Feeding Disorders and Obesity

Cristina Cervino, Valentina Vicennati, Renato Pasquali, and Uberto Pagotto

Contents

Abstract The ability of the endocannabinoid (EC) system to control appetite, food intake and energy balance has recently received great attention, particularly in the light of the different modes of action underlying these functions. The EC system modulates rewarding properties of food by acting at specific mesolimbic areas in the brain. In the hypothalamus, cannabinoid type 1 receptors (CB1) and ECs are integrated components of the networks controlling appetite and food intake. Interestingly, the EC system has recently been shown to control several metabolic functions by acting on peripheral tissues, such as adipocytes, hepatocytes, the skeletal muscles and the endocrine pancreas. The relevance of the system is further strengthened by the notion that visceral obesity seems to be a condition in which an overactivation of the EC system occurs; therefore, drugs interfering with this

C. Cervino V. Vicennati, R. Pasquali and U. Pagotto (✉)
Endocrinology Unit and C.R.B.A., Department of .Clinical Medicine and Gastroenterology, S. Orsola-Malpighi Hospital, Via Massarenti 9, 40138, Bologna, Italy
e-mail: uberto.pagotto@unibo.it

D. Kendall and S. Alexander (eds.), *Behavioral Neurobiology of the Endocannabinoid System*, Current Topics in Behavioral Neurosciences 1,
DOI: 10.1007/978-3-540-88955-7_15,

overactivation by blocking CB1 receptors are considered valuable candidates for the treatment of obesity and related cardiometabolic risk factors.

Keywords Adipocyte • Cannabinoid type 1 receptor • Endocannabinoids • Hepatocyte • Hypothalamus • Obesity • Rimonabant • Taranabant

Abbreviations

AEA	Anandamide
AMPK	5'-AMP-activated protein kinase
AN	Anorexia nervosa
2AG	2-arachidonoyl-glycerol
BED	Binge-eating disorder
BN	Bulimia nervosa
CART	Cocaine-amphetamine-related transcript
CB1	Cannabinoid receptor type 1
CRH	Corticotropin releasing hormone
GABA	Gamma-aminobutyric acid
EC	Endocannabinoid
HDL	High-density lipoprotein
HOMA-IR	Homeostasis model assessment-insulin resistance
LDL	Low-density lipoprotein
MCH	Melanocortin concentrating hormone
NPY	Neuropeptide Y
PPAR	Peroxisome proliferator-activated receptor
PVN	Paraventricular nucleus
RIO	Rimonabant in obesity
THC	Δ^9-Tetrahydrocannabinol

1 Introduction

In physiology, the notion of the "thrifty genotype", first proposed by Neel (1962), is well known. He argued that certain human genotypes were selected because of their selective advantage over the less "thrifty" ones: in particular the "thrifty genotype" was described as "being exceptionally efficient in the intake and/or utilisation of food". Therefore, during famines, individuals with the thrifty genotype would have an advantage because they relied on more consistent, previously stored energy to maintain homeostasis. In recent years, several genes or systems have been described as members of the family of thrifty genes.

In our opinion, the genetic machinery comprising EC signalling should also be included in this family.

2 Historical Background

Marijuana was used for the treatment of appetite loss and to overcome the sensation of hunger in ancient Indian medical practice, and this represents the first evidence of a therapeutic role of the EC system in feeding disorders (Peters and Nahas 1999). However, it was only with the discovery of Δ^9-tetrahydrocannabinol (THC), the main psychoactive component of marijuana (Gaoni and Mechoulam 1964), and, more importantly, with the identification of the endogenous signalling molecules mimicking the marijuana effect (Piomelli 2003), the so-called endocannabinoids (ECs) such as anandamide (AEA) and 2-arachidonoyl glycerol (2AG), that the molecular basis of the orexigenic stimulus started to become clear.

3 Modes of Action by which Endocannabinoids Promote Energy Storage

3.1 Endocannabinoids Promote Energy Storage in the Brain

By analogy with the hyperphagic effect provided by THC, ECs have also been shown to induce an orexigenic stimulus in a dose-dependent manner when injected into the nucleus accumbens or hypothalamus (Williams and Kirkham 2002). Similar findings were derived from experiments in which the first selective CB1 receptor antagonist, rimonabant, was shown to decrease food intake (Simiand et al. 1998).

ECs are synthesised in the areas of the brain involved in the motivation of eating (Cota et al. 2006) in relation to the feeding state of animals, being increased during inter-meal times, reaching a critical level in order to trigger feeding, and rapidly reducing when food is accessed (Hanus et al. 2003). In rodent hypothalamic brain areas, levels of ECs have been shown to increase during fasting condition and to decrease as the animals are re-fed, returning to normal values in satiated animals (Kirkham et al. 2002).

ECs seem to interact with many different hypothalamic neuropeptides to generate, as a final effect, a strong impulse for food intake (Pagotto et al. 2006). They positively modulate the orexigenic signals provided by neuropeptide Y (NPY) (Gamber et al. 2005), but, on the other hand, they inhibit the anorexigenic action of cocaine-amphetamine-related transcript (CART) (Osei-Hyiaman et al. 2005b). In the paraventricular nucleus (PVN) of the hypothalamus they interact with corticotropin releasing hormone (CRH) (Cota et al. 2003; Hermann and Lutz 2005). Post-synaptically released ECs from the parvocellular neurons have been shown to decrease glutamatergic transmission onto CRH-releasing neurons, acting

at pre-synaptic CB1 receptors, finally resulting in an inhibition of CRH release (Di et al. 2003). This mechanism is stimulated by a non-genomic effect of glucocorticoids, suggesting that the well-known effect of glucocorticoids on food intake may partly be caused by the activation of ECs (Di et al. 2003).

A recent study has demonstrated that CB1 receptor stimulation strongly augments the orexin-A-stimulated intracellular pathway, and that this effect can be blocked by the CB1 receptor antagonist rimonabant, suggesting a positive orexigenic role for CB1 in this neural population (Hilairet et al. 2003). Considering the fact that these neurones project to the ventral tegmental area, it is possible that the lateral hypothalamus, and the ECs acting there, represent the functional link between the hypothalamic circuitry controlling consummatory behaviour and limbic structures involved in food reward (Yo et al. 2005). The interactions between ECs, leptin and the orexigenic melanocortin-concentrating hormone (MCH) within the limbic system have recently been characterised in detail. Whereas MCH neurones are inhibited by gamma-aminobutyric acid (GABA)-ergic inputs from the limbic system (Yo et al. 2005), ECs act to reduce GABA release and, thus, might stimulate the excitability of MCH neurones, leading to an increase in food intake. However, this effect appears to be blocked in these neurones via a leptin-mediated inhibition of voltage-gated Ca^{2+} currents, potentially leading to a reduced synthesis and release of ECs and a subsequent reduced excitability of MHC neurones – the overall effect being a reduced orexigenic stimulus (Yo et al. 2005).

The orexigenic cross-talk between EC and ghrelin signalling represents a further intriguing hypothalamic interaction not yet fully explored. Ghrelin stimulation is able to increase hypothalamic EC content, leading, via CB1 receptor activation, to an increase of 5'-AMP-activated protein kinase (AMPK) (Kola et al. 2005). This effect may, in turn, promote appetite (Tucci et al. 2004; Kola et al 2008).

3.2 Endocannabinoids Promote Energy Storage at a Peripheral Level

3.2.1 Adipose Tissue

A key discovery in the emergence of a role of the ECs in the peripheral modulation of metabolic processes was the finding reported independently by two research groups of CB1 receptor expression in rodent white adipocytes (Bensaid et al. 2003; Cota et al. 2003). After these preliminary observations, further studies have shed light on the role of ECs on adipose tissue. Now it is widely accepted that, as in the brain, CB1 activation in the adipose tissue promotes energy storage. ECs stimulate growth and differentiation of pre-adipocytes to the fully mature adipocytes (Gari-Bobo et al. 2006; Bellocchio et al. 2008; Bouaboula et al. 2005; Pagano et al. 2007; Matias et al. 2006) via cross-talk with the peroxisome proliferator-activating receptor-γ (PPAR-γ) (Matias et al. 2006). By inhibiting lipolysis on the one hand (Gasperi et al. 2007; Jbilo et al. 2005), and activating lipoprotein lipase on the other (Cota et al. 2003), and by

stimulating de novo lipogenesis, ECs are able to trigger fat accumulation (Osei-Hyiaman et al. 2005a). ECs have also been reported to increase insulin signalling and glucose uptake, to further promote energy storage (Pagano et al. 2007).

Furthermore, CB1 receptor activation modulates important products of adipocyte endocrine activity such as adiponectin and visfatin (Bensaid et al. 2003; Matias et al. 2006; Perwitz et al. 2006). Adiponectin is a circulating adipokine that plays a crucial role in fat and glucose metabolism, and obesity and type 2 diabetes are characterised by reduced adiponectin levels in tissues and blood (Kadowaki and Yamamuchi 2005). Visfatin is an insulin-mimetic growth factor, levels of which are increased in obesity and type 2 diabetes (Tilg and Moschen 2008). In this scenario, the CB1 receptor agonist WIN55,212 has been shown to reduce adiponectin and increase visfatin expression in cultured adipocytes (Perwitz et al. 2006), whereas rimonabant is able to increase adiponectin expression and release from adipocytes in vitro (Bensaid et al. 2003; Gari-Bobo et al. 2006; Matias et al. 2006).

3.2.2 Liver

The CB1 receptor has also been identified in the liver (Osei-Hyiaman et al. 2005a). Its expression is very low in normal hepatocytes, but it is raised in obesity. ECs are able to increase de novo lipogenesis and the expression of the transcription factor sterol regulatory element-binding protein-1c and its targets acetyl-coenzyme A carboxylase-1 and fatty acid synthase; this occurs particularly in association with a high fat diet (Osei-Hyiaman et al., 2005). Intriguingly, mice with selective deletion of CB1 receptors from their hepatocytes develop obesity on a high fat diet, but are protected from diet-induced hepatic steatosis, insulin and leptin resistance and dyslipidaemia (Osei-Hyiaman et al. 2008). All of these findings clearly highlight the role of hepatic CB1 receptors in the regulation of metabolism (Pacher et al. 2006).

3.2.3 Skeletal Muscle

The CB1 receptor is also expressed in skeletal muscles such as the soleus muscle (Pagotto et al. 2006). ECs decrease mRNA expression of several enzymes involved in muscle oxidation, such as AMPK-α1 and -α2, pyruvate dehydrogenase kinase-4, and PPAR-γ coactivator-1 in cultured myotube cells derived from lean and obese subjects. These effects could be reversed by CB1 receptor antagonist treatment, indicating a crucial negative role of ECs on fatty acid and glucose oxidation in skeletal muscle (Liu et al. 2005; Cavuoto et al. 2007).

3.2.4 Endocrine Pancreas

It is only recently that both CB1 and CB2 receptors have been demonstrated in the endocrine pancreas. The CB1 receptor is mainly present in glucagon-containing

α-cells, while the CB2 receptor has been detected in both α- and β-cells (Juan-Pico et al. 2006; Bermudez-Silva et al. 2008; Starowicz et al. 2008). The stimulation of CB1 receptors by ECs seems to induce glucose intolerance in rats, and this effect can be blocked by AM251, a specific CB1 receptor antagonist. The mechanism underlying EC-mediated glucose intolerance is probably a reduction of glucose-dependent insulin secretion (Bermudez-Silva et al. 2006).

4 Obesity as a Disease Model of Endocannabinoid Overactivation

Recent data, obtained from both animal and human studies, have identified a tight association between the development of obesity and a simultaneous over-activation of ECs, expressed as raised EC production or increased CB1 receptor expression (Matias and Di Marzo 2007). Di Marzo and Kunos were the first to illustrate such an association. Models of obesity such as *ob/ob* and *db/db* mice, characterised by an impairment of leptinergic signalling, have been shown to have increased (pathological) levels of hypothalamic ECs (Di Marzo et al. 2001), and a single intravenous injection of leptin in these animals was able to reduce the overproduction of ECs (Di Marzo et al. 2001).

In wild-type mice on a high fat diet, an increase in hepatic anandamide (AEA) associated with an increased density of CB1 receptors has been observed (Osei-Hyiaman et al. 2005a). The ECs might, therefore, play a role in several hepatic diseases in which steatotic processes progressively replace the normal liver structure. The high fat diet-induced transformation in hepato-steatosis has not been observed in mice pre-treated with rimonabant or in CB1 receptor knockout mice (Osei-Hyiaman et al. 2005a).

Another target of ECs in obesity may be the skeletal muscle. In fact, as mentioned above, the CB1 receptor is present in murine skeletal muscle and its expression is increased in diet-induced obese mice (Pagotto et al. 2006).

Regarding the endocrine pancreas, it was recently shown that cultured β-cells, under conditions mimicking hyperglycaemia, expressed elevated levels of both AEA and 2AG (Matias et al. 2006), suggesting that, under these conditions, such as during pre-diabetes, type 2 diabetes and obesity, EC production and/or degradation in β-cells, instead of remaining under insulin control, becomes dysregulated.

An increasing body of evidence suggests that an up-regulation of EC signalling may also occur in overweight, obese and hyperglycaemic patients. In obese women without comorbidities, blood levels of either AEA alone or both AEA and 2AG were significantly higher compared with lean subjects (Engeli et al. 2005). Significantly higher levels of 2AG, but not AEA, have been detected in the visceral, but not subcutaneous, fat of obese patients (Matias et al. 2006). Interestingly, increased levels of haematic circulating 2AG are present in visceral obese human patients when compared to subcutaneous obese and lean controls (Bluher et al. 2006). The increase in 2AG was also shown to correlate positively with some important

cardiometabolic risk factors, such as body mass index, waist circumference, fasting plasma triglyceride and insulin levels, low high-density lipoprotein (HDL) cholesterol and adiponectin levels (Côtè et al. 2007). However, whether 2AG and/or AEA are important in both obesity and related comorbidities and whether EC overactivation is the effective cause or just a simple consequence of such diseases still remain matters of debate.

5 Endocannabinoids and Central Eating Disorders

There are only a few reports concerning the putative association between alterations in the EC system and eating disorders such as anorexia nervosa. In a recent publication, Monteleone and colleagues reported measurements of plasma levels of AEA, 2AG, and leptin in women with anorexia nervosa (AN), with bulimia nervosa (BN), with binge-eating disorder (BED), and in a group of healthy women. Plasma levels of AEA were significantly enhanced in both anorexic and BED women, but not in bulimic patients. No significant changes occurred in the plasma levels of 2AG in any of the patient groups. Moreover, circulating AEA levels were significantly and inversely correlated with plasma leptin concentrations in both healthy controls and anorexic women. These findings show a derangement in the production of AEA in drug-free symptomatic women with AN or BED. Although the pathophysiological significance of this alteration awaits further clarification, it suggests a possible involvement of AEA in the mediation of the rewarding aspects of the aberrant eating behaviours occurring in AN and BED (Monteleone et al. 2005).

6 How CB1 Receptor Antagonism May Act Against Obesity and Metabolic Complications

A significant body of evidence has recently accumulated suggesting that CB1 blockade may display favourable metabolic effects beyond weight loss alone. In normal rats and in diet-induced obese mice chronically treated with different CB1 receptor antagonists, tolerance to the anorectic effect of the drugs developed in a few days, whereas the reduction of body weight was maintained throughout the treatment period (Colombo et al. 1998; Ravinet Trillou et al. 2003; Hildebrandt et al. 2003). Additional evidence in favour of a peripheral mechanism of action of CB1 blockade came from the CB1 knockout mouse model. These mice showed a significant weight deficit compared with their wild-type littermates (Cota et al. 2003; Osei-Hyiaman et al. 2005a). Pair feeding studies showed that the weight deficit was caused by a reduction in food intake only in young animals, whereas in adult animals it was partially independent of caloric intake (Cota et al. 2003), similar to the dissociation between effects of CB1 receptor antagonists on food intake and body weight. Several studies have been performed in both genetically

obese and diet-induced obese mouse models searching for non-appetite-related pathways involved in CB1 receptor antagonist-mediated body weight loss. Dernbach et al. (2005) was the first to note that, in addition to the well-known effect on food intake, administration of rimonabant for 10 days to obese rats induced an increase in energy expenditure, whilst, in the pair-feeding control group, the lowered food intake led to an expected decrease in the same parameter. The low respiratory quotient observed in the rimonabant-treated group led the authors to speculate that a shift to an increase in fat oxidation could be one of the possible mechanisms by which the pharmacological blockade of the CB1 receptor produced such an effect.

Taking advantage of micro-array analysis, Jbilo et al. (2005) were able to screen the expression of a wide panel of genes in adipocytes from diet-induced obese mice after long-term treatment with rimonabant. They found that the transcriptional patterns of treated obese mice were similar to those obtained in the CB1 receptor knockout mice fed with a high-fat diet, supporting a role for CB1 receptors in this process. Functional analysis of these gene modulations indicated that the drug-induced reduction of adipose mass was due to increased energy expenditure, mainly through futile cycling (calcium and substrate) (Jbilo et al. 2005).

Several reports have documented a direct role of ECs in modulation of proteins involved in thermogenesis. It has also recently been shown that treatment of differentiated brown adipocytes with a CB1 receptor agonist decreased the expression of uncoupling protein 1 (Perwitz et al. 2006). The contribution of brown adipose tissue-mediated thermogenesis in the process of energy expenditure in small animals such as rodents is well established, whereas the role of brown adipose tissue is less clear in humans. However, it has been suggested that several physiological and pharmacological stimuli may be capable of *trans*-differentiating white adipocytes into brown adipocytes in humans (Klaus 2004). One could, therefore, speculate that CB1 receptor antagonists may increase numbers of brown adipocytes, leading to an eventual increase in energy expenditure. On the other hand, we recently showed that CB1 receptor blockade provides a potent stimulus to mitochondriogenesis in adipose tissue contributing further to an increase in energy expenditure (Tedesco et al. 2008).

As described above, CB1 receptor blockade may also affect peripheral tissues via elevation of adiponectin levels (Bensaid et al. 2003; Perwitz et al. 2006; Matias et al. 2006). Adiponectin reduces serum hepatic gluconeogenesis and stimulates fatty acid oxidation in skeletal muscles. Adiponectin stimulates skeletal muscle glucose uptake by increasing insulin receptor tyrosine kinase activity, p38 mitogen-activated protein kinase, and the tyrosine phosphorylation of insulin receptor substrate-1. Insulin resistance in skeletal muscle and in the hepatic parenchyma develops as excess triglycerides accumulate; thus, the improvement in insulin action induced by adiponectin may promote clearance of intracellular lipid stores in these tissues. Adiponectin also promotes mitochondrial fatty acid oxidation and, consequently, a reduction in circulating levels of free fatty acids. High concentrations of free fatty acids and insulin resistance associated with visceral obesity are highly detrimental because they inhibit lipoprotein lipase, the enzyme responsible

for hydrolysing triglycerides in very-low-density lipoprotein and chylomicrons. Low lipoprotein lipase activity leads to an accumulation of triglycerides and lipoprotein remnant particles that are highly atherogenic. Under these circumstances, HDL cholesterol decreases significantly. Adiponectin also favourably affects this metabolic scenario by increasing PPAR-γ activity in skeletal muscle and liver, leading to an increased synthesis of HDL cholesterol through increased hepatic expression of apoproteins A-I and A-II (Kadowaki and Yamamuchi 2005; Guerre-Millo 2008).

7 Pharmacological Implications in Humans

7.1 Rimonabant

Rimonabant has been evaluated in four multicenter, randomised, placebo-controlled clinical trials: rimonabant in obesity (RIO) – Europe, RIO – North America, RIO – lipids, and RIO – diabetes (Van Gaal et al. 2005; Despres et al. 2005; Pi-Sunyer et al. 2006; Scheen et al. 2006). Patients in these studies were randomised to rimonabant 20 mg/day, rimonabant 5 mg/day, or placebo, given in combination with a hypocaloric diet. The patients were additionally advised to increase their physical activity. In all four studies, treatment with rimonabant (20 mg/day) resulted in significantly greater decreases in body weight and waist circumference than did treatment with placebo.

Treatment with rimonabant (20 mg/day) also produced improvements in a number of cardiovascular and metabolic risk factors that were, in most studies, significantly greater than those achieved with placebo. These included increases in HDL cholesterol, and decreases in triglycerides, low-density lipoprotein (LDL) cholesterol–HDL cholesterol ratio, total cholesterol–HDL cholesterol ratio, fasting glucose, fasting insulin, and homeostasis model assessment-insulin resistance (HOMA-IR).

Additional treatment effects were demonstrated in the RIO-Lipids study, which focused on patients with untreated dyslipidaemia and a high risk of cardiovascular disease (Després et al. 2005). Included in these effects were a shift in the distribution of LDL particles towards a larger size and a decrease in the proportion of small LDL particles in the rimonabant (20 mg/day) group compared with the placebo group ($P < 0.001$ and $P = 0.002$, respectively), Also, compared with placebo, rimonabant resulted in greater decreases in plasma levels of leptin and C-reactive protein ($P < 0.001$ and $P < 0.02$), and greater increases in plasma adiponectin ($P < 0.001$). This latter effect on adiponectin nicely confirmed the initial findings from in vitro and animal studies.

Results of the RIO-Diabetes (Scheen et al. 2006) and Serenade (Rosenstock et al. 2008) studies extended the findings with rimonabant in overweight or obese non-diabetic patients to overweight or obese patients with type 2 diabetes that was inadequately controlled by metformin or sulphonylureas, or who were naïve-treated.

HbA_{1C} levels were significantly lower in the rimonabant-treated group than in the placebo group in both studies.

It is important to note that the changes in the levels of HDL cholesterol, triglycerides, fasting insulin, HOMA-IR, HbA_{1C}, and adiponectin in the various studies exceeded those expected for weight loss alone. This is consistent with the direct peripheral metabolic effects of rimonabant described earlier.

Regarding the safety of rimonabant for the treatment of obesity, this agent was generally well tolerated in the four randomised, placebo-controlled studies, with the most common adverse events including gastrointestinal disturbances, upper respiratory tract infections, and dizziness. Results of a meta-analysis based on these trials indicated that patients receiving rimonabant, compared with those taking placebo, were 2.5 times more likely to discontinue treatment because of depressive mood disorders and three times more likely to discontinue because of anxiety (Christensen et al. 2007). According to data presented by the manufacturer at an advisory committee meeting of the US Food and Drug Administration (FDA) in June 2007, rates of depression and anxiety for 2742 patients who received rimonabant 20 mg were 3.9% and 5.9%, respectively, compared with 1.7 and 2.1% for 2474 patients who received placebo. Definite suicidal behaviour/ideation, while uncommon, was higher among 3081 patients who received rimonabant (20 mg/day) than among 2214 who received placebo (0.65% vs. 0.36%) (Chew 2007).

7.2 Taranabant

Taranabant, another CB1 receptor inverse agonist, has been studied in a 2-year, phase 3 trial scheduled for completion in the last quarter of 2007. Interim results for this trial are not available. However, a recent shorter clinical trial in which taranabant was tested in humans confirmed the efficacy of CB1 receptor inhibitors in reducing body weight and ameliorating several metabolic conditions. A single-dose administration of 12 mg taranabant caused a small but significant increase in resting energy expenditure and fat oxidation (Addy et al. 2008). The authors concluded that the modest increases in energy expenditure may, nevertheless, exert profound effects on body weight over a period of months. On the other hand, in the same study, Addy et al. were not able to define what proportion of taranabant's effects on resting energy expenditure were mediated centrally via activation of the autonomic nervous system or peripherally by engagement of CB1 receptor distributed in peripheral organs involved in metabolic functions (Addy et al. 2008).

8 Conclusions

The EC system is now recognised as a crucial player in the control of energy balance. It is clear that it influences a large variety of peripheral organs to modulate metabolic processes. Detailed characterisation of each individual contribution and

the reciprocal interactions among the organs is necessary in future studies to fully understand the physiological and pathophysiological roles of the EC system. The system appears to be over-activated in conditions such as obesity, and pharmacological blockade of CB1 receptors normalises the imbalance providing an attractive strategy to tackle obesity and associated comorbidities.

References

Addy C, Wright H, Van Laere K et al. (2008) The acyclic CB1R inverse agonist taranabant mediates weight loss by increasing energy expenditure and decreasing caloric intake. Cell Metab 7:68–78

Bellocchio L, Cervino C, Vicennati V et al. (2008) Cannabinoid type 1 receptor: another arrow in the adipocytes' bow. J Neuroendocrinol 20(Suppl 1):130–138

Bensaid M, Gary-Bobo M, Esclangon A et al. (2003) The cannabinoid CB1 receptor antagonist SR141716 increases Acrp30 mRNA expression in adipose tissue of obese *fa*/*fa* rats and in cultured adipocyte cells. Mol Pharmacol 63:908–914

Bermudez-Silva FJ, Serrano A, Diaz-Molina FJ et al. (2006) Activation of cannabinoid CB1 receptors induces glucose intolerance in rats. Eur J Pharmacol 531:282–284

Bermudez-Silva FJ, Suarez J, Baixeras E et al. (2008) Presence of functional cannabinoid receptors in human endocrine pancreas. Diabetologia 51:476–487

Bluher M, Engeli S, Kloting N et al. (2006) Dysregulation of the peripheral and adipose tissue endocannabinoid system in human abdominal obesity. Diabetes 5:3353–3360

Bouaboula M, Hilairet S, Marchand J et al. (2005) Anandamide induced PPAR gamma transcriptional activation and 3T3–L1 preadipocyte differentiation. Eur J Pharmacol 517:174–181

Cavuoto P, McAincha AJ, Hatzinikolas G et al. (2007) Effects of cannabinoid receptors on skeletal muscle oxidative pathways. Mol Cell Endocrin 267:63–69

Chew P (2007) Clinical safety. Presented to the Endocrinologic and Metabolic Drugs Advisory Committee, FDA, June 13, 2007. Available at www.fda.gov/ohrms/dockets/ac/07/slides/2007-4306s1-05-Sanofi-Aventis Chew.pdf (slides MM-95, MM-109), accessed Dec 15, 2007

Christensen R, Kristensen PK, Bartels EM et al. (2007) Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. Lancet 370:1706–1713

Colombo G, Agabio R, Diaz G et al. (1998) Appetite suppression and weight gain loss after the cannabinoid antagonist SR141716. Life Sci 63:PL113–PL117

Cota D, Marsicano G, Tschoep M et al. (2003) The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. J Clin Invest 112:423–431

Cota D, Tschoep M, Horvath TL et al. (2006) Cannabinoids, opioids and eating behavior: the molecular face of hedonism? Brain Res Rev 5:85–107

Côtè M, Matias I, Lemieux I et al. (2007) Circulating endocannabinoid levels, abdominal adiposity and related cardiometabolic risk factors in obese men. Int J Obesity 31:692–699

Dernbach H, Haller J, Kaulisch T et al. (2005) Effects of the CB1 antagonist SR141716A (Rimonabant) on energy expenditure and respiratory quotient in diet-induced obese rats. Obesity Rev 6:172–173

Després JP, Golay A, Sjöström L for the Rimonabant in Obesity-Lipids Study Group (2005) Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. N Engl J Med 353:2121–2134

Di Marzo V, Goparaju SK, Wang L et al. (2001) Leptin-regulated endocannabinoids are involved in maintaining food intake. Nature 410:822–825

Di S, Malcher-Lopes R, Halmos KC et al. (2003) Nongenomic glucocorticoid inhibition via endocannabinoid release in the hypothalamus: a fast feedback mechanism. J Neurosci 23:4850–4857

Engeli S, Bohnke J, Feldpausch M et al. (2005) Activation of the peripheral endocannabinoid system in human obesity. Diabetes 54:2838–2843
Gamber KM, Macartur H, Westfall TC (2005) Cannabinoids augment the release of neuropeptide Y in the rat hypotalamus. Neuropharmacology 143:520–523
Gaoni Y, Mechoulam R (1964) Isolation, structure and partial synthesis of an active constituent of hashish. J Am Chem Soc 86:1646–1647
Gari-Bobo M, Elachouri G, Scatton B et al. (2006) The cannabinoid CB1 receptor antagonist rimonabant (SR141716) inhibits cell proliferation and increase markers of adipocyte maturation in cultured mouse 3T3 F442A preadipocytes. Mol Pharmacol 69:471–478
Gasperi V, Fezza F, Pasquariello N et al. (2007) Endocannabinoids in adipocytes during differentiation and their role in glucose uptake. Cell Mol Life Sci 64:219–229
Guerre-Millo M (2008) Adiponectin: an update. Diabetes Metab 34:12–18
Hanus L, Avraham Y, Ben-Shushan D et al. (2003) Short term fasting and prolonged semistarvation have opposite effects on 2-AG levels in the mouse brain. Brain Res 983:144–151
Hermann H, Lutz B (2005) Coexpression of cannabinoid receptor type 1 with the corticotrophin releasing hormone receptor type-1 in distinct region of mouse adult forebrain. Neurosci Lett 375:13–18
Hilairet S, Bouaboula M, Carriere D et al. (2003) Hypersensitization of the Orexin 1 receptor by the CB1 receptor: evidence for crosstalk blocked by the specific CB1 antagonist, SR141716. J Biol Chem 278:23731–23737
Hildebrandt AL, Kelly-Sullivan DM, Black SC (2003) Anti-obesity effects of chronic CB1 receptor antagonist treatment in diet induced obese mice. Eur J Pharmacol 462:125–132
Jbilo O, Ravinet-Trillou C, Arnone M et al. (2005) The CB1 receptor antagonist rimonabant reverses the diet-induced obesity phenotype through the regulation of lipolysis and energy balance. FASEB J 19:1567–1569
Juan-Pico P, Fuentes E, Bermudez-Silva FJ et al. (2006) Cannabinoid receptor regulates Ca(2+) signals and insulin secretion in pancreatic beta-cells. Cell Calcium 39:155–162
Kadowaki T, Yamamuchi T (2005) Adiponectin and adiponectin receptors. Endocrin Rev 26:439–451
Kirkham TC, Williams CM, Fezza F et al. (2002) Endocannabinoid levels in rat limbic forebrain and hypothalamus in relation to fasting, feeding and satiation: stimulation of eating by 2-arachidonoyl glycerol. Br J Pharmacol 136:550–557
Klaus C (2004) Adipose tissue as a regulator of energy balance. Curr Drug Targets 5:241–250
Kola B, Hubina E, Tucci SA et al. (2005) Cannabinoids and ghrelin have both central and peripheral metabolic effects via AMP-activated protein kinase. J Biol Chem 280:25196–25202
Kola B, Farkas I, Christ-Crain M et al. (2008) The orexigenic effect of ghrelin is mediated through central activation of the endogenous cannabinoid system. PLoS ONE Mar 12; 3:e1797 PMID: 18335063
Liu YL, Connoley IP, Wilson CA et al. (2005) Effects of the cannabinoid CB1 receptor antagonist SR141716 on oxygen consumption and soleus muscle glucose uptake in Lep(ob)/Lep(ob) mice. Int J Obesity 29:183–187
Matias I, Di Marzo V (2007) Endocannabinoids and the control of energy balance. Trends Endocrinol Metab 18:27–37
Matias I, Gonthier MP, Orlando P et al. (2006) Regulation, function and dysregulation of endocannabinoids in models of adipose and β-pancreatic cells and in obesity and hyperglicemia. J Clin Endocrinol Metab 91:3171–3180
Monteleone P, Matias I, Martiadis V et al. (2005) Blood levels of the endocannabinoid anandamide are increased in anorexia nervosa and in binge-eating disorder, but not in bulimia nervosa. Neuropsychopharmacology 30:1216–1221
Neel JV (1962) Diabetes mellitus: A "thrifty" genotype rendered detrimental by "progress". Am Hum Genet 14:353–362
Osei-Hyiaman D, De Petrillo M, Pacher P et al. (2005a) Endocannabinoids activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet induced obesity. J Clin Invest 115:1298–1305

Osei-Hyiaman D, Depetrillo M, Harvey-White J et al. (2005b) Cocaine- and amphetamine-related transcript is involved in the orexigenic effect of anandamide. Neuroendocrinology 81:273–282

Osei-Hyiaman D, Liu J, Godlewski G et al. (2008) Hepatic CB1 receptor is required for development of diet-induced steatosis, dyslipidemia, and insulin and leptin resistance in mice. J Clin Invest 118:3160–3169

Pacher P, Batkai S, Kunos G (2006) The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev 58:389–462

Pagano C, Pilon C, Calcagno A et al. (2007) The endogenous cannabinoid system stimulates glucose uptake in human fat cells via phosphatidylinositol 3-kinase and calcium-dependent mechanisms. J Clin Endocrinol Metab 92:4810–4819

Pagotto U, Marsicano G, Cota D et al. (2006) The emerging role of endocannabinoid system in endocrine regulation and energy balance. Endocr Rev 27:73–100

Perwitz N, Fasshauer M, Klein J (2006) Cannabinoid receptor signalling directly inhibits thermogenesis and alters expression of adiponectin and visfatin. Horm Metab Res 38:356–358

Peters H, Nahas GG (1999) A brief history of four millennia (B.C.2000–A.D. 1974). In: Nahas GG, Sutin K, Harvey D, Agurell S (eds) Marihuana and medicine. Humana Press Inc, Totowa (NJ), pp 3–7

Piomelli D (2003) The molecular logic of endocannabinoid signalling. Nat Rev Neurosci 4:873–884

Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J for the RIO-North America Study Group (2006) 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 295:761–775

Ravinet Trillou C, Arnone M, Delgorge C et al. (2003) Anti-obesity effect of SR141716, a CB1 receptor antagonist, in diet induced obese mice. Am J Physiol Regul Integr Comp Physiol 284: R345–R353

Rosenstock J, Hollander P, Chevalier S, Iranmanesh A for the SERENADE study group (2008) The SERENADE trial: effects of monotherapy with rimonabant, the first selective CB1 receptor antagonist, on glycemic control, body weight and lipid profile in drug-naive type 2 diabetes. Diabetes Care Aug 4. PMID: 18678611

Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF for the RIO-Diabetes Study Group (2006) Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. Lancet 368:1660–1672

Simiand J, Keane M, Keane PE et al. (1998) SR 141716, a CB1 cannabinoid receptor antagonist, selectively reduces sweet food intake in marmoset. Behav Pharmacol 9:179–181

Starowicz KA, Cristino L, Matias I et al. (2008) Endocannabinoid dysregulation in the pancreas and adipose tissue of mice fed with a high-fat diet. Obesity 16:553–565

Tedesco L, Valerio A, Cervino C et al. (2008) Cannabinoid type 1 receptor blockade promotes mitochondrial biogenesis through endothelial nitric oxide synthase expression in white adipocytes. Diabetes 57:2028–2036

Tilg H, Moschen AR (2008) Role of adiponectin and PBEF/visfatin as regulators of inflammation: involvement in obesity-associated diseases. Clin Sci (Lond) 114:275–288

Tucci SA, Rogers EK, Korbonits M et al. (2004) The cannabinoid receptor antagonist SR141716 blocks the orexigenic effect of intrahypothalamic ghrelin. Br J Pharmacol 143:520–523

Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rössner S for the RIO-Europe Study Group (2005) 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 365:1389–1397

Williams CM, Kirkham TC (2002) Observational analysis of feeding induced by Δ^9-THC and anandamide. Physiol Behav 76:241–250

Yo JH, Chen YJ, Talmage DA et al. (2005) Integration of leptin signalling in an appetite-related neural circuit. Neuron 48:1055–1066