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Targeting Intermediary Metabolism in the Hypothalamus as a Mechanism to Regulate Appetite

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Abstract——**The central nervous system mediates energy balance (energy intake and energy expenditure) in the body; the hypothalamus has a key role in this process. Recent evidence has demonstrated an important role for hypothalamic malonyl CoA in mediating energy balance. Malonyl CoA is generated by the carboxylation of acetyl CoA by acetyl CoA carboxylase and is then either incorporated into long-chain fatty acids by fatty acid synthase, or converted back to acetyl-CoA by malonyl CoA decarboxylase. Increased hypothalamic malonyl CoA is an indicator of energy surplus, resulting in a decrease in food intake and an increase in energy expenditure. In contrast, a decrease in hypothalamic malonyl CoA signals an energy deficit, resulting in an increased appetite and a decrease in body energy expenditure. A number of hormonal and neural orexigenic and anorexigenic signaling pathways have now been shown to be associated with changes in malonyl CoA levels in the arcuate nucleus (ARC) of the hypothalamus. Despite compelling evidence that malonyl CoA is an important mediator in the hypothalamic ARC control of food intake and regulation of energy balance, the mechanism(s) by which this occurs has not been established. Malonyl CoA inhibits carnitine palmitoyltransferase-1 (CPT-1), and it has been proposed that the substrate of CPT-1, long-chain acyl CoA(s), may act as a mediator(s) of appetite and energy balance. However, recent evidence has challenged the role of long-chain acyl CoA(s) in this process, as well as the involvement of CPT-1 in hypothalamic malonyl CoA signaling. A better understanding of how malonyl CoA regulates energy balance should provide novel approaches to targeting intermediary metabolism in the hypothalamus as a mechanism to control appetite and body weight. Here, we review the data supporting an important role for malonyl CoA in mediating hypothalamic control of energy balance, and recent evidence suggesting that targeting malonyl CoA synthesis or degradation may be a novel approach to favorably modify appetite and weight gain.**

I. Introduction

Obesity is a major health problem and is reaching epidemic proportions in both developed and developing countries. Of concern is that obesity is a major cause of insulin resistance and diabetes (Zimmet et al., 2001). In particular, the incidence of diabetes itself is growing at a rate of 6% annually (Partamian and Bradley, 1965; Kopelman and Hitman, 1998; Kopelman, 2000). This is disconcerting because diabetes is associated with a high incidence of complications, including heart disease and stroke (Kannel and McGee, 1979; Gwilt et al., 1985; Ulvenstam et al., 1985; Ingelsson et al., 2005).

Obesity results from an imbalance between energy intake and energy expenditure. The brain is an integral regulator of energy intake and energy expenditure, and thus whole-body energy homeostasis. The hypothalamus is important to the central regulation of energy homeostasis, in particular the arcuate nucleus (ARC[1]), which is involved in integrating peripheral satiety and adiposity signals via orexigenic and anorexigenic neu-

[1]Abbreviations: ACC, acetyl CoA carboxylase; AdipoR, adiponectin receptor; AgRP, agouti-related peptide; AM251, *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophen yl)-4-methyl-1*H*-pyrazole-3-carboxamide; AMPK, 5′AMP-activated protein kinase; ARC, arcuate nucleus; BBB, blood-brain barrier; CamKK2, Ca^{2+}/calmodulin dependent protein kinase kinase 2; CART, cocaine- and amphetamine-regulated transcript; CB, cannabinoid receptor; CNS, central nervous system; CP55940, (−)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-*trans*-4-(3-hydroxypropyl)cyclohexanol; CPT, carnitine palmitoyl transferase; FAS, fatty acid synthase; GHSR, growth hormone secretagogue receptor; GLP-1, glucagon-like peptide-1; GLUT, glucose transporter; MBH, mediobasal hypothalamus; MC, melanocortin; MCD, malonyl CoA decarboxylase; MEP, methyl 2-tetradecylglycidate/methyl palmoxirate; MSH, melanotropin; mTOR, mammalian target of rapamycin; NPY, neuropeptide Y; PI3K, phosphatidylinositol 3-kinase; POMC, proopiomelanocortin; PPAR, peroxisome proliferator activated receptor; PVN,

ropeptide transmission to other hypothalamic and extrahypothalamic brain regions (Schwartz et al., 2000). A complex signaling system exists that integrates hormonal, energy substrate, and neuronal cues to mediate energy homeostasis. It is interesting that the ARC expresses a number of enzymes involved in fatty acid metabolism, despite the fact that fatty acids are not a major fuel source for this tissue. Rather, over the past few years, it has become evident that modulating the activities of these fatty acid metabolic enzymes in the hypothalamus has a significant impact on the regulation of energy balance (Wisse et al., 2007). In the hypothalamus, malonyl CoA (a critical intermediate in fatty acid metabolism) has emerged as an important contributor to the control of food intake and energy expenditure (Loftus et al., 2000; Gao and Lane, 2003). Malonyl CoA is generated by the carboxylation of acetyl CoA by acetyl CoA carboxylase (ACC) and is then either incorporated into long-chain fatty acids by fatty acid synthase (FAS) or converted back to acetyl CoA by malonyl CoA decarboxylase (MCD) (Gao and Lane, 2003; Lane et al., 2005, 2008). It is interesting that pharmacological inhibition of hypothalamic FAS (e.g., by the compound C75, a potent FAS inhibitor) inhibits food intake, increases energy expenditure, and reduces body weight with preferential reduction of body fat in different rodent models (Loftus et al., 2000; López et al., 2006). Genetic deletion of FAS in the mediobasal hypothalamus (MBH) also induces inhibition of feeding and loss of body weight (Chakravarthy et al., 2007). The inhibition of FAS has been attributed to an increase of malonyl CoA levels in the hypothalamus (Hu et al., 2003), which subsequently is linked to an increase of fatty acid oxidation rates in skeletal muscle (Cha et al., 2005, 2006). Further support for a key role of malonyl CoA in regulating energy balance can be found in experiments in which MCD is modified. Overexpression of MCD in the ARC (which presumably lowers malonyl CoA levels in the ARC) has been demonstrated to increase food intake and body weight (Hu et al., 2005; He et al., 2006). Leptin, an anorexigenic hormone secreted from adipocytes, can increase malonyl CoA levels in the ARC by activating ACC (Gao et al., 2007b). Recent evidence suggests that this up-regulation of malonyl CoA in the ARC mediates the anorectic signaling actions of leptin (Gao et al., 2007b).

The ARC represents a primary and essential nucleus in the hypothalamus, in that it integrates hormonal and nutritional signals to mediate the control of food intake and the regulation of body energy balance (Elmquist et al., 1998; Schwartz et al., 2000). The ARC is a center where hormonal signals (such as leptin, insulin, adiponectin, and ghrelin), as well as nutritional signals (such as circulating glucose and fatty acids) converge (see section II). In the ARC, these complex and diverse signals are further integrated by neuropeptides including orexigenic neuropeptides, such as neuropeptide Y (NPY) and agouti-related peptide (AgRP), and anorexigenic neuropeptides, such as proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) (see section II). It is interesting that increases in hypothalamic malonyl CoA levels are linked to down-regulation of NPY/AgRP and up-regulation of POMC/CART and vice versa (Loftus et al., 2000; Kumar et al., 2002; Gao and Lane, 2003; Dowell et al., 2005; Lane et al., 2005; He et al., 2006; Gao et al., 2007b).

Based on emerging evidence that malonyl CoA is a key intracellular metabolite controlling whole-body energy balance, it is important to gain a better understanding of how hypothalamic malonyl CoA levels are regulated. In addition to FAS activity, the role of AMP-activated protein kinase (AMPK) and MCD in controlling hypothalamic malonyl CoA levels has recently generated considerable research interest. Hypothalamic AMPK has been proposed to be a "master switch" in the control of food intake and body weight, with activation of AMPK at the level of the ARC promoting food intake and increasing body weight, whereas inhibition of AMPK in the ARC suppresses food intake and reduces body weight (Minokoshi et al., 2004; Kahn et al., 2005). As will be discussed, a number of hormonal and energy substrate pathways may act through hypothalamic AMPK signaling (Minokoshi et al., 2004; Kola et al., 2005; Kubota et al., 2007). A role for AMPK signaling through modification of malonyl CoA synthesis will also be discussed. In addition, the important role of the downstream metabolism of malonyl CoA via MCD or FAS in mediating the hypothalamic control of food intake and body energy balance will be discussed.

II. Hypothalamic Metabolism and the Regulation of Appetite

A. Hormonal Regulation of Hypothalamic Appetite Control

A number of different hormones exert dramatic effects on energy homeostasis via interaction with hypothalamic receptors. Many of the orexigenic or anorexigenic effects of these hormones may involve alterations in metabolic processes in the hypothalamus. This eventually affects the activity of different neuronal pathways within the hypothalamus. The two primary neuronal populations of the ARC that are implicated in the regulation of energy homeostasis are the NPY/AgRP-expressing neurons and the POMC/CART-expressing neu-

paraventricular nucleus; Ro27-3225, *N*-(1-oxobutyl)-L-histidyl-L-phenylalanyl-L-arginyl-L-tryptophyl-*N*2-methyl-glycinamide; Ro27-4680, *N*-(1-oxobutyl)-L-histidyl-3-(2-naphthalenyl)-D-alanyl-L-arginyl-L-tryptophyl-*N*2-methyl-glycinamide; SR144528, *N*-[(1*S*)-endo-1,3,3-trimethyl bicycle[2.2.1]heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide; STAT, signal transducer and activator of transcription; TCA, tricarboxylic acid; THC, Δ^9-tetrahydrocannabinol; VMH, ventromedial hypothalamus; VMN, ventromedial nucleus; WAT, white adipose tissue; WT, wild type; WY 13643, [4-chloro-6-[(2,3-dimethylphenyl)amino]-2-pyrimidinyl] thio/pirinixic acid.

rons (Chronwall et al., 1985; Broberger et al., 1998a,b; Hahn et al., 1998; Stanley et al., 2005; Coll et al., 2007, 2008). These ARC neuronal populations form complex neural circuits with second-order neurons located in other hypothalamic nuclei, including the paraventricular nucleus (PVN), the lateral hypothalamic area/prefornical area, the dorsomedial hypothalamus, and the ventromedial hypothalamus (VMH), as well as extrahypothalamic brain regions, including the nucleus tractus solitarius of the brain stem, that participate in the central regulation of energy homeostasis (Fig. 1).

1. Arcuate Nucleus Orexigenic Neuropeptide Y/Agouti-Related Peptide Neurons. The ARC contains the majority of hypothalamic NPY-expressing neurons (Chronwall et al., 1985), the majority of which also coexpress AgRP (Broberger et al., 1998a,b; Hahn et al., 1998). This population of neurons expresses receptors for various circulating satiety factors, and the activation of these neurons promotes positive energy balance/decreased energy expenditure and/or increased food intake (Stanley et al., 2005; Coll et al., 2007, 2008).

NPY is one of the most abundant neuropeptides in the brain (Allen et al., 1983), and although it has diverse functions, it is recognized as one of the most potent orexigenic molecules known. NPY signals via a diverse class of G-protein-coupled receptor subtypes, designated Y1, Y2, Y4, Y5, and Y6 (for review, see Lindner et al. (2008). Levels of hypothalamic NPY are indicative of nutritional status; NPY mRNA content and NPY release increase during fasting and decrease after refeeding (Sanacora et al., 1990; Swart et al., 2001, 2002). Furthermore, increased NPY levels precede hyperphagia (Brady et al., 1990; Sahu et al., 1997; Tiesjema et al., 2007, 2009). Direct pharmacological evidence of the orexigenic effects of NPY are provided by studies demonstrating that its intracerebroventricular administration (Clark et al., 1984; Levine and Morley, 1984; Semjonous et al., 2009) or its direct administration into

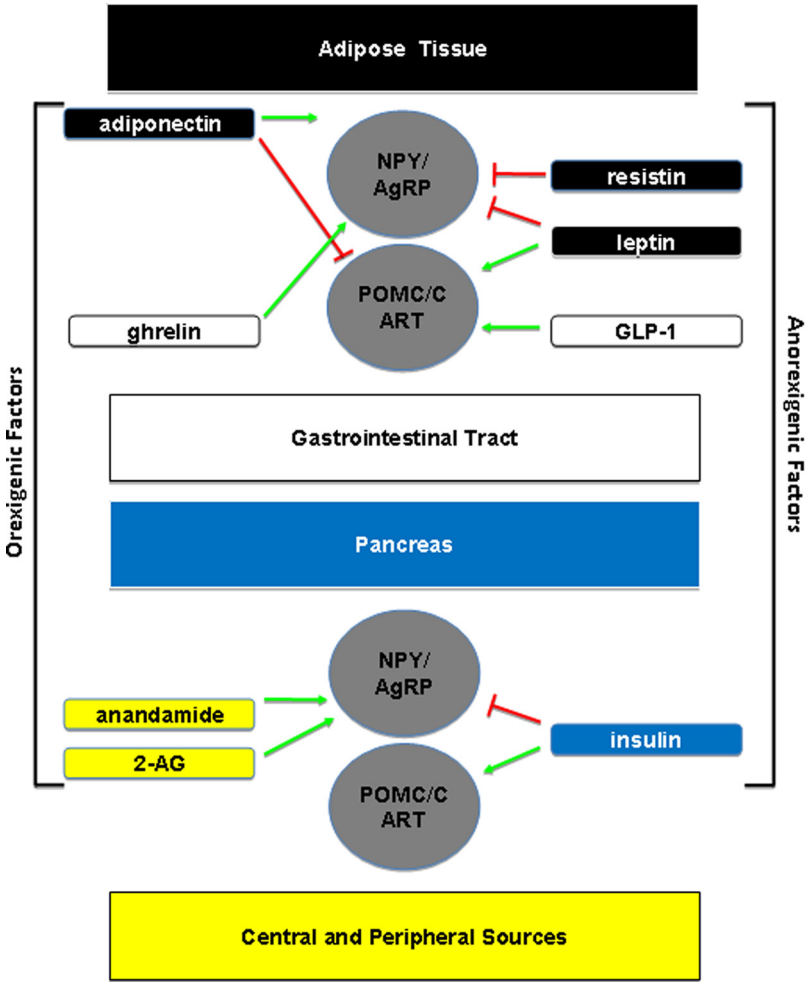

FIG. 1. Schematic representation of factors influencing hypothalamic NPY/AgRP and POMC/CART neurons to modify the central regulation of energy homeostasis. NPY/AgRP and POMC/CART neurons in the arcuate nucleus of the hypothalamus integrate various signals derived from adipose tissue (black symbols), the gastrointestinal tract (white symbols), pancreas (blue symbols), as well as other peripheral and central sources (yellow symbols) to modify energy homeostasis. Orexigenic factors that increase energy intake and/or decrease energy expenditure are presented on the left portion of the figure. Anorexigenic factors that decrease energy intake and/or increase energy expenditure are presented on the right portion of the figure. Inputs depicted in green represent stimulatory effects on the secretion and or expression of NPY, AgRP, POMC, and CART, whereas inputs depicted in red represent inhibitory effects on the secretion and or expression of NPY, AgRP, POMC, and CART as described in the text. 2-AG, 2-arachadonylglycerol.

specific hypothalamic nuclei (Stanley et al., 1993) increases food intake, whereas the administration of receptor-selective antagonists (Y1 and Y5 antagonists) (Mashiko et al., 2007), antisense oligonucleotides (Y5 receptor) (Schaffhauser et al., 1997), and receptor knockout (Y1- and Y5-receptor knockout) (Marsh et al., 1998; Kanatani et al., 2000) attenuates the feeding response elicited by NPY.

In contrast to NPY, which is widely expressed in the CNS, AgRP is expressed only in ARC of the hypothalamus and is cosecreted with NPY (Broberger et al., 1998a,b; Hahn et al., 1998). AgRP is an endogenous antagonist (Ollmann et al., 1997) and inverse agonist (Nijenhuis et al., 2001; Chai et al., 2003; Breit et al., 2006; Tolle and Low, 2008) of receptors in the melanocortin (MC) system (i.e., MC3 and MC4 receptors) (see below). Similar to NPY, the expression of AgRP is upregulated in response to fasting (Kaelin et al., 2004; Fekete et al., 2006; Palou et al., 2009). Furthermore, the central administration of AgRP or a C-terminal AgRP fragment causes prolonged increases in food intake in both MC system-independent and -dependent manners, resulting in obesity (Rossi et al., 1998; Hagan et al., 2000), The importance of AgRP in orexigenic signaling is also demonstrated in genetic models of AgRP deficiency induced via the selective death of AgRP neurons (i.e., NPY/AgRP neurons); prominent effects include reduced food intake, weight loss, and a reduction in body fat (Bewick et al., 2005; Gropp et al., 2005; Luquet et al., 2005; Wortley et al., 2005; Xu et al., 2005). Elevated circulating levels of AgRP and polymorphisms of the human *AgRP* gene have also been documented in human obesity (Katsuki et al., 2001; Argyropoulos et al., 2002).

2. Arcuate Nucleus Anorexigenic Proopiomelanocortin and Cocaine- and Amphetamine-Regulated Transcript Neurons. A subset of neurons in the ARC express POMC and colocalize with approximately 90% of neurons expressing CART (Elias et al., 1998; Kristensen et al., 1998; Valassi et al., 2008). Similar to orexigenic NPY/AgRP neurons, POMC/CART neurons are also responsive to circulating satiety factors, and the activation of this population of neurons promotes negative energy balance/increased energy expenditure and/or decreased food intake.

POMC is the polypeptide precursor of the melanocortin family, including adrenocorticotropin and α-, β-, and γ-melanotropin (MSH). Hypothalamic POMC mRNA expression is regulated by nutritional status; levels are low during fasting and increase after refeeding (Swart et al., 2002; Germano et al., 2007). α-MSH represents the primary melanocortin involved in the regulation of energy balance because it is the primary endogenous ligand/agonist of hypothalamic MC3R and MC4R (Mountjoy et al., 1994; Mountjoy and Wong, 1997; Harrold et al., 1999). The central administration of the selective MC4R agonist *N*-(1-oxobutyl)-L-histidyl-L-phenylalanyl-L-arginyl-L-tryptophyl-*N*2-methyl-glycinamide (Ro27-3225) suppresses food intake (Benoit et al., 2000). In contrast, the central administration of the selective MC4R antagonist, *N*-(1-oxobutyl)-L-histidyl-3-(2-naphthalenyl)-D-alanyl-L-arginyl-L-tryptophyl-*N*2-methyl-glycinamide (Ro27-4680) increases food intake (Benoit et al., 2000). These findings are also transferable to murine models of POMC deficiency, characterized by decreased metabolic rate, obesity, and increased fat and lean mass, effects that can be attenuated by the administration of exogenous melanocortins through the suppression of food intake (Yaswen et al., 1999; Challis et al., 2004; Tung et al., 2006). In addition, various perturbations in the melanocortin system ranging from congenital POMC deficiency (Krude et al., 1998, 2003) to mutations of MC3R (Lee et al., 2002) and mutations of the MC4R (Farooqi et al., 2003) have been associated with human obesity, indicating the importance of the melanocortin system as an important regulator of the homeostatic mechanisms that control food intake and energy expenditure.

CART was originally sequenced as a peptide with unknown function (Spiess and Vale, 1980) and was later confirmed to be the protein product of an mRNA transcript up-regulated after short-term exposure to cocaine and amphetamine (Douglass et al., 1995). Like other hypothalamic neuropeptides regulating energy homeostasis, CART expression is also responsive to nutritional status; fasting decreases hypothalamic CART expression (Li et al., 2002; Robson et al., 2002), whereas CART expression is increased as an early consequence of the consumption of a high-energy/high-fat diet (Wortley et al., 2004; Archer et al., 2005). As such, the central administration of CART via intracerebroventricular infusion inhibits food intake and fat storage but favors lipid oxidation in normal and obese animals (Kristensen et al., 1998; Lambert et al., 1998; Rohner-Jeanrenaud et al., 2002). Furthermore, fasting elicits decreases in CART expression in nonhuman primates (female rhesus monkeys) (Van Vugt et al., 2006), indicative of the evolutionarily conserved nature/importance of CART as a regulator of energy homeostasis. Furthermore, polymorphisms of the *CART* gene, as well as alterations in CART levels, are associated with human obesity (Challis et al., 2000; Yamada et al., 2002).

3. Adipose Tissue-Derived Hormones Regulating Appetite and Energy Homeostasis via Hypothalamic Effects. An important source of hormones that control hypothalamic energy homeostasis is adipose tissue. This includes adipocyte-derived leptin, adiponectin, and resistin.

Leptin is the product of the obese (*ob*) gene, and is predominantly secreted by white adipose tissue (WAT), acting as a circulating satiety factor that elicits at least some of its effects on energy homeostasis by altering the activity of key hypothalamic neurons. Leptin promotes negative energy balance by decreasing food intake in a variety of mammalian species, including mice (Campfield et al., 1995; Halaas et al., 1995), sheep (Henry et al., 1999), nonhuman primates (Tang-Christensen et al.,

1999), and humans (Heymsfield et al., 1999). Leptin receptors are expressed within the hypothalamus (Irani et al., 2007), whereby leptin reduces signaling by orexigenic NPY/AgRP neurons, decreases NPY mRNA (Morton et al., 2003), increases signaling by anorexigenic POMC/CART neurons, and increases POMC expression in the ARC (Schwartz et al., 1997). Conversely, the genetic deletion of leptin receptors in ARC NPY/AgRP neurons or POMC neurons results in increased food intake and fat mass (van de Wall et al., 2008). It is noteworthy that circulating leptin levels positively correlate with adiposity; however, the effects of leptin in the obese state are attenuated, suggesting that leptin resistance is an important contributor to this pathophysiology. The resistance to leptin manifests at various levels, including receptor binding (Irani et al., 2007), transport across the blood-brain barrier (BBB) (Schwartz et al., 1996), as well as the intracellular signaling pathways activated by leptin (Vaisse et al., 1996). Furthermore, restoring hypothalamic leptin receptor signaling in *db/db* mice that lack functional leptin receptors reduces food intake and fat mass in addition to improving peripheral insulin sensitivity (Coppari et al., 2005; Morton et al., 2005). These aspects further indicate the importance of hypothalamic leptin and leptin receptor signaling in the central regulation of energy homeostasis.

Adiponectin is secreted from WAT; in contrast to leptin, however, adiponectin levels are decreased in obesity and inversely related to adiposity (Ahima et al., 2006). The ability of adiponectin to elicit alterations in energy homeostasis via central effects is not definitive. Several reports suggest that adiponectin is unable to cross the BBB (Pan et al., 2006; Spranger et al., 2006); however, adiponectin may gain access to the brain via the circumventricular organs, which lie outside of the BBB. Adiponectin receptors (AdipoR1 and AdipoR2) are expressed in the hypothalamus, with both isoforms present on both NPY and POMC neurons in the ARC (Kos et al., 2007; Guillod-Maximin et al., 2009). In peripheral tissue, adiponectin elicits effects consistent with the promotion of increased energy expenditure, including increased fatty acid β-oxidation (Tomas et al., 2002), and prevents the development of diet-induced obesity (Shklyaev et al., 2003). It is noteworthy that the effects of adiponectin on energy metabolism after central administration are not clearly defined. The central administration of adiponectin increases the expression of uncoupling protein 1 in brown adipose tissue, concomitant with increases in brown adipose tissue thermogenesis and fatty acid β-oxidation (Qi et al., 2004), effects consistent with the promotion of negative energy balance. Furthermore, the central administration of adiponectin via the activation of AdipoR1 receptors and the insulin signaling pathway decreases food intake (Coope et al., 2008). However, these effects are equivocal, because levels of adiponectin in the cerebrospinal fluid increase during fasting and decrease in response to refeeding (Kubota et al., 2007), a pattern of nutritional regulation reminiscent of orexigenic signals. In contrast to its effects promoting negative energy balance, adiponectin, via activation of the AdipoR1 receptor, and activation of AMPK in the ARC has been shown to increase food intake, whereas adiponectin knockout mice display decreased AMPK phosphorylation in the ARC, decreased food intake, increased energy expenditure, and resistance to diet-induced obesity (Kubota et al., 2007). Thus, the effects of adiponectin on the central regulation of energy homeostasis, and the receptor(s) involved in mediating those effects, are not clear and are still the topic of active research.

Resistin was originally identified as a factor secreted from WAT in rodents, the serum levels of which are increased in genetic and diet-induced models of obesity (i.e., *ob/ob* mice) (Steppan et al., 2001; Rajala et al., 2004) as well as in obese human subjects (Savage et al., 2001). Resistin is expressed in various tissues, including the hypothalamus, where it colocalizes with POMC neurons (Morash et al., 2002; Wilkinson et al., 2005). The effects of central resistin administration on energy homeostasis are complex and seem to be dependent on the fed/fasted state. The central administration of resistin induces a transient decrease in food intake in fasted rats (Tovar et al., 2005), an effect associated with a suppression of 1) the normal fasting-induced increase in NPY and AgRP expression and 2) the normal fasting-induced decrease in CART expression (Vázquez et al., 2008). It is noteworthy that resistin is able to induce activation of hypothalamic (VMH) AMPK (see section IV.B), which is associated with a reduction in food intake in the fed state; however, this occurs independently of alterations in hypothalamic NPY, AgRP, POMC, and CART levels. The activation of AMPK in the VMH is consistent, however, with the ability of resistin to increase hepatic glucose production (McCrimmon et al., 2006). The complex effects of resistin on energy expenditure and the expression of resistin in the hypothalamus itself have led to the suggestion that resistin may act in an autocrine/paracrine manner to elicit changes in energy homeostasis (Brown et al., 2009).

4. Gastrointestinal Tract-Derived Hormones Regulating Appetite and Energy Homeostasis via Hypothalamic Effects. Two important gastrointestinal tract-derived hormones involved in hypothalamic control of energy homeostasis are ghrelin and glucagon-like peptide-1 (GLP-1). Ghrelin, an acylated peptide hormone, was first identified as the endogenous ligand for the growth hormone secretagogue receptor (GHSR) (Kojima et al., 1999). The expression levels of ghrelin are highest in the endocrine cells (α-cells) lining the stomach and proximal small intestine, although it is expressed in a variety of other tissues (Kojima et al., 1999), including the hypothalamic ARC nucleus, from where it is also released (Korbonits et al., 2001; Mozid et al., 2003). GHSRs are found in various regions of the brain and, in the hypo-

thalamus, GHSR mRNA is found to colocalize with NPY mRNA (Willesen et al., 1999). The circulating levels of ghrelin are influenced by prandial state; levels rise in the preprandial state and decrease in the postprandial state, thereby suggesting a role for ghrelin in meal initiation (Ariyasu et al., 2001; Cummings et al., 2001). Indeed intravenous or intracerebroventricular administration of ghrelin increases food intake, thereby promoting positive energy balance (Nakazato et al., 2001; Wren et al., 2001a). These effects are mediated by the activation of hypothalamic NPY/AgRP neurons and augmented NPY expression (Nakazato et al., 2001) and are prevented by NPY Y1 receptor antagonists (Shintani et al., 2001) and GHSR antagonists ([D-Lys-3]-GHRP-6 in mice) (Asakawa et al., 2003). It is noteworthy that GSHR-deficient mice that are resistant to diet-induced obesity do not respond to the hyperphagic effects of ghrelin (Zigman et al., 2005). Furthermore, there does not seem to be a large contribution of GHSR activation to most forms of human obesity (Nogueiras et al., 2008). In fact, most obese humans have decreased circulating ghrelin levels compared with lean humans, and there is an inverse relationship between body-mass index and ghrelin (Tschöp et al., 2001). This raises the possibility that circulating ghrelin levels are decreased to limit positive energy balance in the obese state.

GLP-1 is an insulinotropic factor cleaved from preproglucagon in L-cells of the distal intestinal tract and is expressed in various brain regions; nerve terminals immunoreactive for GLP-1 innervate the hypothalamus (Jin et al., 1988; Drucker, 1990). Only a single receptor, GLP-1R, has been identified for GLP-1, and it is also expressed in the hypothalamus, with high levels in the ARC (Alvarez et al., 1996; Merchenthaler et al., 1999), particularly in POMC-expressing neurons, (Ma et al., 2007), suggesting that GLP-1 may regulate energy homeostasis. Indeed, the anorectic effect of GLP-1 is well characterized. The peripheral administration of GLP-1 activates hypothalamic neurons and decreases food intake and meal size (Abbott et al., 2005; Chelikani et al., 2005; Neary et al., 2005). Furthermore, the direct central administration of GLP-1 via intracerebroventricular injection decreases food intake in fasted rats, and this effect is prevented by the GLP-1R antagonist, exendin$_{9-39}$ (Turton et al., 1996). It is noteworthy that the GLP-1R antagonist, exendin$_{9-39}$ increases food intake in satiated rats, thereby indicating that GLP1R signaling is an important physiological regulator of food intake and energy homeostasis (Turton et al., 1996).

5. Pancreas-Derived Hormones Regulating Appetite and Energy Homeostasis via Hypothalamic Effects. Insulin is produced by pancreatic β-cells, and its circulating concentration is proportional to body fat mass (Bagdade et al., 1967). Although the effects of insulin on energy homeostasis via direct effects on peripheral tissues are well characterized, its effects on energy homeostasis via the brain are still being elucidated. Insulin is transported across the BBB via a saturable process (Woods et al., 2003), and insulin receptors are widely expressed in the brain, expressed in relatively high content in areas implicated in the regulation of energy homeostasis such as the ARC, and localize to both NPY/AgRP and POMC/CART neurons (Havrankova et al., 1978; Benoit et al., 2002). Indeed, previous reports demonstrate the ability of exogenously administered insulin to decrease appetite and food intake in rodents, nonhuman primates, and humans (Woods et al., 1979, 1984; Ikeda et al., 1986; McGowan et al., 1993; Hallschmid et al., 2004). The anorexigenic effects of insulin are consistent with its abilities to decrease the expression of NPY in the ARC (Schwartz et al., 1991, 1992) and the expression of AgRP (Könner et al., 2007); the latter effect, however, seems not to alter food intake but instead decreases hepatic glucose production. The intracerebroventricular administration of insulin also increases the expression of POMC in the ARC, subsequently decreasing food intake and body weight (Brown et al., 2006). Likewise, the systemic and intracerebroventricular administration of an insulin mimetic compound (Air et al., 2002) also decreases adiposity secondary to increased melanocortin signaling (Nogueiras et al., 2007). Thus, hypothalamic NPY/AgRP and POMC/CART signaling seem to be of central importance to the mechanisms by which insulin regulates food intake and energy homeostasis.

6. Endocannabinoids Regulating Appetite and Energy Homeostasis via Hypothalamic Effects. A role for the cannabinoids and endocannabinoids in the regulation of appetite was documented decades ago. In the 1960s, characterization of the cannabinoid Δ^9-tetrahydrocannabinol (THC) led to the conclusion that this family of molecules had orexigenic properties (Mechoulam et al., 1970; Abel, 1971, 1975; Kirkham, 2005). In recent years, the discovery of endocannabinoids (anandamide and 2-arachidonoylglycerol) and cannabinoid receptors in mammalian cells has provided a physiological basis for these effects. In line with their orexigenic properties, the levels of endocannabinoids in the hypothalamus increase during fasting in rodents and decrease after refeeding (Kirkham et al., 2002). There are two major cannabinoid receptors (CB_1 and CB_2) and a possible third non-CB_1/non-CB_2 cannabinoid receptor subtype (Kirkham, 2005). Localization studies demonstrate a wide distribution of CB_1 receptors throughout key regions involved in appetite regulation. Indeed, CB_1 receptors are expressed in the ARC and LHA (Fernández-Ruiz et al., 1997; Jelsing et al., 2009). Furthermore, the CB receptor agonists anandamide and (−)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-*trans*-4-(3-hydroxypropyl)cyclohexanol (CP55940) augment the release of NPY in hypothalamic explants, although these effects are attenuated by the selective CB_1 receptor antagonist *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophen yl)-4-methyl-1*H*-pyrazole-3-carboxamide (AM251) (Gamber et al., 2005). In

addition, a number of studies in rodents have demonstrated that cannabinoid receptor agonists stimulate feeding, whereas antagonists inhibit feeding (for review, see Kirkham, 2005). Specifically, THC- and anandamide-induced food intake is reversed by the selective CB_1 receptor antagonist rimonabant but not the CB_2 receptor antagonist *N*-[(1*S*)-endo-1,3,3-trimethyl bicycle[2.2.1] heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide (SR144528) (Williams and Kirkham, 1999; Hao et al., 2000; Jamshidi and Taylor, 2001; Kirkham et al., 2002). Thus, the CB_1 receptor is integral to the stimulatory effects of cannabinoids and endocannabinoids on food intake. Recent genetic studies in animals support these observations, as CB_1 receptor deficient mice have a reduced appetite and are resistant to diet-induced obesity (Ravinet Trillou et al., 2004), while chronic oral treatment with rimonabant decreases food intake and body weight in genetically obese Zucker Fatty rats (Vickers et al., 2003). Similar findings have been observed in humans, as studies carried out by Hollister and colleagues in the 1970s revealed that THC increased the consumption of chocolate milk shakes and enhanced food appreciation (Hollister, 1971). using a residential laboratory setting, Foltin, Haney and colleagues obtained supportive data to that of Hollister, whereby inhalation of cannabis smoke increased the consumption of sweet snack foods (Foltin et al., 1986; Foltin et al., 1988; Haney et al., 1999; Hart et al., 2002; Haney et al., 2005). Recently, the first peer-reviewed trial in humans to determine whether CB_1 receptor antagonism could be used as a treatment for obesity, RIO-Europe, demonstrated that rimonabant (20 mg/day) significantly reduced body weight versus placebo. As such, rimonabant became the first clinically approved CB_1 receptor antagonist for the treatment of obesity in Europe; because of recent findings demonstrating an increased risk of anxiety, depression, and suicide (Christensen et al., 2007a,b; Soyka, 2008) after rimonabant therapy, however, its FDA application was suspended as well as its clinical use throughout Europe.

B. Hypothalamic Intermediary Fuel Metabolism

Like all tissues, the energetic requirements of the brain are met by the production of ATP from various fuel sources. The central dogma of cerebral energy metabolism suggests that glucose is an obligate energetic fuel necessary to fully sustain neuronal activity. The catabolism of carbohydrates (e.g., glucose, fructose, and lactate) therefore is important in meeting the ATP requirements of the brain (Fig. 2). This is particularly evident in that the rates of cerebral glucose utilization, based on the uptake of 2-[^{14}C]deoxyglucose, approach 60 μmol/g/h (recalculated from Brown and Lorden, 1989; Choi et al., 2001; Simpson et al., 2007). Furthermore, direct measurements in the in vitro brain slice preparation demonstrated that approximately 385 nmol/g/h of glucose is completely oxidized, which sharply contrasts with the extremely low rates of fatty acid (i.e., palmitate) oxidation, which amount only to 0.02 nmol/g/h (Carey, 1975). This suggests that fatty acids are not an important energy substrate for the brain. Nonetheless, fatty acids and their metabolites are recognized as important cellular messengers in the brain. This supposition is evinced from the extremely low rates of fatty acid β-oxidation observed in brain slice preparations compared with the rates of fatty acid incorporation into various intracellular lipids (Carey, 1975), as well as the low rates of fatty acid β-oxidation relative to fatty acid activation (i.e., esterification) in neuron-derived neuro2A cells (Pei et al., 2003). The mechanism(s) by which fatty acids and their metabolites influence the CNS, particularly the hypothalamic regulation of energy homeostasis, has become an area of intense investigation (section II.D). Therefore, intermediary fuel metabolism in the hypothalamus seems to represent an important facet involved in the regulation of energy homeostasis.

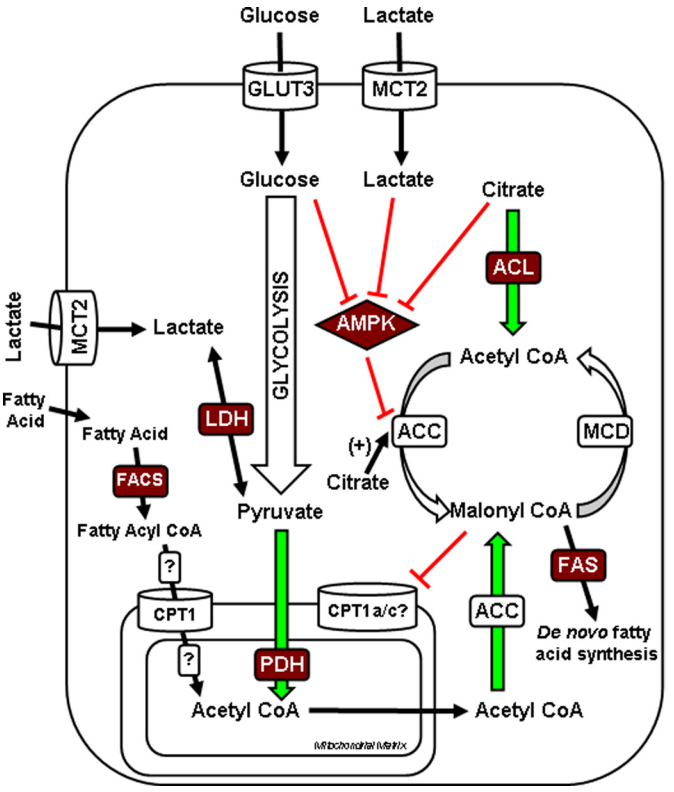

FIG. 2. Regulation of malonyl CoA content via enzymatic control and intermediary fuel metabolism. Malonyl CoA is synthesized via ACC, which is itself inhibited by activation of AMPK. Furthermore, malonyl CoA is degraded via MCD and serves as the substrate for FAS-mediated de novo fatty acid synthesis. Malonyl CoA levels can be influenced by a number of circulating nutrients, such as glucose, lactate, and citrate, which may increase malonyl CoA content in the hypothalamus via inhibition of AMPK. Moreover, citrate serves as a substrate for ATP-citrate lyase (ACL), which increases acetyl CoA production for the subsequent conversion into malonyl CoA via ACC. Citrate can also increase malonyl CoA production by stimulating the polymerization and activation of ACC. Finally, dietary fructose has been shown to activate AMPK, which would result in a subsequent inhibition of ACC and reduction in malonyl CoA levels.

1. Glucose Metabolism. Glucose used for the generation of ATP in the brain originates from the circulation being transported across the BBB by the facilitative

glucose transporter GLUT1, which is localized to microvascular endothelial cells that comprise the BBB and is distributed between both the luminal and abluminal membranes and an intracellular pool (Gerhart et al., 1989; Farrell and Pardridge, 1991; Simpson et al., 1999). The presence of GLUT1 in the abluminal membrane of endothelial cells comprising the BBB facilitates the exit and subsequent delivery of glucose to the cerebral extracellular space. From the cerebral extracellular space, glucose can enter neurons via GLUT3 transporters, which have a higher affinity and higher capacity to transport glucose relative to GLUT1 (Maher et al., 1991, 1996; Maher and Simpson, 1994). A close coupling under resting conditions between cerebral oxygen consumption and glucose utilization suggests that the majority of glucose that is consumed is completely oxidized (Dienel and Hertz, 2001).

Before oxidation, glucose must be converted to pyruvate via glycolysis. The catabolism of glucose via glycolysis occurs in the cytosol, and results in the net generation of two molecules of ATP and two molecules of NADH per molecule of glucose metabolized. Under aerobic conditions, pyruvate is oxidized (i.e., glucose oxidation) by the pyruvate dehydrogenase complex to form acetyl CoA, or it is carboxylated by pyruvate carboxylase to oxaloacetate, which feeds into the tricarboxylic acid (TCA) cycle, and results in the net generation of citrate. It is noteworthy that under conditions of physiological stress or neuronal stimulation, the coupling between cerebral blood flow and oxygen consumption is lost, because glucose utilization is increased to a much greater extent than oxygen consumption (Fox et al., 1988; Fellows et al., 1993). This is indicative of an increased production of lactate, the end product of nonoxidative glycolysis. Lactate can also arise from nonoxidative glycolysis in astrocytes and is proposed to serve as a metabolic fuel for neurons by mechanisms operative in the astrocyte-neuron lactate shuttle hypothesis (Pellerin, 2005). With regard to this mechanism lactate can be efficiently oxidized (for review, see Pellerin, 2003) after its cellular uptake via monocarboxylate transporter 2 (Pierre and Pellerin, 2005) and subsequently converted to pyruvate. The TCA cycle is a series of eight enzymatic reactions occurring in the mitochondrial matrix that, in neurons, oxidizes acetyl-CoA (derived primarily from glucose and lactate metabolism) in a cumulative manner, liberating CO_2 and concomitantly generating reducing equivalents in the form of NADH and $FADH_2$. The reducing equivalents are subsequently fed into the mitochondrial electron transport chain for use in the production of ATP via oxidative phosphorylation. Citrate is one of the products of the TCA cycle and is produced from the condensation of acetyl CoA and oxaloacetate. Mitochondrial citrate can accumulate and can gain access to the cytosol after its translocation by a citrate transporting protein present on the inner mitochondrial membrane (Mycielska et al., 2009). In the cytosol, citrate can activate ACC to produce malonyl CoA (Beaty and Lane, 1983) and generate acetyl CoA via the ATP citrate lyase reaction (for review, see Wolfgang and Lane, 2008). Taken together, the formation of cytosolic acetyl CoA and the activation of ACC increases the synthesis of cytosolic malonyl CoA, a molecule increasingly recognized as an important satiety signal in the hypothalamus (see sections II.C and III.E).

2. Fatty Acid Metabolism. Fatty acids do not serve as a major substrate for energy metabolism in the brain. However, cerebral fatty acid metabolism is important, because a large portion of the dry weight of the brain is attributable to lipids and because fatty acids and fatty acid metabolites act as important molecules that influence the central regulation of energy homeostasis. The mechanism by which plasma fatty acids gain access into the brain, across the BBB, is not well characterized. However, radiolabeled fatty acids administered systemically do gain access to various brain regions (Miller et al., 1987; Chang et al., 1994; Freed et al., 1994; Arai et al., 1995) protected by the BBB. Both passive diffusion and protein carrier-mediated models for the translocation of plasma fatty acids across the BBB have been proposed. The passive diffusion model suggests that plasma fatty acids, derived primarily from fatty acid-albumin complexes cross the luminal and abluminal leaflets of endothelial cells comprising the BBB by reversible flip-flop (for review, see Hamilton and Brunaldi, 2007) to reach the cerebral extracellular space. Recent evidence also indicates the importance of the fatty acid transport proteins CD36 and FATP1 in mediating the bidirectional and vectorial transport (i.e., luminal to abluminal) of fatty acid across an in vitro BBB model (Mitchell et al., 2009). Similar mechanisms (passive diffusion and protein-carrier mediated transport) probably account for the movement of fatty acids from the cerebral extracellular space and across the neuronal membrane.

Fatty acids that gain access to the cytosolic compartment are trapped and activated by the action of fatty acyl-CoA synthetase enzymes, which esterify a CoA moiety to the acyl chain, thereby generating a fatty acyl CoA molecule. These fatty acyl CoA molecules have several fates, including mitochondrial uptake and subsequent fatty acid β-oxidation (the rates of which are extremely low in brain) or the conversion into various structural and signaling lipid molecules, including phospholipids, triacylglycerol, diacylglycerol, and fatty acyl carnitine species. With regard to palmitate metabolism, in vitro studies using the rabbit brain slice preparation and radiolabeled palmitate ([1-^{14}C]palmitate) have demonstrated that the majority of palmitate is incorporated into the neutral lipid fraction, which is itself primarily represented via triacylglycerol and nonesterified free fatty acids (Carey, 1975). Furthermore, the desaturation and elongation of palmitate is very low, whereas a larger portion can be found in fatty acids of chain length less than C_{16} (Carey, 1975). The largest lipid pool containing

radiolabeled palmitate is the phospholipid pool, where the majority of palmitate label is incorporated into phosphatidylcholine (Miller et al., 1987).

Although fatty acid β-oxidation occurs only to a minor extent in the brain and is not important with regard to ATP production, it is nonetheless important in determining the eventual metabolic fate of fatty acids that have entered cerebral tissue. A number of radiolabeled, aqueous oxidative metabolic byproducts can be extracted from the brain after the administration of radiolabeled palmitate, including various fatty acyl CoA and fatty acyl carnitine species, as well as various amino acids and ketone bodies. Studies using mitochondrial preparations from rat brain indicate that there is approximately a 10-fold greater incorporation of radioactivity into aqueous extracts, than radioactivity evolved as radio-labeled CO_2. The majority of the radiolabel is present in amino acids (including GABA, glutamate, glutamine, aspartate, asparagine) and organic acids including citrate, malate, 3-OH-butyrate, and acetyl CoA; the greatest amount of radiolabel is present in citrate (Kawamura and Kishimoto, 1981; Miller et al., 1987).

Important insights into the relative balance between the incorporation of palmitate into lipid and aqueous metabolic pools in the brain have been provided by studies examining the effects of methyl 2-tetradecylglycidate/methyl palmoxirate (MEP). MEP is a fatty acid analog that is esterified to CoA (Tutwiler and Dellevigne, 1979; Tutwiler and Ryzlak, 1980) after entry into cells, the formed MEP-CoA ester acting as a selective, irreversible inhibitor of mitochondrial carnitine palmitoyl transferase 1 (CPT-1) (Kiorpes et al., 1984), which is itself an emerging target for the central regulation of energy homeostasis (section II.D). MEP alters the distribution of radiolabeled palmitate between lipid and aqueous metabolic pools in the brain. MEP decreases the presence of palmitate-derived radiolabel in aqueous metabolic pools, without altering the distribution between various long-chain acyl CoA moieties; and increasing palmitate-derived radiolabel in lipid pools, specifically triacylglycerol (Chang et al., 1994, 1997). These findings may have relevance to the proposed mechanism(s) of the central regulation of energy homeostasis by compounds altering malonyl CoA, a potent endogenous inhibitor of CPT-1, which may also influence the relative distribution of fatty acid between lipid and aqueous metabolic pools in the brain.

C. Enzymatic Control of Hypothalamic Malonyl CoA

Although the brain does not readily oxidize fatty acids for energy production (Hertz and Dienel, 2002; Zauner et al., 2002), the presence of major enzymes involved in the fatty acid biosynthetic pathway (i.e., ACC, FAS) in neuronal regions of the hypothalamus involved in energy balance has sparked a recent surge of interest as to what role these enzymes might have in the brain. It is noteworthy that many of the hormones and metabolic fuels mentioned in the previous sections affect hypothalamic malonyl CoA levels. Thus, it is important to gain a better understanding of the enzymatic regulation of malonyl CoA in the hypothalamus (Fig. 2), which is now believed to be a key satiety signal in the brain (Wolfgang and Lane, 2006a,b; 2008; Lane et al., 2008). One of the strongest pieces of evidence illustrating the key role of malonyl CoA as a satiety signal that regulates appetite is observed during the most primordial of physiological behaviors, fasting and feeding (Fig. 3). During states of fasting, hypothalamic levels of malonyl CoA rapidly decrease and act as a signal of hunger (Hu et al., 2003; Cha et al., 2006; López et al., 2006), whereas during feeding, hypothalamic levels of malonyl CoA rapidly rise and act as a signal to stop eating (Hu et al., 2003; Cha et al., 2006; López et al., 2006).

1. Acetyl CoA Carboxylase. The production of malonyl CoA is primarily attributed to the enzymatic activity of ACC, which catalyzes the carboxylation of acetyl CoA to malonyl CoA (Fig. 3) (Thampy, 1989; Bianchi et al., 1990). There are two isoforms, ACCα and ACCβ, the β isoform predominating in tissues with a high oxidative capacity (Thampy, 1989). This has led to the suggestion that the malonyl CoA produced by this isoform is preferentially involved in the regulation of fatty acid oxidation. In contrast, malonyl-CoA produced by the predominant ACCα isoform in the liver is preferentially involved in the regulation of fatty acid synthesis (An et al., 2004; Mao et al., 2006). The role of ACC in the brain probably involves regulation of malonyl CoA as substrate for the synthesis of lipids for membranes as well as for the control of appetite. The regulation of ACC is under phosphorylation/dephosphorylation control, 5′AMP-activated protein kinase (AMPK) having a major role in its regulation (Fig. 3) (Kudo et al., 1995; Dyck and Lopaschuk, 2006), whereby ACC phosphorylation results in reduced ACC activity.

In support of ACC regulating malonyl CoA synthesis in the hypothalamus, in collaboration with the Moran laboratory, we demonstrated that the anorexigenic effects of leptin involve the activation of ACC and a subsequent increase in malonyl CoA content in the ARC (Gao et al., 2007b). However, when ARC ACC was inhibited with 5-(tetradecyloxy)-2-furoic acid, leptin was unable to reduce food intake and subsequent body weight, because it could no longer alter ARC malonyl CoA content. These effects occurred despite the leptin-induced inhibition of ARC AMPK, suggesting that malonyl CoA is indeed the downstream signal of AMPK in regulating appetite. Furthermore, mice deficient for ACCβ have increased appetite (Oh et al., 2005), supporting the hypothesis that ACC is an important regulator of appetite via its control of malonyl CoA production in the hypothalamus. Unfortunately, genetic deficiency of ACCα in mice is lethal to the embryo (Abu-Elheiga et al., 2005), and thus it cannot be determined whether the malonyl CoA produced by ACCα is also important toward the

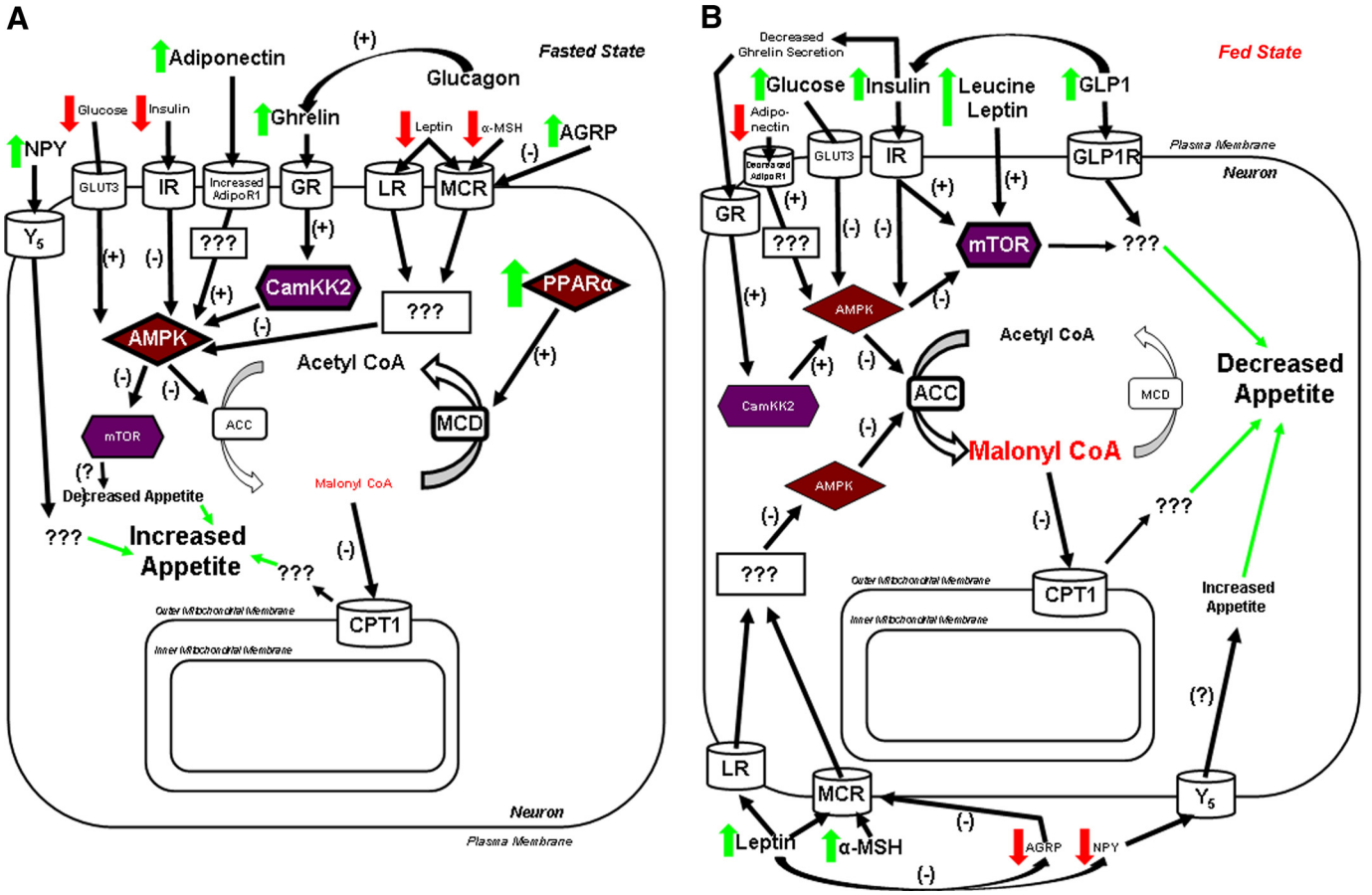

FIG. 3. Appetite control during a fast or after refeeding. A, during a prolonged fast or starvation, blood glucose, insulin, leptin, and α-MSH levels are now decreased, which contribute to the activation of hypothalamic AMPK. Furthermore, increased ghrelin secretion (which is potentiated by increased plasma glucagon levels) and AgRP levels also contribute to the activation of hypothalamic AMPK. This increase in AMPK activity ultimately leads to the inhibition of ACC and possibly mTOR. Fasting is also associated with increased activity of the nuclear transcription factor PPARα, which increases expression of MCD. Inhibition of ACC and increased MCD activity ultimately result in a decline in hypothalamic malonyl CoA levels, which stimulate appetite through undefined mechanisms. B, after ingestion of a meal, increase blood glucose levels induce the secretion of insulin from pancreatic β-cells, both of which can inhibit AMPK. Insulin also decreases the secretion of ghrelin, which is an orexigen that normally stimulates appetite, possibly via CamKK2-mediated activation of AMPK. In addition, the gastrointestinal tract begins to secrete GLP-1, which induces satiety and potentiates pancreatic secretion of insulin. Meanwhile, leptin and α-MSH levels increase, whereas AgRP and NPY decrease. These changes in leptin, α-MSH, and AgRP levels contribute to the inhibition of AMPK. Increased protein content of the meal may increase circulating concentrations of branched-chain amino acids, such as leucine, which activate mTOR. The decrease in AMPK activity ultimately leads to the activation of ACC and increases malonyl CoA content. This increase in malonyl CoA has been proposed to act on hypothalamic CPT-1 to induce a reduction in appetite, although the mechanisms by which it does so are not yet defined.

regulation of appetite. Because malonyl CoA is subject to a high degree of compartmentalization (Saddik et al., 1993; Mao et al., 2006), it will be important for future studies to elucidate potential differences in the ability of ACCβ versus ACCα to regulate appetite.

2. Malonyl CoA Decarboxylase. Until recently, it was much less clear as to what enzymes might be responsible for the degradation of malonyl CoA. MCD has emerged as an important enzyme in controlling malonyl CoA degradation, and its catalytic activity is responsible for the decarboxylation of malonyl CoA back into acetyl CoA (Fig. 3) (Dyck et al., 1998). Studies in both rat and mouse have demonstrated that MCD is indeed involved in regulating malonyl CoA levels in multiple tissues (Dyck et al., 1998, 2004, 2006; An et al., 2004; He et al.) and that inhibition of MCD can limit rates of fatty acid oxidation in oxidative tissues such as the heart (Dyck et al., 1998, 2004, 2006) or triacylglycerol content in lipid synthesizing tissues such as the liver (An et al., 2004). Support for MCD in the regulation of hypothalamic malonyl CoA content and appetite was demonstrated by He et al. (2006) as adenoassociated virus-mediated overexpression of MCD in the MBH of the rat resulted in a dramatic increase in food intake, weight gain, and eventually, obesity. However, it is important to note that levels of malonyl CoA in the MBH were not actually reported in this study.

In addition, peroxisome proliferator activated receptor alpha (PPARα), which is a major transcription factor involved in the regulation of fatty acid oxidation, has also been shown to control levels of malonyl CoA via regulating MCD expression (Young et al., 2001; Lee et al., 2004). Indeed, hypothalamic PPARα has been shown to play a role in the regulation of appetite, because intracerebroventricular administration of [4-chloro-6-[(2,3-dimethylphenyl)amino]-2-pyrimidinyl]thio-acetic acid/pirinixic acid

(WY 13643) normalized malonyl CoA levels and restored the decline in food intake observed in mice with FAS genetically deleted from the VMN (Chakravarthy et al., 2007).

It has also been suggested that MCD is a direct target for activation by AMPK in skeletal muscle (Saha et al., 2000), but our laboratory has been unable to reproduce these findings in the heart. Whether AMPK has a direct role in modulating MCD in the hypothalamus to regulate appetite has yet to be determined.

3. 5′AMP-Activated Protein Kinase. AMPK acts as a "fuel sensor" that increases fatty acid β-oxidation during periods of increased energy demand or decreases fatty acid β-oxidation during periods of low demand, secondary to respective decreases and increases in ACC activity and malonyl CoA levels (Dyck and Lopaschuk, 2006). AMPK is a serine/threonine kinase that responds to metabolic stresses that deplete cellular ATP, increase AMP, or increase the creatine-to-phosphocreatine ratio (Hardie and Hawley, 2001; Hardie, 2004, 2007; Dyck and Lopaschuk, 2006) and is very active in tissues with a high oxidative capacity, such as the heart and skeletal muscle (Kudo et al., 1995; Verhoeven et al., 1995; Dyck and Lopaschuk, 2006), as well as tissues with a high lipogenic capacity, such as the liver (Clarke and Hardie, 1990; Ruderman et al., 2003). AMPK is a heterotrimeric protein consisting of an α catalytic subunit and β and γ regulatory subunits. A number of different isoforms for each of these subunits exists, with a variable tissue distribution (Woods et al., 1994, 1996; Gao et al., 1996; Daniel and Carling, 2002; Hamilton et al., 2002; Dyck and Lopaschuk, 2006; Hardie, 2007). The β and γ subunits regulate the catalytic activity of the α subunit, the γ subunit being important in conferring the AMP sensitivity of the AMPK complex (Dyck and Lopaschuk, 2006).

In general, activation or inhibition of AMPK usually requires changes in the ratio of AMP to ATP or creatine to phosphocreatine, as seen with myocardial ischemia (Kudo et al., 1995; Altarejos et al., 2005; Dyck and Lopaschuk, 2006). In the hypothalamus, increasing GLUT2 expression or glucose delivery increases ATP levels and inhibits AMPK (Minokoshi et al., 2004; Li et al., 2006). In addition, it is now clear that AMPK activity can also be altered without changes in nucleotide levels (Kudo et al., 1995; Altarejos et al., 2005). For instance, the orexigenic peptide ghrelin stimulates activation of AMPK independent of changes in ATP levels (Andersson et al., 2004). Moreover, the adipokines also regulate AMPK activity in the hypothalamus, where adiponectin increases AMPK activity and subsequent appetite (Kubota et al., 2007), and leptin, an anorexigen, decreases AMPK activity and subsequent appetite (Minokoshi et al., 2004; Gao et al., 2007b). Last, the cannabinoids, which are widely known to be potent stimulants of appetite (Cota et al., 2003a,b), also increase AMPK activation in the hypothalamus (Kola et al., 2005).

A limitation with these studies is that the vast majority did not measure malonyl CoA content in the hypothalamus, and simply relied on subsequent changes in the AMPK downstream target, ACC, as an indicator of alterations in malonyl CoA and malonyl CoA-induced changes in appetite (Andersson et al., 2004; Minokoshi et al., 2004; Kubota et al., 2007). However, pharmacological activation of AMPK with 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside, administered via intracerebroventricular injection, increased ACC phosphorylation and decreased hypothalamic malonyl CoA content, resulting in increased food intake in BALB/c mice (Hu et al., 2005). Ghrelin has also been shown to activate AMPK and inhibit ACC in the VMN, which was associated with a decrease in malonyl CoA levels and an enhanced CPT-1 activity and food intake (López et al., 2008). However, inhibition of VMN AMPK with a dominant-negative adenovirus or inhibition of CPT 1 with etomoxir prevented this ghrelin-mediated effect. In combination, the results of these studies strongly support the hypothesis that malonyl CoA is the downstream effector molecule responsible for the AMPK-mediated control of appetite.

4. Fatty Acid Synthase. FAS is an important enzyme in de novo fatty acid synthesis and converts malonyl CoA into malonyl ACP. The first report of a role for FAS in appetite control via regulation of malonyl CoA was from Loftus et al. (2000); the FAS inhibitors C75 and cerulenin caused potent anorexigenic effects associated with a reduction in hypothalamic NPY expression and increase in malonyl CoA content. Since then, a number of studies have shown that targeting hypothalamic FAS can regulate appetite and body weight through its ability to control levels of malonyl CoA (Cha et al., 2004, 2005, 2006; López et al., 2006; Chakravarthy et al., 2007). For example, López et al. (2006) demonstrated that the anorexigenic effects of the estrogen receptor antagonist tamoxifen were due to a down-regulation of FAS and subsequent increase in malonyl CoA content in the VMN region of the hypothalamus. Furthermore, these authors showed that the increase in hypothalamic malonyl CoA brought about by tamoxifen was due solely to the decrease in FAS expression and was completely independent of changes in AMPK or ACC activity. Mice with FAS deleted [FAS(−/−)] specifically in the ARC and PVN regions of the hypothalamus have provided further support for the role of FAS in the regulation of appetite and body weight through its control of malonyl CoA levels (Chakravarthy et al., 2007). These mice have a reduced appetite and weigh significantly less than their WT littermates, but if the WT littermates are pair-fed, they lose comparable amounts of body weight, indicating that the anorexigenic effect observed in ARC/PVN FAS(−/−) mice is due to hypophagia.

It is noteworthy that the anorexic effects of FAS inhibition via C75 may not be due entirely to alterations in malonyl CoA content; Wortman et al. (2003) showed that the anorexigenic effects of C75 could also be attributed

to an increase in glucose metabolism, because C75 did not affect food intake in rats subjected to a ketogenic diet. However, if these animals were supplemented with sucrose (in drinking water), the C75 effect on appetite was restored. It should be noted, however, that increasing glucose metabolism increases ATP levels and inhibits AMPK (Minokoshi et al., 2004; Li et al., 2006), which would decrease ACC phosphorylation/increase ACC activity and subsequently increase malonyl CoA levels, suggesting that malonyl CoA might still be the primary signaling molecule responsible for the hypophagic effects of C75. Another issue of importance with regard to C75 and other FAS inhibitors is that they also activate the mammalian target of rapamycin (mTOR) (Proulx et al., 2008), which could play a role in their hypophagic effect, because mTOR and AMPK seem to be inversely related and intertwined in the regulation of appetite (Ropelle et al., 2008).

D. Alterations in Hypothalamic Fuel Supply and Metabolism That Signal Changes in Appetite

1. Glucose, Pyruvate, Lactate. Glucose and the end products of glycolysis, lactate and pyruvate, are important metabolic fuels influencing the hypothalamic regulation of energy homeostasis. Central glucose metabolism has been established as an important regulator of feeding as long-term, intracerebroventricular infusion of glucose into the third ventricle causes a reduction in body weight partially attributable to a reduction in food intake (Davis et al., 1981). Recent reports have delineated the mechanisms underlying the anorexigenic effects of centrally administered glucose and lactate, indicating that after intracerebroventricular or intraperitoneal administration, both energy substrates increase hypothalamic malonyl CoA content, secondary to reductions in the phosphorylation of AMPK, an effect that subsequently decreases the phosphorylation, thereby disinhibiting the activity of ACC (Wolfgang et al., 2007; Cha et al., 2008; Cha and Lane, 2009). The anorexigenic effects of both glucose and lactate are also accompanied by expected changes in the expression of orexigenic and anorexigenic neuropeptides. The central administration of glucose increases the expression of hypothalamic POMC (Wolfgang et al., 2007; Cha et al., 2008) and CART (Cha et al., 2008) and decreases the expression of hypothalamic NPY and AgRP (Wolfgang et al., 2007; Cha et al., 2008). The central administration of lactate increases the expression of anorexigenic POMC and decreases the expression of NPY (Cha and Lane, 2009). The effects of glucose and lactate are prevented by 2-deoxyglucose (Wolfgang et al., 2007) and oxamate, an inhibitor of lactate dehydrogenase (Cha and Lane, 2009), respectively. Because oxamate inhibits lactate dehydrogenase, it indicates that lactate must be converted to pyruvate and subsequently to acetyl CoA to exert its effects. Although not examining the effects of pyruvate on food intake per se, a previous report characterizing the effects of hypothalamic pyruvate, as well as dichloroacetate (which promotes generation of pyruvate-derived acetyl CoA via the pyruvate dehydrogenase reaction), on the regulation of plasma glucose levels supports this mechanism (Lam et al., 2005a). This may be particularly relevant to the generation of cytosolic malonyl CoA, because pyruvate-derived acetyl CoA is readily exported from mitochondria as acetyl carnitine (Lysiak et al., 1986), which in the cytosol can be converted back into acetyl CoA via the enzymatic activity of carnitine acetyl-transferase (for review, see Lopaschuk et al., 2010), thereby providing substrate for the generation of malonyl CoA.

2. Fructose. In contrast to glucose and lactate, the intraperitoneal and central administration of fructose actually increases food intake (Miller et al., 2002; Cha et al., 2008; Lane and Cha, 2009). This orexigenic effect of fructose is attributed to the different mechanisms by which it enters glycolysis. Fructose enters the glycolytic pathway at the triose level, after the generation of fructose-1-phosphate via 2-ketohexokinase. Because 2-ketohexokinase consumes ATP at a greater rate than does phosphofructokinase-1 (one of the regulatory steps of glycolysis), fructose can decrease intracellular ATP, while increasing AMP levels (Cha et al., 2008; Lane and Cha, 2009). These effects lead to the phosphorylation/activation of AMPK, the subsequent phosphorylation/inhibition of ACC, and eventual decrease in hypothalamic malonyl-CoA content (Cha et al., 2008; Lane and Cha, 2009). These effects of fructose increase food intake consistent with its inability to decrease the hypothalamic expression of NPY and AgRP mRNA. Therefore, subtle differences in the mechanisms by which fructose and glucose are metabolized via the glycolytic pathway account for completely opposite effects on food intake.

3. Fatty Acids. Recent reports indicate that long-chain fatty acids, via the formation of long-chain acyl CoA, elicit anorexigenic effects at the level of the hypothalamus. Indeed, previous reports demonstrate that the intracerebroventricular administration of oleic acid decreases food intake, an effect accompanied by decreased expression of NPY and AgRP mRNA in the hypothalamus (Obici et al., 2002). These effects may be due to the conversion of oleic acid to oleoyl CoA. These effects may be due to the conversion of oleic acid to oleoyl CoA, because the ability of oleic acid to regulate peripheral glucose homeostasis is abolished by *N*-(((2*E*,4*E*,7*E*)-undeca-2,4,7-trienylidene)amino)nitrous amide (triacsin C), an inhibitor of fatty acyl CoA synthase that decreases the conversion of fatty acids into their respective activated fatty acyl CoA moieties (Lam et al., 2005b). It is noteworthy that a role for mitochondrial CPT-1 is also implicated in the central effects of long-chain fatty acyl CoA on food intake, as octanoic acid, is unable to recapitulate the anorexigenic effects of oleic acid, (Obici et al., 2002). Medium-chain octanoyl CoA does not require CPT-1 to gain access to the mitochondrial matrix, whereas long-chain acyl CoA does. Furthermore, pharmacological or genetic inhibition of hypothalamic CPT-1

increases long-chain acyl CoA content, eliciting anorexigenic effects (Obici et al., 2003). The ability of CPT-1 inhibition in these studies to elevate long-chain acyl CoA content, by genetic or pharmacological means, contrasts with previous reports demonstrating that inhibition of CPT-1 within the brain does not alter long-chain acyl CoA content but increases fatty acid incorporation into phospholipids and neutral lipids as described above. As such, the effects of CPT-1 inhibition on hypothalamic long-chain acyl CoA content are not definitive and thus may require caution when interpreted.

It is of interest that the CPT-1 isoform CPT-1b is not expressed in the hypothalamus (Obici et al., 2003), whereas the hypothalamic expression of CPT-1a is minimal, and its binding affinity for malonyl CoA is relatively low (Esser et al., 1996). Regardless, recent studies have demonstrated that CPT-1c, a brain-specific isoform of CPT-1, binds malonyl CoA with an affinity similar to that of CPT-1b (Wolfgang et al., 2006). Mice that have of CPT-1c genetically deleted eat less and have a lower body weight than their WT littermates, effects mimicking those of elevated hypothalamic malonyl CoA content (Wolfgang et al., 2006), strengthening the hypothesis that malonyl CoA is a key player in the regulation of appetite. However, CPT-1c-deficient mice become obese more quickly than their WT littermates when fed a high-fat diet (Wolfgang et al., 2006), despite eating less. Despite this complication, the data so far do support a role for malonyl CoA in reducing appetite via a potential effect on CPT-1c, and it will be important in future studies to further delineate the potential mechanisms by which the malonyl CoA-CPT-1c interaction signals to the brain to reduce appetite. One such mechanism might involve an increase in cytosolic long-chain acyl CoA levels that acts as a signal for nutrient abundance (Obici et al., 2003). In support of this, intracerebroventricular delivery of oleic acid, but not octanoic acid (which bypasses CPT-1 for mitochondrial access) has appetite-suppressing properties (Obici et al., 2002). Furthermore, we have shown, in collaboration with the Moran laboratory (Gao et al., 2007b), that the anorexigenic effects of leptin result in an accumulation of PVN palmitoyl CoA levels, which can be prevented with intracerebroventricular treatment of the broad ACC inhibitor 5-(tetradecyloxy)-2-furoic acid. However, the brain specific CPT-1c isoform does not catalyze carnitine transferase activity (Wolfgang et al., 2006), which leads one to wonder how CPT-1 inhibition in the hypothalamus would result in long-chain acyl CoA accumulation. In our collaboration with the Moran laboratory (Gao et al., 2007b), we showed that intracerebroventricular leptin increased FAS expression in the PVN, which would explain why we did not observe an accumulation of malonyl CoA levels in the PVN, because increased FAS expression and activity would increase the use of malonyl CoA for the synthesis of palmitoyl CoA.

4. Citrate. Citrate is an intermediate of the TCA cycle and is therefore a common intermediate in the metabolism of both carbohydrates and fatty acids that is produced in mitochondria and can gain access to the cytosolic space (section II.B). Citrate is also found circulating in plasma and in the cerebrospinal fluid at similar levels. Recent reports indicate that the intracerebroventricular administration of citrate elicits anorexigenic effects (Roman et al., 2005; Cesquini et al., 2008; Stoppa et al., 2008). Citrate from the cerebral extracellular space may gain entry to the cytosolic compartment of neurons via a recently identified sodium-citrate cotransporter found on the plasma membrane of neurons (Inoue et al., 2002). Once in the cytosol, citrate may be cleaved by ATP-citrate lyase, generating acetyl CoA (Fig. 2). Furthermore, citrate can also promote the polymerization and activation of ACC. Taken together, these effects may promote increased generation of malonyl CoA. Indeed, citrate increases hypothalamic malonyl CoA content (Stoppa et al., 2008), secondary to decreasing the phosphorylation and activation of AMPK, which subsequently prevents the phosphorylation and inhibition of ACC (Cesquini et al., 2008; Stoppa et al., 2008). The anorexigenic effects of citrate are also associated with decreased hypothalamic NPY mRNA expression, but increased POMC mRNA expression (Stoppa et al., 2008). As well, centrally administered citrate also increases energy expenditure, evinced by a decrease in fat mass and body weight after 7-day administration (Stoppa et al., 2008). It is noteworthy that the central administration of citrate also increases peripheral insulin sensitivity without increasing insulin secretion, an effect that may be related to the ability of centrally administered citrate to decrease circulating corticosterone levels (Stoppa et al., 2008). Whether these effects on insulin sensitivity also manifest at the level of the hypothalamus is not known; however, citrate-induced increases in hypothalamic insulin sensitivity would be consistent with its anorexigenic properties.

III. Signaling Pathways Involved in the Hypothalamic Regulation of Appetite

As mentioned in the previous section, a large number of endogenous hormones and energy substrates can influence appetite and meal size (Ahima and Antwi, 2008; Gardiner et al., 2008; Hameed et al., 2009). This section will deal with the downstream metabolic signaling pathways activated by these various anorexigenic and orexigenic compounds, many of which are shared and integrated, often affecting hypothalamic levels of malonyl CoA (Wolfgang and Lane, 2006b, 2008). It is also important to note that although many of these signaling pathways can affect appetite and induce weight loss in patients with obesity, activation of these pathways can also have peripheral effects that affect whole-body energy metabolism and energy expenditure (Cha et al.,

2005, 2006; Chakravarthy et al., 2007; Gao et al., 2007a; Kubota et al., 2007), which also contributes to their beneficial effects against obesity. However, in this review, we will deal primarily with the impact of these hypothalamic signaling pathways on the regulation of appetite. We direct the reader to excellent reviews (Xue and Kahn, 2006; Ahima and Lazar, 2008; Wolfgang and Lane, 2008; Sandoval et al., 2009) that address the peripheral metabolic effects induced by hypothalamic signaling.

A. Hormonal Signaling of Appetite

1. Insulin/leptin. As discussed in section II, insulin and leptin are both linked to overall adiposity and act as potent anorexigens in the hypothalamus to reduce food intake and induce weight loss by decreasing the expression of NPY/AgRP and enhancing the expression of POMC in the ARC (Schwartz et al., 2000). Insulin and leptin act on many different signaling pathways that all contribute toward reducing appetite. This includes activation of the PI3K-Akt-mTOR pathway; a large number of studies have now shown that direct activation of mTOR leads to hypophagia and weight loss (Cota et al., 2006; Ropelle et al., 2008; Cota, 2009) (section III.C). In addition, activation of the PI3K-Akt axis inhibits FOXO and prevents its nuclear localization (Matsuzaki et al., 2003; Aoki et al., 2004). Activation of FOXO in the hypothalamus has been shown to increase appetite by increasing transcription of both NPY and AgRP in hypothalamic neurons (Kim et al., 2006). Leptin and insulin can result in the inhibition of AMPK (Minokoshi et al., 2004), which would result in ACC activation and elevated hypothalamic malonyl CoA levels (section III.E).

Although the aforementioned pathways seem to be used by insulin and leptin to mediate their hypophagic effects, there are differences. Leptin binds to its receptor to induce activation of the Janus kinase family, which phosphorylates and activates the signal transducer and activator of transcription 3 (STAT3) pathway (Schwartz et al., 2000). The STAT3 pathway has been shown to be necessary for leptin-induced hypophagia (Buettner et al., 2006) (section III.B). Leptin may also induce its anorexigenic effects independently of STAT3-mediated transcription, because leptin has been shown to maintain ATP-sensitive K^+ (K_{ATP}) channels in an open configuration, which decreases neuronal firing and may control neuropeptide gene expression (Spanswick et al., 1997). In contrast, insulin has not been shown to activate STAT3 in the hypothalamus. Rather, insulin probably mediates its affects on PI3K/Akt → Forkhead box O (FOXO) and PI3K/Akt → mTOR in the hypothalamus via activation of insulin receptor substrate 2; mice with neuronal insulin receptor substrate 2 deficiency become severely obese as a result of extreme hyperphagia (Brüning et al., 2000).

2. Adiponectin. Adiponectin, although having an effect similar to that of leptin with regard to its metabolic effects in muscle (Dyck, 2009), has the exact opposite effect of leptin with regard to AMPK activity in the hypothalamus. Through its actions on AdipoR1, adiponectin increases AMPK activity and subsequent ACC phosphorylation, increasing food intake and even overcoming the hypophagic effects of leptin (Kubota et al., 2007). Although malonyl CoA levels were not measured in that particular study, it is highly likely that the downstream effect of adiponectin was mediated via ACC-induced changes in malonyl CoA content (section II.C). It may also be possible that the adiponectin effects were mediated via mTOR (section III.C), because AMPK and mTOR are inversely related with regard to their regulation of appetite (Ropelle et al., 2008). Thus, future studies should also be aimed at investigating whether or not mTOR is involved in mediating the hyperphagic effects of adiponectin.

3. Neuropeptide Y. The anorexigenic effects of NPY are mediated primarily via its actions on the Y1 and Y5 NPY receptor subtypes (Ramos et al., 2005). Although the Y1 receptor was initially believed to be the primary receptor mediating effects of NPY on appetite, the Y1 receptor has a low affinity for the N-terminally truncated NPY [2–36]NPY, a potent appetite stimulant (Blomqvist and Herzog, 1997). However, the recent identification of the Y5 receptor suggests it may be the primary receptor involved in NPY-mediated appetite stimulation, because it is very similar to the Y1 receptor and extremely responsive to the orexigenic actions of [2–36]NPY (Gerald et al., 1996; Michel et al., 1998).

In nearly every cell type studied to date, NPY receptors act via pertussis toxin-sensitive G-proteins (i.e., members of the G_i and G_o family), which result in the inhibition of adenylyl cyclase and decreased cyclic AMP production (Weinberg et al., 1996; Michel et al., 1998). Furthermore, some studies have suggested that NPY may increase intracellular calcium concentration (Motulsky and Michel, 1988; Perney and Miller, 1989; Prieto et al., 2000), whereas others suggest a decrease (Ewald et al., 1988). If NPY action does increase intracellular calcium in critical regions of the hypothalamus associated with appetite regulation, such as the ARC and PVN, it is possible that NPY may increase appetite via activation of Ca^{2+}/calmodulin dependent protein kinase kinase 2 (CamKK2) and AMPK, resulting in a reduction in malonyl CoA content (Anderson et al., 2008; Sleeman and Latres, 2008). Surprisingly, there is a lack of studies demonstrating definitive downstream signaling responses mediated via NPY in the hypothalamus that result in appetite stimulation. It will be important for future studies to aggressively address this area, because directly targeting the Y1 and Y5 NPY receptor subtypes to treat obesity-associated hyperphagia will probably be associated with adverse effects, some of which may include increased blood pressure, neurogenic inflammation, and analgesia (Ramos et al., 2005).

4. α-Melanotropin. α-MSH mediates hypophagic effects via its actions on the MC3R and MC4R. Although a key role for the MC4R in mediating the hypophagic effects of α-MSH has been clearly demonstrated in rodents (Ludwig et al., 1998; Kask et al., 1999), the involvement of the MC3R is not yet well established (Abbott et al., 2000). It is noteworthy that stimulation of the MC4R with leptin in the PVN is associated with decreased AMPK activity (Minokoshi et al., 2004), which suggests that α-MSH-induced hypophagia may be due to alterations in hypothalamic malonyl CoA content (sections III.E and IV).

5. Gastrointestinal Tract Hormones. Gastrointestinal tract hormones often act as satiety signals to limit meal size (Antin et al., 1975; Little et al., 2005; Smith and Gibbs, 1992a,b,c); most research has focused on GLP-1 with regard to reducing appetite (Antin et al., 1975; Miesner et al., 1992; Smith and Gibbs, 1992c; Turton et al., 1996; Näslund et al., 1999; Meier et al., 2002; Abbott et al., 2005; Chelikani et al., 2005; Little et al., 2005). Unfortunately, the vast majority of studies investigating their appetite-suppressing properties have not delineated the potential mechanisms involved. However, in skeletal muscle, GLP-1 has been shown to have an insulin-like effect and is able to activate the PI3K/Akt and mTOR signaling pathways (Acitores et al., 2004; González et al., 2005). It is possible that GLP-1 signaling in the hypothalamus acts on these signaling pathways, which have well characterized roles in appetite regulation (section III.C) (Acitores et al., 2004; González et al., 2005; Cota et al., 2006; Kim et al., 2006; Cota, 2009).

Gastrointestinal tract hormones can also act to increase appetite; of these, ghrelin is the most highly characterized (Wren et al., 2000, 2001a,b; Nakazato et al., 2001; Naleid et al., 2005; Cummings, 2006), where its hyperphagic effects have been shown to coincide with AMPK activation in the hypothalamus (Andersson et al., 2004). ARC NPY/AgRP neurons express the GHSR, where ghrelin binding is linked to increases in intracellular Ca^{2+} (Cummings, 2006), which may activate CaMKK2 (Lee et al., 2008). Indeed, recent studies have shown that ghrelin activates AMPK and phosphorylates ACC via activation of CaMKK2 and that inhibition of CaMKK2 decreases appetite (Anderson et al., 2008). Thus, it is highly likely that ghrelin-induced AMPK activation may inhibit ACC activity and subsequent malonyl CoA production (Sleeman and Latres, 2008). In support of this, ghrelin has been shown in a recent study to decrease malonyl CoA levels in the VMN, which was associated with an enhanced CPT-1 activity and food intake (López et al., 2008). Inhibition of AMPK with a dominant-negative adenovirus or inhibition of CPT-1 with etomoxir prevented this ghrelin-mediated effect.

6. Nutrients. Nutrient regulation of appetite involves many of the same signaling mechanisms that are affected by hormones such as insulin and leptin. For example, increased glucose delivery to the hypothalamus results in the inhibition of AMPK activity (Minokoshi et al., 2004; Li et al., 2006). This arises from an increase in ATP levels, results in the activation of ACC, and elevates hypothalamic malonyl CoA content (Wolfgang et al., 2007). Increased CNS glucose metabolism is also postulated to regulate peripheral blood glucose homeostasis and blood triacylglycerol levels according to the astrocyte-neuron lactate shuttle hypothesis, whereby glucose metabolism to lactate in astrocytes provides lactate for neurons, where it is rapidly converted back into pyruvate and leads to activation of K_{ATP} channels (Chih and Roberts, 2003; Pellerin and Magistretti, 2004; Lam et al., 2007).

It is now apparent that amino acids, particularly branched chain amino acids such as leucine, also possess hypophagic effects (Cota et al., 2006; Ropelle et al., 2008; Cota, 2009; Newgard et al., 2009). Amino acids such as leucine are believed to mediate their hypophagic effects via activation of mTOR (Cota et al., 2006), but they have also been shown to inhibit AMPK and decrease phosphorylation of ACC (Ropelle et al., 2008), suggesting that their hypophagic effects might be mediated via alterations in hypothalamic malonyl CoA content. It will be important for future studies to delineate whether both mTOR activation and AMPK inhibition are required for the hypophagic effects of leucine.

7. Cannabinoids. Cannabinoids such as anandamide have also been demonstrated to stimulate appetite via acting upon cannabinoid receptors in the hypothalamus (Jamshidi and Taylor, 2001; van Thuijl et al., 2008). Similar to ghrelin, they also activate AMPK (Kola et al., 2005; van Thuijl et al., 2008) and thus probably increase appetite via inhibition of ACC and decreasing hypothalamic malonyl CoA content (section II.C). However, the cannabinoid effect on AMPK activation will probably inhibit mTOR activity as well (Ropelle et al., 2008), which may also contribute to cannabinoid-induced hyperphagia (section III.C).

B. Regulation of Appetite via the Signal Transducer and Activator of Transcription 3 Pathway

To date, the STAT3 pathway is one of the most thoroughly studied pathways in the regulation of appetite and is thought to be a key participant in mediating the anorexigenic effects of leptin (Bates and Myers, 2003; Myers, 2004; Buettner et al., 2006). Upon leptin binding to its receptor, cytoplasmic STAT3 is recruited to tyrosine residue 1138 of the leptin receptor, whereby it undergoes Janus kinase 2-dependent phosphorylation on tyrosine residue 705 (Myers, 2004). This allows STAT3 to form homodimers that translocate into the nucleus to mediate transcription of its target genes. Using intracerebroventricular delivery of a cell-permeant STAT3 phosphopeptide inhibitor that prevents tyrosine residue 705 phosphorylation of STAT3, Buettner et al. (2006) provided clear evidence that ARC STAT3 is responsible for the anorexigenic effects of lep-

tin, because leptin could not induce hypophagia or weight loss in rats treated with this inhibitor. In addition, mice with a neuron-specific disruption of STAT3 throughout the central nervous system have a significant increase in appetite and become obese (Gao et al., 2004). Likewise, mice with STAT3 signaling abrogated via mutation of tyrosine residue 1178 to alanine in the leptin receptor have a phenotype mimicking the hyperphagia and obesity observed in leptin receptor-deficient *db/db* mice (Bates et al., 2003). It is noteworthy that the anorexigenic effects of estrogen also seem to be me mediated via STAT3 signaling, because estradiol treatment could not induce a reduction in food intake and subsequent body weight in mice with disruption of neuronal STAT3 (Gao et al., 2007a).

Although the described studies illustrate a key role for STAT3 involvement in the anorexigenic effects of key hormones and adipokines, a previous collaboration with the Moran laboratory (Gao et al., 2007b) showed that leptin was able to activate STAT3, although it could not induce hypophagia and subsequent weight loss, in mice treated intracerebroventricularly with an ACC inhibitor. Moreover, delivery of a constitutively active AMPK adenovirus to the hypothalamus prevents the ability of leptin to inhibit AMPK and subsequent food intake, yet leptin-induced STAT3 phosphorylation at tyrosine residue 705 was still observed (Minokoshi et al., 2004). Thus, STAT3 phosphorylation seems to contribute to the anorexigenic effects of leptin, although it is not likely to be the sole mediator.

Although recent studies have undoubtedly highlighted the involvement of the STAT3 pathway in regulating appetite, it will be important in future studies to delineate the downstream target transcripts of STAT3 that are critical in mediating these anorexigenic effects. Furthermore, the relative importance of the STAT3 pathway versus the other pathways to be described below in mediating the hypophagic effects of anorexigens such as leptin and insulin will need to be determined. C75-induced weight loss is not accompanied by concomitant activation of STAT3 (Loftus et al., 2000), but leptin-induced weight loss is accompanied by concomitant rises in hypothalamic malonyl CoA content (Gao et al., 2007b); this stresses the importance of malonyl CoA as a regulator of appetite. Moreover, intracerebroventricular delivery of an adeno-associated viral vector to overexpress MCD in the MBH decreased malonyl CoA levels and prevented the hypophagic effect of leptin, despite activation of STAT3 (He et al., 2006).

C. Regulation of Appetite via the Mammalian Target of Rapamycin Pathway

Much attention has started to focus on the potential role of mTOR in the regulation of appetite (Cota et al., 2006; Ropelle et al., 2008; Cota, 2009). Key studies by Wang and Proud (2006) and Stipanuk (2007)) first implicated mTOR as a key player in the regulation of appetite, because intracerebroventricular treatment with leucine (a potent activator of mTOR and subsequent protein synthesis) induced potent hypophagia and weight loss in rats, effects that were prevented by intracerebroventricular treatment with rapamycin (mTOR inhibitor) (Cota et al., 2006). Furthermore, mTOR was also a key component of the anorexigenic effects of leptin, because leptin could not induce a reduction in food intake and subsequent body weight if rats were pretreated intracerebroventricularly with rapamycin. In contrast, supplementation of leucine in drinking water did not affect appetite in mice subjected to diet-induced obesity (Zhang et al., 2007), although activation of mTOR was not assessed in this study. In another study, mice with a genetic deficiency for mitochondrial branched chain amino acid aminotransferase, a leucine catabolizing enzyme, ate more than their WT littermates despite elevated mTOR activity and subsequent protein synthesis (She et al., 2007). However, the hyperphagia observed in these animals is confounded by the presence of elevated rates of protein degradation, resulting in a futile cycle of continuous protein synthesis and degradation that induced large increases in thermogenesis.

It is noteworthy that mTOR and AMPK are located in the same neuronal subpopulations and are inversely related with regard to changes in feeding behavior (Ropelle et al., 2008). An increase in AMPK activity and decrease in mTOR activity increase appetite, whereas a decrease in AMPK activity and increase in mTOR activity reduce appetite (Minokoshi et al., 2004; Cota et al., 2006; Ropelle et al., 2008). Agents that directly increase mTOR activity in the hypothalamus, such as leucine, also decrease AMPK activity (Ropelle et al., 2008). In addition, leptin-induced hypophagia is accompanied via a decrease in AMPK activity (Minokoshi et al., 2004) and increase in mTOR activity in the hypothalamus (Cota et al., 2006). Yet, because AMPK itself can decrease mTOR activity (Inoki et al., 2003; Dyck and Lopaschuk, 2006), it is uncertain whether the leptin effect on mTOR activity is a direct effect of leptin per se or a secondary effect that is due to a reduction in AMPK activity. More recently, it has also been shown that FAS inhibitors, whose hypophagic effects are also accompanied via a decrease in AMPK activity, stimulate the activation of mTOR (Proulx et al., 2008). Moreover, treatment of mice with the mTOR inhibitor rapamycin prevents the anorexigenic effects of the FAS inhibitors C75 and cerulenin. Because mTOR activation with agents such as leucine also decreases AMPK activity, it will be important for future studies to determine whether mTOR activation in the hypothalamus increases malonyl CoA levels, and whether targeting enzymes that reduce malonyl CoA levels can prevent the effects of mTOR activation on appetite. Such studies will allow us to better understand whether both pathways are required to reduce appetite, or whether mTOR or malonyl CoA is the predominant satiety signal.

IV. Alterations in Hypothalamic 5′AMP-Activated Protein Kinase and Malonyl CoA That Modify Feeding Behavior and Influence Obesity

A. Obesity and Hyperphagia

Obesity is defined as an excess amount of body fat in relation to lean body mass, such that adverse health consequences may occur, resulting in a reduced life expectancy (Haslam and James, 2005; Lopaschuk et al., 2007), whereas being overweight is defined as an increase in body weight in relation to height. The World Health Organization (2000) describes obesity as one of the most obviously visible yet widely neglected public-health problems that threatens to overwhelm both developed and developing countries. The estimated number of deaths attributable to obesity is ~300,000 in the United States alone and has overtaken smoking as the primary preventable cause of illness and premature death (Mokdad et al., 2004).

Although there are many different genetic and environmental factors that can contribute toward the progression of obesity (for review, see Neel et al., 1998; Hebebrand and Hinney, 2009), the most common factor leading to weight gain and eventual obesity is consuming calories in excess of energy expenditure. Thus, hyperphagia is a common feature of obesity, and studies in rodents have demonstrated that high-fat diet-induced obesity reduces the ability of anorexigens, such as insulin and leptin, to reduce food intake (El-Haschimi et al., 2000; Wang et al., 2001; Woods et al., 2004). Such observations illustrate that fuel sensing in the hypothalamus is impaired during nutrient excess/hyperphagia, which probably plays a significant role in the development of obesity. The following sections will highlight the key alterations in components of the signaling cascades that influence hypothalamic malonyl CoA content and how they can be targeted as potential therapies designed to limit appetite in the prevention of obesity.

B. Alterations in Hypothalamic 5′AMP-Activated Protein Kinase Signaling

High-fat diet-induced obesity results in a significant decline in AMPK activity in key areas of the hypothalamus, such as the PVN, and the ability of intracerebroventricular leptin to decrease AMPK activity further is lost (Martin et al., 2006). This inability of leptin to decrease hypothalamic AMPK activity during obesity is thus postulated to be a key component responsible for biological leptin resistance (Martin et al., 2006). However, the fact that high-fat diet-induced obesity already significantly decreases AMPK activity in the PVN but did not have an effect on food intake implies that it is not the absolute level of AMPK activity that is responsible for determining appetite or meal size but rather that dynamic changes in hypothalamic AMPK activity are probably necessary to influence changes in appetite.

It is noteworthy that a recent study in obese Zucker rats demonstrated that these animals possess hypothalamic hypersensitivity to glucose (Colombani et al., 2009). This hypersensitivity was associated with increased hypothalamic mitochondrial activity and increased protein expression of electron transport chain complexes. Thus, increased hypothalamic mitochondrial activity may result in elevated ATP levels, which may inhibit AMPK and may possibly explain why high-fat diet-induced obesity decreases AMPK activity in the PVN.

In our hands, high-fat diet-induced obesity in C57BL/6 mice actually increases AMPK phosphorylation, which is suggestive of increased AMPK activity (W. Keung, A. Palaniyappan, G. D. Lopaschuk, unpublished data). Our findings are consistent with hyperphagia associated with obesity, because increased AMPK activity would result in excessive calorie consumption and contribute toward the obese phenotype. However, it should be noted that our study assessed AMPK phosphorylation in the whole hypothalamus, whereas the study by Martin et al. (2006) assessed AMPK phosphorylation in distinct hypothalamic nuclei such as the PVN and ARC. Furthermore, our studies were performed in C57BL/6 mice, whereas those of Martin et al. (2006) were carried out in FVB mice.

Regardless, one of the most important findings from the study of Martin et al. (2006) is that leptin resistance, which is the inability of leptin to induce an anorexic response, may be due to a lack of AMPK inhibition in response to leptin treatment during obesity (Martin et al., 2006). Moreover, recent findings by Liu et al. (2007) demonstrated that hypothalamic leptin receptor expression is decreased in rats subjected to diet-induced obesity. This result is consistent with the lack of AMPK inhibition in response to leptin treatment that was observed in the study by Martin et al. (2006) and suggests that restoring leptin-mediated inhibition of hypothalamic AMPK may be a viable target for the treatment of hyperphagia and obesity.

C. Alterations in Hypothalamic Acetyl CoA Carboxylase Signaling

The changes in hypothalamic ACC activity during obesity have not been thoroughly investigated but should be expected to follow the changes in AMPK. Because Martin et al. (2006) demonstrated that AMPK phosphorylation and activity were decreased in the PVN region of the hypothalamus after high-fat diet-induced obesity, ACC activity would be expected to be elevated. These changes in ACC activity, however, would not be consistent with a hyperphagic effect in obesity, because increased ACC activity would increase malonyl CoA levels and possibly cause a satiety effect. However, as mentioned in the previous section, it is possible that the absolute level of ACC activity and subsequent effect on malonyl CoA levels is not directly responsible for determining appetite or meal size; rather, dynamic changes in hypothalamic ACC activity and subsequent malonyl CoA content are necessary to influence appetite.

In our hands, we have actually observed that high-fat diet-induced obesity has no effect on hypothalamic ACC activity (W. Keung, A. Palaniyappan, G. D. Lopaschuk, unpublished data). These data do not coincide with the increase we observed in AMPK activity, but we are once again limited by the fact that ACC was assessed in the whole hypothalamus in this study. As Gao et al. (2007b) have shown previously, ACC activity and control of malonyl CoA content in the ARC and PVN are critical components of appetite regulation, and it is entirely possible that if we had assessed ACC activity in these specific hypothalamic regions, we would have obtained different results.

D. Alterations in Hypothalamic Malonyl CoA Decarboxylase Signaling

Although studies have shown that targeting hypothalamic MCD can influence malonyl CoA content and appetite (He et al., 2006), no studies published to date have investigated MCD activity in the hypothalamus in the obese state. However, a recent case report of a girl with MCD deficiency who displayed an extremely low appetite (de Wit et al., 2006) is consistent with the hypothesis that malonyl CoA is a powerful regulator of energy intake. It is noteworthy that subjecting mice to high-fat diet-induced obesity actually resulted in a strong trend toward a reduction in MCD protein expression in the whole hypothalamus (W. Keung, A. Palaniyappan, G. D. Lopaschuk, unpublished data). Once more, it is possible that if we had assessed specific hypothalamic regions such as the ARC and PVN, MCD protein expression might have been significantly decreased. However, a decrease in MCD expression would not be consistent with a hyperphagic effect contributing toward the development of obesity in these animals. Regardless, when we assessed hypothalamic malonyl CoA content in these animals, we observed no difference between lean and obese mice, which suggests that perhaps the increase in AMPK activity and decrease in MCD activity cancelled each other out with regard to the lack of effect on malonyl CoA content.

Because of the lack of extensive studies investigating the changes in hypothalamic malonyl CoA regulation during obesity, it is vital that future research focus on elucidating the changes that take place during obesity with regard to AMPK, ACC, and MCD in different hypothalamic nuclei. Further understanding of how these enzymes are altered in obesity will be important in determining the ideal target for treating hyperphagia and obesity.

E. Alterations in Hypothalamic Fatty Acid Synthase Signaling

To our knowledge, there are no published reports demonstrating whether FAS mRNA and protein expression are altered in obesity, although one would speculate that FAS protein expression and activity would be increased in hypothalamic nuclei/regions implicated in appetite control. Increased FAS activity in ARC or PVN would lower malonyl CoA levels and contribute to the hyperphagia associated with obesity. Similar to AMPK, ACC, and MCD, future research should focus on obesity-induced changes in FAS expression and activity in the hypothalamus to determine which enzyme target(s) is the most clinically relevant for altering malonyl CoA levels to treat obese individuals.

F. Cachexia and Hypophagia

Whereas the previous sections dealt with the alterations in hypothalamic malonyl CoA regulation that contribute toward hyperphagia and obesity, it is important that we also briefly touch upon a different area of disease and appetite. Cachexia often results from excessive inflammation and results in severe weight loss (Morley et al., 2006; Yeh et al., 2007) that arises equally from muscle and fat. It is noteworthy that a reduction in neuronal nitric-oxide synthase is believed to play a role in causing the cachexia associated with cancer (Wang et al., 2005; Morley and Farr, 2008). Inhihition of neuronal nitric-oxide synthase in the hypothalamus is associated with a reduction in AMPK activity, which may result in elevated hypothalamic malonyl CoA content (Morley and Farr, 2008), decreasing appetite and resulting in cachexia. Furthermore, the Lou/C rat strain exhibits resistance to obesity caused by a reduction in caloric intake of ~40% that has recently been shown to arise from a lack of AMPK activation in response to starvation (Taleux et al., 2008). In addition, as mentioned in section IV.D, a recent case report described a female patient with MCD deficiency who displayed a dramatic reduction in appetite (de Wit et al., 2006). These observations suggest that, as opposed to the therapeutic approach to treating obesity-associated hyperphagia, therapy aimed at stimulating AMPK, FAS, or MCD or at inhibiting ACC can be used to reduce hypothalamic malonyl CoA content. Such therapy could be a novel approach to counteract the cachexia that is often observed in patients with cancer.

V. Optimizing Hypothalamic Intermediary Metabolism as a Pharmacological Intervention to Modify Appetite

A. Targeting the 5'AMP-Activated Protein Kinase–Acetyl CoA Carboxylase–Malonyl CoA Decarboxylase–Fatty Acid Synthase–Malonyl CoA Axis to Modify Appetite

As we have highlighted in sections II to IV, numerous studies support the idea that targeting either AMPK, ACC, or MCD to modify hypothalamic malonyl CoA content has powerful effects on appetite, and thus these components may be potential to be a pharmacological targets to reduce hyperphagia associated with obesity. Strategies that reduce hypothalamic AMPK activity,

such as intracerebroventricular delivery of insulin, glucose, or lactate, decrease food intake and are associated with a reduction in body weight in experimental rodents (Minokoshi et al., 2004; Cha and Lane, 2009). In addition, strategies that activate ACC, such as intracerebroventricular delivery of citrate, are also associated with reduced food intake and a reduction in body weight in experimental rodents (Cesquini et al., 2008; Stoppa et al., 2008). To date, there are no reported studies determining whether hypothalamic MCD inhibition can be used as a target to reduce food intake and subsequent body weight in experimental rodents. It is noteworthy that the expression of this enzyme in the hypothalamus dramatically increases during fasting (G. D. Lopaschuk, unpublished data) (Fig. 4), suggestive of a lower malonyl CoA content. Furthermore, a recent case report observed a dramatic reduction in appetite in a girl harboring MCD deficiency (de Wit et al., 2006), which would presumably increase hypothalamic malonyl CoA content, thereby supporting MCD as a therapeutic target in the brain for reducing obesity-associated hyperphagia. Preliminary data in our laboratory supports this proposal, because both oral and intracerebroventricular delivery of novel MCD inhibitors decreased food intake and body weight in mice (G. D. Lopaschuk, unpublished data) (Fig. 4). As mentioned in previous sections, inhibition of hypothalamic FAS with inhibitors such as C75 and cerulenin has potent hypophagic and subsequent anorexigenic effects that are associated with an increase in hypothalamic malonyl CoA content (Loftus et al., 2000; Cha et al., 2004, 2005; Wolfgang and Lane, 2006b, 2008; Wolfgang et al., 2007). Furthermore, genetic deletion of FAS in the ARC and PVN is also associated with elevated hypothalamic malonyl CoA content and reduced food intake and body weight gain in mice (Chakravarthy et al., 2007). These findings support the proposal that targeting FAS may be a possible therapeutic approach for reducing obesity-associated hyperphagia.

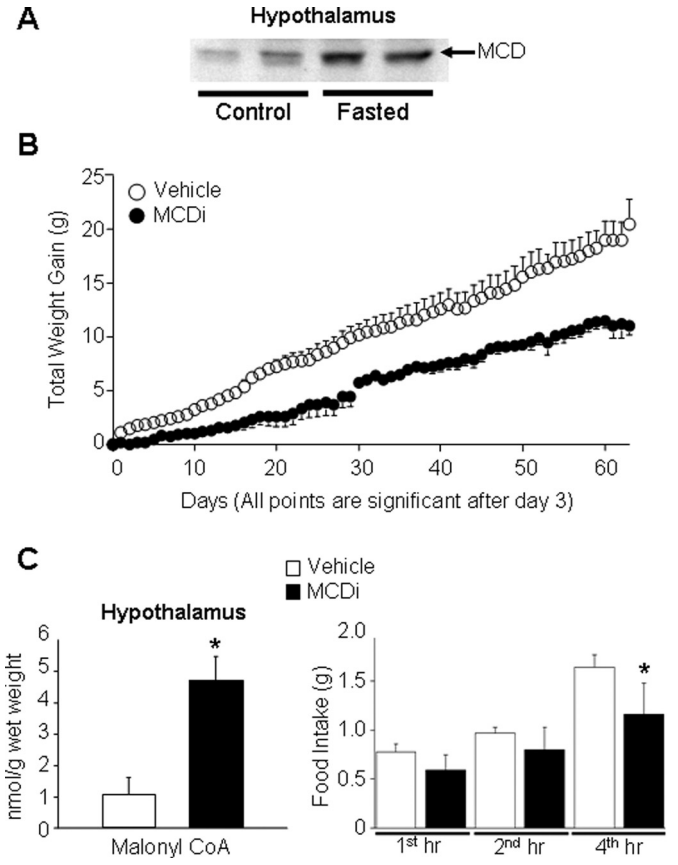

FIG. 4. Hypothalamic inhibition of MCD increases malonyl CoA levels and decreases food intake and subsequent body weight. A, immunoblot showing that MCD protein expression is increased in the hypothalamus during fasting. B, intracerebroventricular delivery of novel MCD inhibitors (MCDi) decreases body weight gain in mice subjected to a high-fat diet (60% calories from fatty acids). Intracerebroventricular delivery of MCDi increases whole-hypothalamus malonyl CoA content (C) and decreases food intake by 4 h of refeeding after a period of fasting (D). *, $P < 0.05$, significantly different from vehicle control treated counterpart.

An important limitation that one needs to consider with regard to targeting either AMPK, ACC, MCD, or FAS as novel targets to regulate hypothalamic malonyl CoA content and subsequent appetite, however, is the fact that altering hypothalamic malonyl CoA content has powerful effects on peripheral energy metabolism (for excellent reviews on this topic, see Xue and Kahn, 2006; Ahima and Lazar, 2008; Wolfgang and Lane, 2008; Sandoval et al., 2009). For example, increasing hypothalamic malonyl CoA has prominent effects on skeletal muscle mitochondrial biogenesis, elevating rates of mitochondrial fatty acid oxidation and uncoupling protein activity (Cha et al., 2005, 2006; Wolfgang and Lane, 2008). However, increased uncoupling protein activity is associated with increased thermogenesis (Bouillaud et al., 1985; Gong et al., 1997; Hinz et al., 1999; Sprague et al., 2007), and it is unknown what the consequences would be for uncontrolled thermogenesis in obese humans. Furthermore, it will be difficult to find a practical solution for targeting these enzymes to increase malonyl CoA selectively in the hypothalamus. An agent that managed to cross the blood-brain barrier and increase malonyl CoA content in the hypothalamus would probably also target peripheral tissues and increase malonyl CoA content there as well. Such an effect would counter the peripheral decrease in malonyl CoA and subsequent increase in peripheral fatty acid oxidation rates that are conferred by elevations of hypothalamic malonyl CoA content (Cha et al., 2005, 2006; Wolfgang and Lane, 2008). This is a potential area of concern because increasing skeletal muscle fatty acid oxidation rates is a novel approach for the treatment of obesity-induced skeletal muscle insulin resistance (Watt et al., 2006; Savage et al., 2007; Bruce et al., 2009). In contrast, reducing fatty acid oxidation rates in the heart is also associated with protection against ischemic heart disease (Ussher and Lopaschuk, 2006, 2008, 2009; Jaswal and Lopaschuk, 2007; Jaswal et al., 2009) and may actually benefit insulin-resistant muscle (Finck et al., 2005; Koves et al., 2008; Muoio and Newgard, 2008). In this scenario, peripheral increases in malonyl CoA con-

tent may actually benefit obese humans independently from hypothalamic malonyl CoA-induced hypophagic effects. It will be extremely important in future studies to delineate in greater detail the signaling mechanisms regulating hypothalamic control of peripheral energy expenditure to optimize targeting hypothalamic malonyl CoA content as a possible therapy for obesity-associated hyperphagia.

B. Targeting Hypothalamic Intermediary Metabolism via Hormone Receptor Signaling to Modify Appetite

Aside from targeting the AMPK–acetyl CoA carboxylase–malonyl CoA decarboxylase–FAS–malonyl CoA axis, there are a number of other possible targets that can influence appetite via modification of hypothalamic intermediary metabolism, which may ultimately affect malonyl CoA content (Fig. 5). Leptin deficiency in humans is associated with severe obesity (Montague et al., 1997), and thus leptin treatment of such persons would likely prove to be beneficial. However, treatment with leptin does have limitations, such as a very short half-life [~25 min in humans (Klein et al., 1996)], and in a small number of human trials is actually not associated with a reduction in energy intake (Fogteloo et al., 2003; Zelissen et al., 2005). Furthermore, the phenomenon of leptin resistance observed in rodents may also be a confounding factor limiting the use of leptin as a treatment for hyperphagia in obese humans, although a recent study in humans suggests that central leptin resistance may be nonexistent (Eikelis et al., 2007).

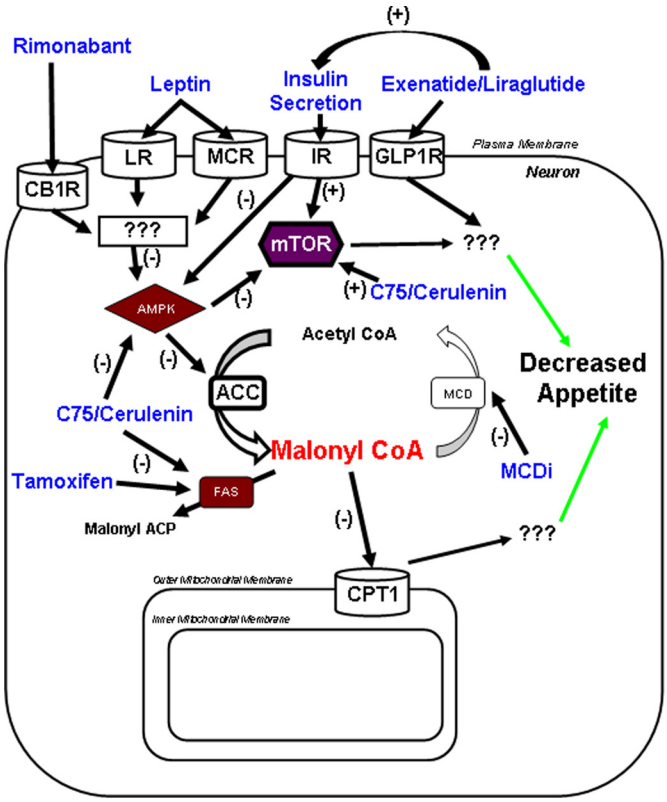

FIG. 5. Potential pharmacological agents that may target the CNS to regulate appetite. A schematic depicting known possible pharmacological agents that may increase hypothalamic malonyl CoA to reduce appetite.

Inhibition of hypothalamic adiponectin signaling represents another potential target for reducing appetite in obese persons (Kubota et al., 2007), although a recent study suggests that adiponectin does not cross the BBB (Spranger et al., 2006). In addition, peripheral adiponectin action has such beneficial effects on insulin sensitivity and cardiovascular outcome that one would have to be careful in targeting adiponectin or adiponectin receptors as a possible treatment for obesity associated hyperphagia (Shibata et al., 2005, 2007a,b; Shinmura et al., 2007; Li et al., 2009).

The branched-chain amino acids, such as leucine, also represent a possible novel target for treating obesity-associated hyperphagia, through their ability to activate mTOR in the hypothalamus (Cota et al., 2006; Ropelle et al., 2008; Cota, 2009). Unfortunately, a recent study has shown that although branched chain amino acid supplementation reduces food intake and body weight in diet-induced obese rats, there was no improvement in insulin resistance versus control supplemented diet-induced obese rats (Newgard et al., 2009). Moreover, pair-fed diet-induced obese rats did exhibit a reversal of glucose intolerance and insulin resistance, suggesting that branched chain amino acids make an independent contribution to the development of obesity-induced insulin resistance and support previous proposals suggesting that peripheral mTOR activation leads to the development of insulin resistance (Um et al., 2004, 2006).

Another recent target for treating obesity-associated hyperphagia is the inhibition of cannabinoid receptors. Rimonabant was the first selective cannabinoid receptor antagonist approved as an antiobesity agent. It was initially met with much promise and also demonstrated beneficial effects against cardiovascular risk factors such as smoking (Gelfand and Cannon, 2006; Cahill and Ussher, 2007; Woods, 2007). Unfortunately, the clinical utility of rimonabant has been severely hampered because of adverse effects, including its ability to increase the risk of anxiety and depression, which is itself associated with an increased risk for suicide (Christensen et al., 2007a,b; Soyka, 2008). As such, the use of rimonabant in humans has currently been suspended.

Last, the recently approved type 2 diabetes therapeutics exenatide and liraglutide have also been shown to reduce food intake and body weight in rodent studies (Mack et al., 2006; Raun et al., 2007a,b). Human trials support the rodent data, because both exenatide and liraglutide decrease body weight in patients with type 2 diabetes (Poon et al., 2005; Riddle et al., 2006; Kim et al., 2007; Vilsbøll et al., 2007). These effects are probably due to their GLP-1 mimetic actions, because GLP-1 signaling in the hypothalamus is associated with reductions in food intake (Baggio et al., 2004a,b; Tang-Christensen et al., 2000). Regardless, it will be important for future studies to further delineate in detail the mecha-

nisms involved in inducing the GLP-1-dependent hypophagic effect in the hypothalamus, because exenatide and liraglutide do appear at the moment to have more clinical promise than targeting hypothalamic adipokine signaling, branched chain amino acid metabolism, or cannabinoid receptor antagonism.

VI. Summary

The hypothalamic ARC integrates hormonal and nutritional signals to mediate the control of food intake and the regulation of body energy balance. Malonyl CoA in the ARC has recently emerged as an important "metabolic" signaling molecule involved in mediating energy homeostasis. Increases in hypothalamic ARC malonyl CoA signal an "energy surplus" in the body, whereas decreases in malonyl CoA signal an "energy deficit." Many of the complex signaling systems that integrate hormonal, fuel substrate, and neuronal modulation of energy homeostasis can modify hypothalamic malonyl CoA levels. How alterations in malonyl CoA mediate downstream pathways involved in energy homeostasis is still poorly understood. However, direct modification of enzyme activity involved in modulating malonyl CoA levels (i.e., MCD, FAS, ACC, and AMPK) can have profound impacts on body energy balance. A better understanding of how malonyl CoA regulates energy balance should provide a novel approach to targeting intermediary metabolism in the hypothalamus as a mechanism to control appetite and body weight.

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