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The dysregulation of the endocannabinoid system in diabetes—a tricky problem

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Abstract

Endocannabinoids (ECs) are small lipid mediators that play a critical role in energy metabolism. Human studies have shown that the EC tone in peripheral tissues positively correlates with increased adiposity. Furthermore, pharmacological inhibition of EC signaling results in weight loss in humans. However, the mechanisms that cause the dysregulation of the EC system in obesity are not well-understood. Since the clinical utility of currently available EC blockers is severely limited due to their side effects like depression and suicidal ideation that are caused by central effects, it is important to delineate the role of central and peripheral effects of EC signaling in regulating glucose and lipid metabolism.

Keywords

Endocannabinoids; Leptin action; Adipose tissue; Mediobasal hypothalamus; Fat metabolism

The increasing prevalence of obesity in developed and developing countries will worsen a pandemic of type 2 diabetes mellitus (DM2)—a major scourge of modern societies. Obesity and DM2 are two major risk factors that contribute to the development of cardiovascular disease, the number one cause of death throughout the world. Obesity along with a sedentary lifestyle often leads to insulin resistance and metabolic inflexibility that may eventually progress to DM2. The link between excessive nutrient intake and DM2 is poorly understood; yet delineating this relationship is one of the signal tasks ahead of us. Evidence is accumulating that insulin resistance (as defined by a lack of insulin action *in vivo*) is not necessarily due to a decrease of insulin receptor signaling in target organs like liver or adipose tissue. Instead, it may be due to either impaired insulin signaling in nonclassical organs like the hypothalamus that mediate important aspects of insulin action or due to the dysregulation of other signaling networks that interfere with distal steps of the insulin receptor signaling cascade. One such signaling system that seems to play an important role in linking obesity to diabetes is the endocannabinoid (EC) system.

The EC system and appetite regulation

ECs are bioactive lipid mediators such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG) that are synthesized and released on demand. EC signaling participates in the regulation of myriad physiological functions ranging from pain perception, mood, and blood

pressure to synaptic plasticity via activating the G-protein coupled receptors CB1 and CB2. CB1 receptors are highly abundant in the central nervous system (CNS), but are also expressed in many peripheral tissues such as white adipose tissue (WAT), liver, and muscle and have been shown to regulate energy metabolism [1]. CB2 receptors are primarily expressed by immune and hematopoietic cells. Recent studies indicate that CB2 receptors are also present in the pancreas and human WAT, yet their role in energy metabolism is not clearly defined [1–3]. Long before the EC system had been discovered, it was known that cannabis consumption gives you the “munchies.” The underlying biology of this phenomenon has become clear with the realization that the CB1 receptor plays a critical role in appetite regulation. Systemic CB1 receptor activation increases food intake, whereas CB1 receptor blockade suppresses food intake. Further studies indicated that the modulation of brain CB1 receptor signaling mediates these effects on food intake [4, 5]. Since excess caloric intake is a major risk factor for the metabolic syndrome, it was initially thought that CB1 receptor antagonists like rimonabant improve glucose and lipid homeostasis by reducing food intake. However, it turned out that the role of the EC system in modulating energy homeostasis is not limited to appetite regulation.

Leptin regulates hypothalamic EC levels

The effects of CB1 receptor antagonists on energy homeostasis have considerable similarities to those of leptin, an adipocyte-derived hormone that also regulates food intake and nutrient partitioning chiefly through brain pathways. In leptin-deficient ob/ob mice, exogenous leptin administration suppresses food intake, increases energy expenditure, and improves glucose and lipid metabolism [6–8]. A potential crosstalk between the EC system and leptin signaling was suggested by the observation that, in mouse models of impaired leptin signaling either due to leptin deficiency (ob/ob mice), impaired leptin signaling (db/db mice that express a defective leptin receptor), or acquired leptin resistance (diet-induced obese mice), EC tone was increased. Elevated EC levels were found in the hypothalamus, but also in peripheral organs like the liver, pancreas, and WAT [4, 9, 10]. In leptin-sensitive ob/ob mice, acute leptin treatment reduced hypothalamic EC levels and systemic CB1 receptor blockade suppressed food intake in both db/db and ob/ob mice [4]. These findings suggest that ECs regulate food intake downstream of leptin signaling.

Food intake-independent effects of CB1 antagonists

Intriguingly, long-term treatment with the CB1 receptor antagonist rimonabant made mice only temporarily hypophagic, whereas they continuously lost weight throughout the treatment course [11, 12]. Furthermore, CB1 receptor knock-out (KO) mice are resistant to diet-induced obesity although their food intake is not different from that of wild-type mice [13, 14]. Indeed, similar findings have been made in obese humans where large clinical trials have proven that rimonabant significantly lowered body weight and improved many features of the metabolic syndrome: Triglycerides, blood pressure and insulin resistance were reduced and high-density lipoproteins cholesterol was increased in both obese, but nondiabetic, persons and DM2 patients. These metabolic improvements were greater than those expected from the degree of weight loss in these patients, again suggesting that rimonabant improves the metabolic syndrome independent of food intake [15–17]. The mechanisms by which CB1 receptor antagonists improve lipid profile and glucose homeostasis include an increase in energy expenditure and β -oxidation [18, 19] and a suppression in lipogenesis in the liver and possibly WAT [10, 14]. One of the mediators involved may be adiponectin, an insulin-sensitizing adipokine, which is usually decreased in obesity. CB1 antagonists increase adiponectin levels and, therefore, increase insulin sensitivity [20, 21].

The EC system is dysregulated in obesity

Obese human individuals have elevated AEA and 2-AG plasma levels compared to nonobese controls, indicating an increased systemic EC tone in obesity [22–24]. Since visceral fat plays an important role in the pathogenesis of the metabolic syndrome, it is particularly interesting that ECs are also elevated in this tissue in obese humans [9]. Interestingly, in humans, only plasma levels of 2-AG and not those of AEA positively correlate with increased visceral adiposity [23, 24]. Furthermore, a reduction of visceral adiposity in obese men by lifestyle intervention led to a decrease in 2-AG plasma levels [25]. What are likely reasons for the hyperactivity of the EC system in obesity? Increased adiposity potentially increases EC levels, as it has been shown that human adipocytes are capable of synthesizing ECs [26]. Immune cells such as macrophages represent an additional source for ECs in WAT [27]. The fact that excess caloric intake leads to increased macrophage infiltration into WAT could contribute to the elevated EC levels in visceral fat depots of obese individuals, particularly as proinflammatory stimuli that trigger macrophage activation and infiltration have been shown to stimulate the synthesis of ECs by these cells [28]. However, it is still not clear what the relative quantitative contributions of macrophages versus adipocytes in releasing ECs are. It should be pointed out that, in high-fat diet-fed mice, increased levels of ECs have also been detected in other metabolically important organs such as the pancreas, muscle, brown adipose tissue, heart, and kidney [2, 29] and diverse mechanisms may be at work controlling EC tone in different tissues. Furthermore, the diet composition could modulate systemic EC tone as certain polyunsaturated fatty acids potentially serve as precursors for EC production [29, 30]. Glucocorticoids stimulate EC biosynthesis, and since glucocorticoids are elevated in obesity, they could be an important contributor to the increased EC tone observed in obese individuals [31].

The major degrading enzyme for AEA is fatty acid amide hydrolase (FAAH). FAAH expression in WAT negatively correlates with elevated AEA plasma concentrations in obese human subjects [22]. The exact reason for the low FAAH expression levels in obese individuals is not fully understood, but it may be a consequence of insulin resistance in adipocytes. In vitro, insulin induces FAAH expression and thereby decreases EC levels in adipocytes derived from insulin-sensitive humans, whereas in adipocytes of insulin-resistant humans, insulin fails to increase FAAH expression [32]. In keeping with this, hyperinsulinemia in lean human subjects increased FAAH gene expression in the subcutaneous fat compartment, but failed to do so in obese individuals [33]. Thus, insulin resistance may be a contributor to the increased EC tone in obesity and not just a consequence of increased EC levels. Vice versa, elevated ECs increase adiposity and, as a consequence, cause further insulin resistance, starting and perpetuating a vicious cycle [14, 23, 24].

Central pathways regulate peripheral EC tone

Another possible mechanism that may contribute to an increased EC tone in obesity comes from the concept that the brain regulates metabolism in peripheral organs, like liver and WAT, and our realization that this brain control of metabolism is impaired in obesity and DM2. The brain assesses whole-body energy homeostasis by sensing the levels of nutrients and hormones and in turn orchestrates nutrient partitioning by either circulating factors or the autonomic nervous system [34, 35]. Studies investigating the mechanisms by which leptin regulates carbohydrate and lipid metabolism have advanced our understanding of this CNS control of metabolism and highlighted its importance as almost all effects of this major adiposity signal are mediated via the brain. Systemic administered leptin leads to a selective loss of adiposity while preserving lean body mass. This occurs in part independent of food

intake by increasing mitochondrial oxidation of fatty acids and suppression of lipogenesis in WAT [36, 37]. Since ECs promote lipogenesis in WAT [14, 20], one could speculate that leptin controls WAT lipogenesis by regulating the EC tone in WAT via the brain. Indeed, at least in Sprague–Dawley rats, leptin suppresses lipogenesis and EC tone in epididymal WAT when it is directly infused into the mediobasal hypothalamus (MBH), a key brain area for the regulation of whole-body energy homeostasis. This regulation of WAT metabolism by MBH leptin is independent of caloric intake, circulating glucose, and insulin levels, but it does depend on the ability of MBH leptin to decrease EC levels, since systemic CB1 receptor activation blunts the suppression of lipogenesis in epididymal WAT by MBH leptin (see Fig. 1) [38]. As obesity is almost invariably associated with central leptin resistance, it is conceivable that part of the hyperactivity of the EC system in obesity is due to a failure of central leptin to restrain WAT EC tone. At present, it remains unclear if and how central pathways regulate the EC tone in other fat depots such as subcutaneous, mesenteric, and perirenal WAT where ECs may be differentially regulated under high-fat diet conditions [2].

An important question that still needs to be answered is if the effects of systemic CB1 receptor activation on lipogenesis are mediated through direct WAT CB1 receptor activation or if this occurs through central CB1 receptors. This has clinical relevance since drugs likerimonabant or taranabant [39] have recently been taken off the market due to their side effect profile of increased anxiety, depression, and suicidal ideation. These psychiatric side effects result from the central actions of these drugs that do cross the blood–brain barrier.

Peripheral versus central effects of EC signaling

Potential direct effects of ECs on WAT metabolism are depicted in Fig. 1. In cultured adipocytes, CB1 receptor activation increases lipoprotein lipase (LPL) activity as well as fatty acid synthase (FAS) mRNA expression [14, 20]. Both enzymes potentially increase triglyceride content in adipocytes: LPL through enhanced very low-density lipoprotein hydrolysis and fatty acid uptake and FAS through increased de novo lipogenesis. Glucose uptake is enhanced due to the translocation of glucose transporter 4 (GLUT4) resembling insulin action in WAT in an in vitro model of transfected adipocytes (Fig. 1), although it remains unclear whether this reflects in vivo physiology [40, 41]. This may sound paradoxical, as high EC levels seem to be associated with systemic insulin resistance rather than with insulin-like actions, but it is not yet clear if ECs impair peripheral glucose utilization (uptake into muscle and WAT) versus hepatic insulin action (i.e., insulin's ability to suppress hepatic glucose production) or both. Furthermore, it has not been investigated if ECs still have these insulin-like properties in adipocytes from insulin-resistant individuals. Thus, whether these direct effects of CB1 receptor activation also occur in vivo and have physiological relevance in the regulation of WAT metabolism is unclear at present.

Since the promise of CB1 antagonists, likerimonabant, to be effective drugs against obesity and the metabolic syndrome is severely diminished by their unfavorable side effects, a better understanding of the peripheral and central effects of CB1 antagonists is an important task ahead of us as it would provide a rationale to develop peripherally restricted CB1 antagonists [16, 17, 42]. Nogueiras et al. tried to address this question by comparing the effects of intracerebroventricular (ICV) versus systemic CB1 receptor blockade on energy metabolism [43]. Systemic CB1 receptor blockade increased lipid mobilization and enhanced glucose uptake more so than ICV. However, systemic administration does lead to both central and peripheral CB1 antagonism, whereas the ICV dose chosen in the study is unlikely to result in CB1 antagonism in the whole CNS (3 mg/rat/day systemic versus only 5 µg/rat/day ICV). One approach to uncouple central from peripheral EC effects in the regulation of WAT, for example, would be to block EC signaling in the brain during systemic CB1 agonism. Another approach could be to denervate WAT and infuse CB1

agonists or antagonists systemically [38]. The denervation would obliterate any CNS effects on WAT metabolism that are mediated through the autonomic nervous system, which plays a pivotal role in the brain control of metabolism. To gather more definitive data, tissue-specific CB1 receptor KO models would be valuable in defining peripheral EC action. The first and so far only tissue-specific KO is a hepatocyte-specific CB1 receptor KO (LCB1 KO) which has a revealing phenotype. LCB1 KO mice do become obese when challenged with a high-fat diet, but are markedly less susceptible to high-fat diet-induced insulin resistance, hepatic steatosis, and dyslipidemia compared to controls [19]. Intriguingly, these findings suggest that the major sequelae of the metabolic syndrome (for which high-fat diet feeding is a common model in rodents) can be dissociated from adiposity by peripheral CB1 antagonism. Furthermore, LCB1 KO mice develop a similar degree of obesity as wild-type mice when challenged by a high-fat diet which indicates that the fat mass-reducing effects of systemic CB1 receptor antagonists occur via extrahepatic CB1 receptors. Further studies into the role of peripheral CB1 receptor signaling via either tissue-specific KO models of muscle, pancreas, and WAT or via the use of peripherally restricted CB1 agonist and antagonists will be critically important.

Taken together, the dysregulation of the EC system in human obesity and DM2 plays an important role in the development of dyslipidemia, impaired glucose tolerance, and hepatic steatosis and adiposity. Since leptin has the ability to restrain the EC tone at least in WAT, it is possible that part of the elevated peripheral EC tone is caused by hypothalamic leptin resistance. Whether this applies to other tissues like liver and muscle remains to be investigated. Likewise, how other hormones like insulin or nutrients that also participate in the brain control of metabolism impact the EC system needs further study. We have a long way to go in understanding the details of the brain control of metabolism and the peripheral mediators that exert this control in target tissues like WAT and liver. Finally, the development of peripherally restricted CB1 receptor antagonists may be a promising strategy to tackle the metabolic syndrome and these may avoid the prohibitive side effects of the currently available CB1 receptor antagonists.

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Abbreviations

2-AG	2-arachidonoylglycerol
ACC	acetyl-CoA carboxylase
AEA	anandamide
CNS	central nervous system
DM2	type 2 diabetes mellitus
ECs	endocannabinoids
FAAH	fatty acid amide hydrolase
FAS	fatty acid synthase
GLUT4	glucose transporter 4
HSL	hormone-sensitive lipase

ICV	intracerebroventricular
KO	knock-out
LCB1	hepatocyte-specific CB1 receptor knock-out
LPL	lipoprotein lipase
MBH	mediobasal hypothalamus
NE	norepinephrine
Pepck	phosphoenolpyruvate kinase
PPARγ	peroxisome proliferator-activated receptor γ
Srebp1c	sterol regulatory element-binding protein-1c
UCP2	uncoupling protein 2
WAT	white adipose tissue

References

1. Pacher P, Batkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev.* 2006; 58:389–462. 58/3/389 [pii]. 10.1124/pr.58.3.2 [PubMed: 16968947]
2. Starowicz KM, Cristino L, Matias I, Capasso R, Racioppi A, Izzo AA, Di Marzo V. Endocannabinoid dysregulation in the pancreas and adipose tissue of mice fed with a high-fat diet. *Obesity (Silver Spring).* 2008; 16:553–565. oby2007106 [pii]. 10.1038/oby.2007.106 [PubMed: 18239598]
3. Roche R, Hoareau L, Bes-Houtmann S, Gonthier MP, Laborde C, Baron JF, Haffaf Y, Cesari M, Festy F. Presence of the cannabinoid receptors, CB1 and CB2, in human omental and subcutaneous adipocytes. *Histochem Cell Biol.* 2006; 126:177–187.10.1007/s00418-005-0127-4 [PubMed: 16395612]
4. Di Marzo V, Goparaju SK, Wang L, Liu J, Batkai S, Jarai Z, Fezza F, Miura GI, Palmiter RD, Sugiura T, Kunos G. Leptin-regulated endocannabinoids are involved in maintaining food intake. *Nature.* 2001; 410:822–825. [PubMed: 11298451]
5. Williams CM, Kirkham TC. Anandamide induces overeating: mediation by central cannabinoid (CB1) receptors. *Psychopharmacology (Berl).* 1999; 143:315–317. [PubMed: 10353436]
6. Weigle DS, Bukowski TR, Foster DC, Holderman S, Kramer JM, Lasser G, Lofton-Day CE, Prunkard DE, Raymond C, Kuijper JL. Recombinant ob protein reduces feeding and body weight in the ob/ob mouse. *J Clin Invest.* 1995; 96:2065–2070. [PubMed: 7560100]
7. Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, Lallone RL, Burley SK, Friedman JM. Weight-reducing effects of the plasma protein encoded by the obese gene. *Science.* 1995; 269:543–546. [PubMed: 7624777]
8. Pelleymounter MA, Cullen MJ, Baker MB, Hecht R, Winters D, Boone T, Collins F. Effects of the obese gene product on body weight regulation in ob/ob mice. *Science.* 1995; 269:540–543. [PubMed: 7624776]
9. Matias I, Gonthier MP, Orlando P, Martiadis V, De Petrocellis L, Cervino C, Petrosino S, Hoareau L, Festy F, Pasquali R, Roche R, Maj M, Pagotto U, Monteleone P, Di MV. Regulation, function, and dysregulation of endocannabinoids in models of adipose and beta-pancreatic cells and in obesity and hyperglycemia. *J Clin Endocrinol Metab.* 2006; 91:3171–3180. [PubMed: 16684820]
10. Osei-Hyiaman D, DePetrillo M, Pacher P, Liu J, Radaeva S, Batkai S, Harvey-White J, Mackie K, Offertaler L, Wang L, Kunos G. Endocannabinoid activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet-induced obesity. *J Clin Invest.* 2005; 115:1298–1305. [PubMed: 15864349]

11. Ravinet Trillou C, Arnone M, Delgorge C, Gonalons N, Keane P, Maffrand JP, Soubrie P. Anti-obesity effect of SR141716, a CB1 receptor antagonist, in diet-induced obese mice. *Am J Physiol Regul Integr Comp Physiol*. 2003; 284:R345–353. 00545.2002 [pii]. 10.1152/ajpregu.00545.2002 [PubMed: 12399252]
12. Poirier B, Bidouard JP, Cadrouvele C, Marniquet X, Staels B, O'Connor SE, Janiak P, Herbert JM. The anti-obesity effect of rimonabant is associated with an improved serum lipid profile. *Diabetes Obes Metab*. 2005; 7:65–72. DOM374 [pii]. 10.1111/j.1463-1326.2004.00374.x [PubMed: 15642077]
13. Ravinet Trillou C, Delgorge C, Menet C, Arnone M, Soubrie P. CB1 cannabinoid receptor knockout in mice leads to leanness, resistance to diet-induced obesity and enhanced leptin sensitivity. *Int J Obes Relat Metab Disord*. 2004; 28:640–648. 0802583 [pii]. 10.1038/sj.ijo.0802583 [PubMed: 14770190]
14. Cota D, Marsicano G, Tschop M, Grubler Y, Flachskamm C, Schubert M, Auer D, Yassouridis A, Thone-Reineke C, Ortmann S, Tomassoni F, Cervino C, Nisoli E, Linthorst ACE, Pasquali R, Lutz B, Stalla GK, Pagotto U. The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *J Clin Invest*. 2003; 112:423–431. [PubMed: 12897210]
15. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *JAMA*. 2006; 295:761–775. [PubMed: 16478899]
16. Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet*. 2005; 365:1389–1397. S0140-6736(05) 66374-X [pii]. 10.1016/S0140-6736(05)66374-X [PubMed: 15836887]
17. Despres JP, Golay A, Sjostrom L. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Engl J Med*. 2005; 353:2121–2134. [PubMed: 16291982]
18. Liu YL, Connoley IP, Wilson CA, Stock MJ. Effects of the cannabinoid CB1 receptor antagonist SR141716 on oxygen consumption and soleus muscle glucose uptake in Lep(ob)/Lep (ob) mice. *Int J Obes (Lond)*. 2005; 29:183–187. 0802847 [pii]. 10.1038/sj.ijo.0802847 [PubMed: 15558076]
19. Osei-Hyiaman D, Liu J, Zhou L, Godlewski G, Harvey-White J, Jeong WI, Batkai S, Marsicano G, Lutz B, Buettner C, Kunos G. Hepatic CB1 receptor is required for development of diet-induced steatosis, dyslipidemia, and insulin and leptin resistance in mice. *J Clin Invest*. 2008; 118:3160–3169. 10.1172/JCI34827 [PubMed: 18677409]
20. Bellocchio L, Cervino C, Vicennati V, Pasquali R, Pagotto U. Cannabinoid type 1 receptor: another arrow in the adipocytes' bow. *J Neuroendocrinol*. 2008; 20(Suppl 1):130–138. JNE1682 [pii]. 10.1111/j.1365-2826.2008.01682.x [PubMed: 18426512]
21. Bensaid M, Gary-Bobo M, Esclangon A, Maffrand JP, Le Fur G, Oury-Donat F, Soubrie P. The cannabinoid CB1 receptor antagonist SR141716 increases Acp30 mRNA expression in adipose tissue of obese fa/fa rats and in cultured adipocyte cells. *Mol Pharmacol*. 2003; 63:908–914. [PubMed: 12644592]
22. Engeli S, Bohnke J, Feldpausch M, Gorzelniak K, Janke J, Batkai S, Pacher P, Harvey-White J, Luft FC, Sharma AM, Jordan J. Activation of the peripheral endocannabinoid system in human obesity. *Diabetes*. 2005; 54:2838–2843. [PubMed: 16186383]
23. Cote M, Matias I, Lemieux I, Petrosino S, Almeras N, Despres JP, Di Marzo V. Circulating endocannabinoid levels, abdominal adiposity and related cardiometabolic risk factors in obese men. *Int J Obes (Lond)*. 2007; 31:692–699. 0803539 [pii]. 10.1038/sj.ijo.0803539 [PubMed: 17224929]
24. Bluher M, Engeli S, Kloting N, Berndt J, Fasshauer M, Batkai S, Pacher P, Schon MR, Jordan J, Stumvoll M. Dysregulation of the peripheral and adipose tissue endocannabinoid system in human abdominal obesity. *Diabetes*. 2006; 55:3053–3060. [PubMed: 17065342]
25. Di Marzo V, Cote M, Matias I, Lemieux I, Arsenault BJ, Cartier A, Piscitelli F, Petrosino S, Almeras N, Despres JP. Changes in plasma endocannabinoid levels in viscerally obese men following a 1 year lifestyle modification programme and waist circumference reduction:

- associations with changes in metabolic risk factors. *Diabetologia*. 2009; 52:213–217.10.1007/s00125-008-1178-6 [PubMed: 18972095]
26. Gonthier MP, Hoareau L, Festy F, Matias I, Valenti M, Bes-Houtmann S, Rouch C, Robert-Da Silva C, Chesne S, Lefebvre d'Helencourt C, Cesari M, Di Marzo V, Roche R. Identification of endocannabinoids and related compounds in human fat cells. *Obesity*. 2007; 15:837–845. [PubMed: 17426318]
 27. Di Marzo V, De Petrocellis L, Sepe N, Buono A. Biosynthesis of anandamide and related acylethanolamides in mouse J774 macrophages and N18 neuroblastoma cells. *Biochem J*. 1996; 316(Pt 3):977–984. [PubMed: 8670178]
 28. Varga K, Wagner JA, Bridgen DT, Kunos G. Platelet- and macrophage-derived endogenous cannabinoids are involved in endotoxin-induced hypotension. *FASEB J*. 1998; 12:1035–1044. [PubMed: 9707176]
 29. Matias I, Petrosino S, Racioppi A, Capasso R, Izzo AA, Di Marzo V. Dysregulation of peripheral endocannabinoid levels in hyperglycemia and obesity: effect of high fat diets. *Mol Cell Endocrinol*. 2008; 286:S66–78. S0303-7207(08) 00060-9 [pii]. 10.1016/j.mce.2008.01.026 [PubMed: 18343566]
 30. Berger A, Crozier G, Bisogno T, Cavaliere P, Innis S, Di Marzo V. Anandamide and diet: inclusion of dietary arachidonate and docosahexaenoate leads to increased brain levels of the corresponding N-acylethanolamines in piglets. *Proc Natl Acad Sci U S A*. 2001; 98:6402–6406. 101119098 [pii]. 10.1073/pnas.101119098 [PubMed: 11353819]
 31. Malcher-Lopes R, Di S, Marcheselli VS, Weng FJ, Stuart CT, Bazan NG, Tasker JG. Opposing crosstalk between leptin and glucocorticoids rapidly modulates synaptic excitation via endocannabinoid release. *J Neurosci*. 2006; 26:6643–6650. 26/24/6643 [pii]. 10.1523/JNEUROSCI.5126-05.2006 [PubMed: 16775153]
 32. D'Eon TM, Pierce KA, Roix JJ, Tyler A, Chen H, Teixeira SR. The role of adipocyte insulin resistance in the pathogenesis of obesity-related elevations in endocannabinoids. *Diabetes*. 2008; 57:1262–1268. [PubMed: 18276766]
 33. Murdolo G, Kempf K, Hammarstedt A, Herder C, Smith U, Jansson PA. Insulin differentially modulates the peripheral endocannabinoid system in human subcutaneous abdominal adipose tissue from lean and obese individuals. *J Endocrinol Invest*. 2007; 30:RC17–RC21. doi:3973 [pii]. [PubMed: 17923791]
 34. Bartness TJ, Kay Song C, Shi H, Bowers RR, Foster MT. Brain-adipose tissue cross talk. *Proc Nutr Soc*. 2005; 64:53–64. S002966510500008X [pii]. [PubMed: 15877923]
 35. Buettner C, Camacho RC. Hypothalamic control of hepatic glucose production and its potential role in insulin resistance. *Endocrinol Metab Clin North Am*. 2008; 37:825–840. S0889-8529(08) 00060-1 [pii]. 10.1016/j.ecl.2008.09.001 [PubMed: 19026934]
 36. Shimabukuro M, Koyama K, Chen G, Wang MY, Trieu F, Lee Y, Newgard CB, Unger RH. Direct antidiabetic effect of leptin through triglyceride depletion of tissues. *Proc Natl Acad Sci USA*. 1997; 94:4637–4641. [PubMed: 9114043]
 37. Wang ZW, Zhou YT, Lee Y, Higa M, Kalra SP, Unger RH. Hyperleptinemia depletes fat from denervated fat tissue. *Biochem Biophys Res Commun*. 1999; 260:653–657. [PubMed: 10403821]
 38. Buettner C, Muse ED, Cheng A, Chen L, Scherer T, Pocai A, Su K, Cheng B, Li X, Harvey-White J, Schwartz GJ, Kunos G, Rossetti L. Leptin controls adipose tissue lipogenesis via central, STAT3-independent mechanisms. *Nat Med*. 2008; 14:667–675. [PubMed: 18516053]
 39. Addy C, Wright H, Van Laere K, Gantz I, Erondy N, Musser BJ, Lu K, Yuan J, Sanabria-Bohorquez SM, Stoch A, Stevens C, Fong TM, De Lepeleire I, Cilissen C, Cote J, Rosko K, Gendrano IN 3rd, Nguyen AM, Gumbiner B, Rothenberg P, de Hoon J, Bormans G, Depre M, Eng WS, Ravussin E, Klein S, Blundell J, Herman GA, Burns HD, Hargreaves RJ, Wagner J, Gottesdiener K, Amatruda JM, Heymsfield SB. The acyclic CB1R inverse agonist taranabant mediates weight loss by increasing energy expenditure and decreasing caloric intake. *Cell Metab*. 2008; 7:68–78. S1550-4131(07) 00367-1 [pii]. 10.1016/j.cmet.2007.11.012 [PubMed: 18177726]
 40. Motaghedi R, McGraw TE. The CB1 Endocannabinoid system modulates adipocyte insulin sensitivity. *Obesity*. 2008; 16:1727–1734. [PubMed: 18551116]

41. Pagano C, Pilon C, Calcagno A, Urbanet R, Rossato M, Milan G, Bianchi K, Rizzuto R, Bernante P, Federspil G, Vettor R. The endogenous cannabinoid system stimulates glucose uptake in human fat cells via phosphatidylinositol 3-kinase and calcium-dependent mechanisms. *J Clin Endocrinol Metab.* 2007; 92:4810–4819. jc.2007-0768 [pii]. 10.1210/jc.2007-0768 [PubMed: 17785353]
42. Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. *Lancet.* 2006; 368:1660–1672. [PubMed: 17098084]
43. Nogueiras R, Veyrat-Durebex C, Suchanek PM, Klein M, Tschop J, Caldwell C, Woods SC, Wittmann G, Watanabe M, Liposits Z, Fekete C, Reizes O, Rohner-Jeanrenaud F, Tschop MH. Peripheral, but not central, CB1 antagonism provides food intake-independent metabolic benefits in diet-induced obese rats. *Diabetes.* 2008; 57:2977–2991. db08-0161 [pii]. 10.2337/db08-0161 [PubMed: 18716045]

Fig. 1.

Central leptin signaling regulates adipose tissue metabolism and EC tone. The acute infusion of leptin into the MBH controls several physiological functions like food intake, hepatic glucose production, insulin production, and adipose tissue metabolism. The control of adipose tissue metabolism by hypothalamic leptin involves several molecular pathways: (1) Lipogenesis is inhibited by curtailing the expression of the transcription factors sterol regulatory element-binding protein-1c (*Srebp1c*) and peroxisome proliferator-activated receptor γ (*PPAR* γ) and their target genes *FAS*, acetyl-CoA carboxylase (*ACC*), and *LPL*. Lower *LPL* expression results in decreased fatty acid uptake into adipocytes. (2) Lipolysis is stimulated by post-translational activation of hormone-sensitive lipase (*HSL*). (3) Futile cycles are induced as exemplified by an increase in the expression of phospho-enolpyruvate kinase (*Pepck*) and uncoupling protein 2 (*UCP2*). These central effects of leptin on adipose tissue metabolism depend on sympathetic innervations. The finding that central leptin also lowers adipose tissue EC tone has several implications. First, ECs could be important local mediators in the brain control of adipose tissue metabolism as CB1 receptor activation has been shown to increase *LPL* activity and mRNA levels of lipogenic enzymes such as *FAS*. ECs also potentially increase glucose uptake by inducing GLUT4 translocation to the membrane. This is mainly based on in vitro data (*dashed lines*) and awaits in vivo confirmation. The important role that ECs play in the brain regulation of adipose tissue metabolism is highlighted by the fact that the ability of hypothalamic leptin to suppress lipogenesis is lost when CB1 receptor agonists are infused into the circulation. Finally, as obesity and DM2 are tightly associated with central leptin resistance, it is possible that the elevated EC tone in peripheral organs like adipose tissue that is commonly found in these conditions is due to a failure of the brain-mediated restrain of the EC tone