved in the malonyl-CoA regulation of food intake in the hypothalamus. Obici and Rossetti have shown that CPT1 inhibition can decrease food intake [121].

Although the mechanism by which hypothalamic malonyl-CoA mediates food intake and peripheral glucose production has not been definitely established, compelling evidence has now been obtained to suggest that malonyl-CoA has an important role in mediating food intake. We also suggest that the actions of AMPK on food intake are also linked to alterations in hypothalamic malonyl-CoA.

3.5. Hypothalamic effects on peripheral energy expenditure

While hormones and metabolites such as leptin, adiponectin, insulin, and glucose have hypothalamic effects on food intake, they can also have central mediated peripheral actions, including central mediated effects on hepatic glucose production [84–86]. These hormones and metabolites also have central actions on peripheral energy metabolism. For instance, the decrease in body weight seen with hypothalamic administration of leptin is due both to a decrease in food intake and an increase in peripheral energy expenditure. While adiponectin and leptin share a number of common hypothalamic signaling pathways (such as the melanocortin pathway), the effect of adiponectin on decreasing body weight appears to be primarily due to an increase in peripheral energy expenditure [91,97], as opposed to a decrease in food intake [95].

The hypothalamic effects of α-lipoic acid, which inhibits AMPK, also appears to be mediated by an increase in peripheral energy expenditure [94]. A possible explanation for these effects may involve a central mediated effect of malonyl-CoA on peripheral muscle fatty acid oxidation and energy expenditure. Inhibiting hypothalamic fatty acid synthase (with C75) in mice is associated with an increase in skeletal muscle fatty acid oxidation, a decrease in malonyl-CoA, and an increase in UCP3 and PGC-1 [122].

Daniel Lane has proposed a “malonyl-CoA signal” from brain to skeletal muscle that is linked via the sympathetic nervous system.

4. Conclusions

Malonyl-CoA is a major regulator of fatty acid oxidation in the myocardium and plays a major role in the cardiovascular pathologies of ischemic heart disease and diabetic cardiomyopathy. Indeed inhibition of fatty acid oxidation using MCD inhibitors has proven to be beneficial during myocardial ischemia and reperfusion. In addition, malonyl-CoA has also recently been implicated in playing a role in the hypothalamus controlling feeding and peripheral energy expenditure, suggesting that it may also play an important role in the development of obesity, insulin resistance and the metabolic syndrome.

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