Endocannabinoids and related *N*-acylethanolamines in the control of appetite and energy metabolism: emergence of new molecular players

Didier M. Lambert and Giulio G. Muccioli

Purpose of review

Endocannabinoids (anandamide and 2-arachidonoylgycerol) and related *N*-acylethanolamines (*N*-oleoylethanolamine) exhibit opposite effects in the control of appetite. The purpose of this review is to highlight the similarities and differences of three major lipid-signaling molecules by focusing on their mode of action and the proteins involved in the control of food intake and energy metabolism.

Recent findings

Anandamide and 2-arachidonoylglycerol promote food intake and are the main endogenous ligands of the cannabinoid receptors. One of them, the cannabinoid receptor 1, is responsible for the control of food intake and energy expenditure both at a central and a peripheral level, affecting numerous anorexigenic and orexigenic mediators (leptin, neuropeptide Y, ghrelin, orexin, endogenous opioids, corticotropin-releasing hormone, α-melanocyte stimulating hormone, cocaine and amphetamine-related transcript). In the gut, *N*-oleoylethanolamine plays an opposite role in food regulation, by interacting with two molecular targets different from the cannabinoid receptors: the nuclear receptor peroxisome proliferator-activated receptor α and a G-protein coupled receptor GPR119.

Summary

Recent findings on the molecular mechanisms underlying the promotion of food intake or, in contrast, the suppression of food intake by anandamide and *N*-oleoylethanolamine, are summarized. Potential strategies for treating overweight, metabolic syndrome, and type II diabetes are briefly outlined.

Keywords

2-arachidonoylglycerol, anandamide, CB_1 cannabinoid receptor, GPR-119, oleoylethanolamide, peroxisome proliferator activated receptor-α

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Medicinal Chemistry and Radiopharmacy Unit, School of Pharmacy, Faculty of Medicine, Université catholique de Louvain, Brussels, Belgium

Correspondence to Professor Didier M. Lambert, PhD, Groupe Cannabinoïdes and Endocannabinoïdes, Unité de Chimie pharmaceutique et de Radiopharmacie, Ecole de Pharmacie, Faculté de Médecine, Université catholique de Louvain, Avenue E. Mounier 73, UCL-CMFA 73.40, B-1200 Bruxelles, Belgique
Tel: +32 2 764 73 47; fax: +32 2 764 73 63; e-mail: didier.lambert@uclouvain.be

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Abbreviations

CB_1	cannabinoid receptor 1
FAAH-1	fatty acid amide hydrolase
NAPE	*N*-acylphosphatidylethanolamine
PPARα	peroxisome proliferator-activated receptor α

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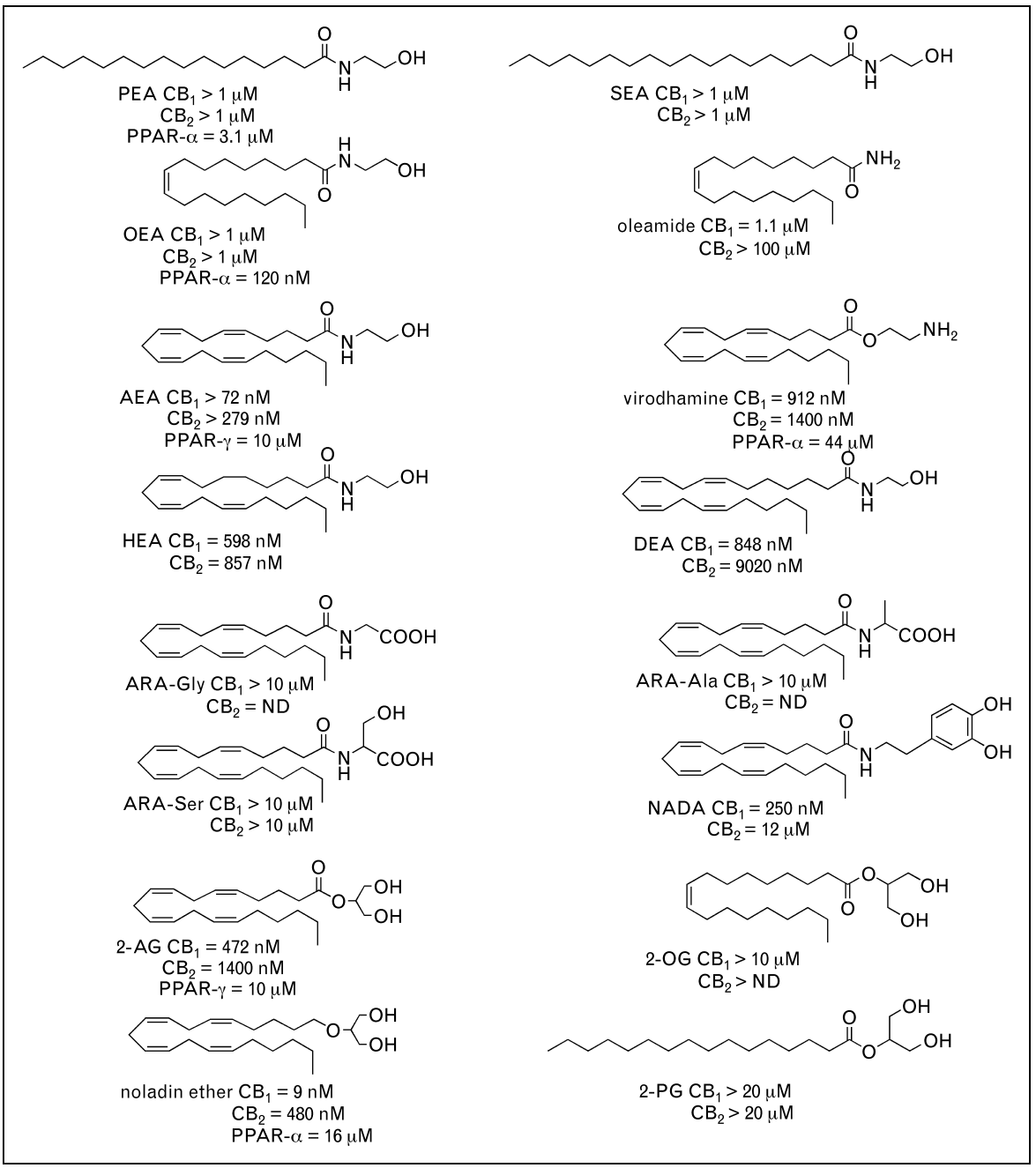
Introduction

Fifteen years have elapsed since the discovery by Devane *et al.* [1] of *N*-arachidonoylethanolamine, christened anandamide, as an endogenous ligand of the cannabinoid receptors. This discovery led to the elucidation of a whole signaling system which, in addition to the CB_1 and CB_2 cannabinoid receptors, comprises a set of enzymes involved either in the biosynthetic pathways or catabolism, as well as a putative endocannabinoid transporter protein [2]. Today, anandamide is part of a variety of cannabinoid receptor endogenous ligands, together with diverse *N*-acylethanolamines, arachidonoyl amino acids, monoacylglycerides, and even related ethers which have been identified in mammals and been shown to bind to the cannabinoid receptors [3] (Fig. 1). The arrival on the drug market in Europe (but not in the USA) of the cannabinoid CB_1 receptor antagonist/inverse agonist rimonabant for the treatment of obese and overweight patients with associated cardiovascular disease risk factors (type 2 diabetes and dyslipidemia), highlights the physiological mechanisms by which endocannabinoids exert their effect on appetite regulation, feeding and energy expenditure [4•]. The present review summarizes the recent data describing these mechanisms, focusing on the role of anandamide, 2-arachidonoylglycerol, and oleoylethanolamide which seem to be the principal regulators of food intake and energy metabolism among the endocannabinoids and related *N*-acylethanolamines.

Endocannabinoids: to be or not to be

Anandamide is one of the major *N*-acylethanolamines studied over the last 15 years. Its isolation from pig brain and identification as an endogenous ligand of the cannabinoid receptors launched the quest for detecting its presence in different biological organisms as well as the search for the identification of structurally related fatty acid derivatives in mammals. The abundance and

Figure 1 Endocannabinoid and related endogenous derivatives



The structures of the endocannabinoids and related *N*-acylethanolamines and acylglycerolesters are shown. The affinity for the cannabinoid receptors and peroxisome proliferator activated receptors (PPARs) are also provided. Note that for the PPAR data, functional data (EC_{50}) are more often reported than affinity data (K_i or IC_{50}). ARA-Ala, *N*-arachidonoylalanine; ARA-Gly, *N*-arachidonoylglycine; ARA-Ser, *N*-arachidonoylserine; DEA, *N*-docosotetraenoylethanolamine; HEA, *N*-homo-γ-linolenoylethanolamine; NADA, *N*-arachidonoyldopamine; 2-OG, 2-oleoylglycerol; PEA, *N*-palmitoylethanolamine; 2-PG, 2-palmitoylgycerol; SEA, *N*-stearoylethanolamine.

chemical diversity of endogenous compounds sharing with anandamide the cannabinoid receptors or its synthesizing and catabolic pathways raised the following question: what is an endocannabinoid? To be consistent with other neurotransmission systems, an endocannabinoid in the strict sense is an endogenous compound able to activate the endocannabinoid receptors, which are to date the G-protein-coupled CB_1 and CB_2 cannabinoid receptors. There are, however, a large variety of affinities and activities amongst the so-called 'endocannabinoids' (Fig. 1). Within these restrictive criteria, in this review, anandamide and 2-arachidonoylglycerol have been considered

as endocannabinoids, whereas *N*-oleoylethanolamine is referred to as 'related *N*-acylethanolamine'.

Even if the molecular targets mediating their physiological properties are different, however, related *N*-acylethanolamines and anandamide, and to a lesser extent 2-arachidonoylglycerol, share some biosynthetic and catabolic pathways. The diverse biosynthetic routes leading to anandamide and *N*-acylethanolamines are increasingly being characterized. One of these routes involves a calcium-dependent *N*-acyltransferase (NAT) activity synthesizing the *N*-acylphosphatidylethanolamine (NAPE) precursors which, upon transformation by a NAPE-specific phospholipase D, give rise to the *N*- acylethanolamines [5]. Although the enzyme responsible for this NAT activity in the brain awaits identification, a recent report [6••] describes the identification of a calcium-independent NAT enzyme (iNAT) synthesizing anandamide and *N*-acylethanolamine precursors highly expressed in rat testis. The recent generation of NAPE phospholipase D knockout mice possessing similar anandamide levels compared with the wild-type mice suggests that this enzyme may not be the primary enzyme responsible for anandamide biosynthesis [7••]. Accordingly, additional enzymatic routes have recently been proposed. For example, a serine hydrolase-catalyzed double-deacylation of NAPEs, to generate the corresponding glycerophospho-*N*-acylethanolamines, followed by a phosphodiesterase-mediated cleavage to generate *N*-acylethanolamines, has been described. In this pathway NAPEs are synthesized by the serine hydrolase α/β-hydrolase 4 (Abh4) [8•]. Another possible pathway for anandamide biosynthesis involves the phospholipase C-catalyzed cleavage of NAPE to generate phosphoanandamide, which is subsequently dephosphorylated by phosphatases affording the endocannabinoid [9•]. With respect to 2-arachidonoylglycerol synthesis, two *sn*-1 selective diacylglycerol lipases (*sn*-1-DAGLα and *sn*-1-DAGLβ) are responsible for the synthesis of 2-arachidonoyl glycerol from *sn*-1-acyl-2-arachidonoylglycerol precursors [10]. These precursors are synthesized from phosphatidylinositol by phospholipase C. A suggested alternative route is the hydrolysis of phosphatidylinositol in 2-arachidonoyl-lysophosphatidylinositol (lysoPI) by a phospholipase A_1. This compound would, in turn, be hydrolyzed by a lysophospholipase C resulting in 2-arachidonoylglycerol [11]. Of great relevance to the topic of this review is the fact that endocannabinoids and related *N*-acylethanolamines were detected and quantified in many tissues linked to food intake and control of energy metabolism, including the brain, liver, gastrointestinal tract, and adipose tissue [12•]. Importantly, the levels of these lipidic mediators vary with nutritional status (e.g. anandamide and oleoylethanolamide in the gut) and with the appearance of obesity (e.g. anandamide and 2-arachidonoylglycerol plasma levels in obese patients; see below).

The first step of signal cessation of endocannabinoids (and related compounds) requires their passage through the cell membrane to reach their catabolic enzymes. The question of the presence of an anandamide, as well as *N*-acylethanolamines and 2-arachidonylglycerol, uptake is subject to debate. A decisive step seemed to be achieved with the identification, using a small azidoaffinity labeled inhibitor LY2318912, of a high-affinity and saturable binding site involved in the transport of endocannabinoids [13]. Some close analogues of this molecule, however, have also been found to inhibit several brain serine hydrolases, including the enzymes responsible for the inactivation of endocannabinoids, raising once again the question of the presence of an active uptake [14,15].

With regards to the endocannabinoid catabolic pathways, at least four enzymes are known to be involved in the termination of endocannabinoid signaling, namely and in order of their cloning, fatty acid amide hydrolase (nowadays termed FAAH-1) [16], monoacylglycerol lipase [17,18], *N*-acylethanolamine acid amidase [19], and a fatty acid amide hydrolase-2 (FAAH-2) [20•]. Moreover, some biochemical and pharmacological evidence suggests that additional hydrolases may be able to regulate endocannabinoid tone [21–23]. Among these enzymes, the role of FAAH-1 in obesity has been investigated both in animal models and in humans.

Lymphocytes from obese leptin-deficient *ob/ob* mice showed decreased FAAH-1 activity and expression [24]. Leptin, through binding to its receptor and via activation of a STAT-3 signaling pathway, activates a CRE-like binding site on the FAAH-1 promoter. Such a decrease in FAAH-1 mRNA level was also observed in human obese patients [25]. Indeed, adipose tissue FAAH-1 mRNA levels were strongly decreased in obese women patients (average BMI of 38) compared with lean controls (BMI of 23.5). By contrast, plasma anandamide and 2-arachidonoylglycerol levels were found to be increased in obese patients. None of these parameters were affected by a 5% weight loss. Interestingly, visceral fat accumulation seems to be a key event in the dysregulation of the peripheral endocannabinoid system. Circulating 2-arachidonoylglycerol levels are correlated with visceral fat mass, whereas in visceral adipose tissue CB1 and FAAH expression are negatively correlated to visceral fat mass [26•].

A single nucleotide polymorphism (cytosine 385 → adenosine) of the FAAH-1 gene has been reported [27]. To investigate a potential relationship between the FAAH cDNA 385 A/A (P129T) polymorphism and overweight disorders, a study involving 2667 patients was conducted and led to a strong correlation between the FAAH 385A/385A genotype and overweight/obesity. This effect was observed in both Caucasian and African–American populations but, interestingly, the Pro129Thr mutation

was not associated with weight disorders in the Asian patients. The median BMI was significantly higher in the FAAH 385A/385A homozygous group than in the heterozygous and wild-type groups ($P < 0.0001$) [28]. In a Danish study involving a population-based cohort of 5801 white patients, however, the Pro129Thr variant of FAAH was not found to be associated with any fat accumulation phenotype [29]. Recently, Aberle and coworkers [30•] observed in obese and dyslipidaemic patients exhibiting the Pro129Thr FAAH mutation an enhanced decrease in triglycerides and total cholesterol during a 6-weeks low-fat diet compared with the wild-type individuals. The reasons for such differences, however, are yet to be identified and understood.

The cannabinoid CB_1 receptor

The appetite-stimulating properties of cannabis preparations as well as of Δ^9-tetrahydrocannabinol have been known for a long time (the so-called 'munchies'), even if the molecular mechanisms of these actions were only recently elucidated and continue to be investigated. Similarly, endocannabinoids such as anandamide and 2-arachidonoylglycerol [31,32] have been reported to increase food intake and promote weight gain in rats via the activation of hypothalamic CB_1 cannabinoid receptors [33]. Indeed, mice deficient in this receptor eat less, are leaner and more resistant to diet-induced obesity compared with their wild-type littermates [34,35]. In a similar fashion, cannabinoid antagonists/inverse agonists [36–42] reduce food intake and body weight both in animal models and in humans. Rimonabant-induced reduction in food intake is observed in lean as well as in genetically and diet-induced obese animals [43,44]. Although a rapid development of tolerance to the rimonabant anorectic effect has been observed, the effect on body weight was found to be more sustained over time. Following treatment discontinuation, however, the body weight returns to the levels of the untreated animals [45,46]. Besides the selectivity of rimonabant, its absence of effect in mice lacking the CB_1 receptor confirmed the CB_1-mediated mechanism of action and the pivotal role of the endocannabinoid system in regulating food intake [34,35,37]. In fact, besides the effect on body weight, the adjustments of the glycaemic and lipid parameters as well as reduction in the visceral fat mass are important hallmarks of rimonabant administration in rodents [37,47••,48]. In addition, blockade of the CB_1 cannabinoid receptor was recently shown to reduce the obesity-associated hepatic steatosis in a rodent model [47••]. In humans, the results from clinical studies using rimonabant in treating the metabolic syndrome (RIO studies) have been published [49–52] and there was found to be a reduction in body weight, a decrease in waist circumference (a sign of decreased visceral fat mass) and improvements in lipid and glucose profiles. Note that, similarly to the results for rodents, body weight and waist circumference returned to the levels of untreated patients following treatment discontinuation [51]. Extensive reviews on the therapeutic outcome of rimonabant have recently been published [53–55,56•].

One of the key features is that the weight loss is the consequence of the blockade of the endocannabinoid system, both at a central and a peripheral level. Resulting from activation of the endocannabinoid system at the central level, there is an enhancement in food intake and a decrease in satiety. A number of interactions between the endocannabinoid system and orexigenic and anorexigenic neuropeptides have been described that could explain part of the impact of this system on food intake [34,36,57] (Table 1 [34–36,58–69]).

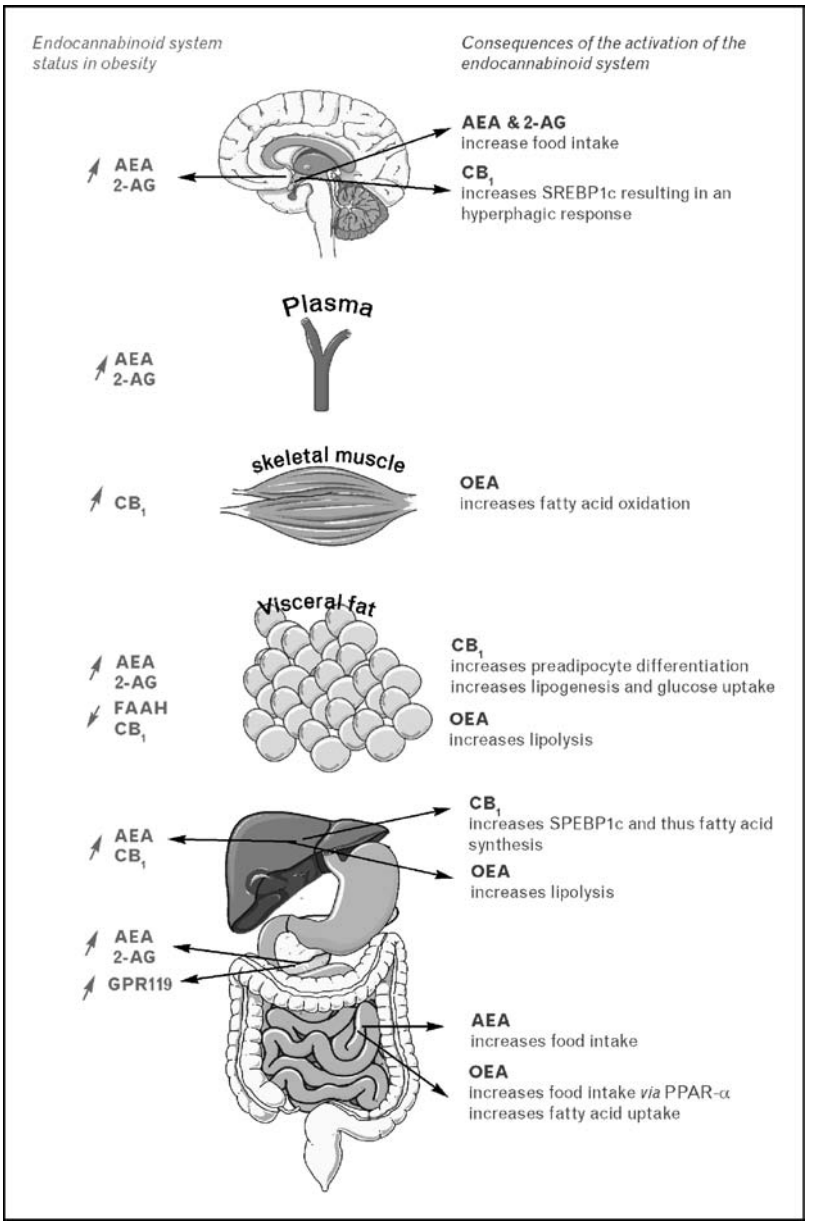
At peripheral sites different organs and tissues, expressing the CB_1 receptor, are involved in controlling energy homeostasis: white and brown adipose tissues [12•,36, 46,70•,71], the liver [47••,72], the gut [73], the pancreas [74–77], the brain [31], and skeletal muscles [78••,79•].

Table 1 Crosstalk of the endocannabinoid system with anorexigenic and orexigenic mediators

Mediator	Peptides actions	Link between the eCB system and the peptide	Reference
Leptin	↑ anorexigenic and ↓orexigenic neuropeptides	Leptin reduces AEA and 2-AG hypothalamic levels Blocking the CB_1 receptor increases leptin levels	[34,35]
NPY	↑ food intake	AEA increases hypothalamic NPY release	[34,58]
Ghrelin	↑ food intake via activation of the growth hormone secretagogue receptor	Blocking the CB_1 receptor reduces plasmatic ghrelin levels in fasted rats.	[59–61]
Orexin	Implicated in food intake in satiated rats	CB_1 and orexin 1 receptor heterodimerize CB_1 receptor potentiates the orexin 1 receptor	[62–64]
Endogenous opioids	↑ food intake	Cannabinoid and opioid ligands have synergistic effects on food intake	[65,66]
CRH	↓ food intake and affects energy balance	CB_1 and CRH are coexpressed in the hypothalamus	[36,67]
α-MSH	↓ food intake via melanocortin receptor 4 activation	Cannabinoid and melanocortin systems have synergistic effects on food intake	[68]
CART	The peptide product of CART is a tonically active anorectic mediator	CART is a downstram mediator of AEA orexigenic effects	[36,69]

The mediator, its described actions on food intake, and reported interactions with the endocannabinoid system are listed. AEA, anandamide; 2-AG, 2-arachidonoylglycerol; CART, cocaine and amphetamine-related transcript; CB_1 cannabinoid receptor 1; NPY, neuropeptide Y; CRH, corticotropin-releasing hormone; α-MSH, α-melanocyte stimulating hormone.

Figure 2 Overview of the endocannabinoid dysregulation in obesity



The endocannabinoid system is dysregulated in obese situations as described by the labels on the left. Obesity is characterized by an overall increase in endocannabinoid levels at central and peripheral sites (including circulating plasmatic levels). Upregulation of cannabinoid receptor CB_1 expression was also described in animal models in the liver [72], skeletal muscle [78••], and visceral fat [46,80]. Note that in humans decreased CB_1 receptor and fatty acid amide hydrolase (FAAH) expression was found in fat tissues [25,26•]. On the right side of the panel are given the effects on food intake and energy metabolism of activation of the endocannabinoid system. Both orexigenic – activation of the CB_1 receptor and anandamide (AEA) or 2-arachidonoylglycerol (2-AG) increased levels – and anorexigenic – action of oleoylethanolamide (OEA) through peroxisome proliferator activated receptor α and possibly GPR119 – pathways are shown. SREBP1c, sterol regulatory element binding protein 1c.

During obesity, the peripheral endocannabinoid system is overactive (Fig. 2) [25,26•,46,72,78••,80]. The observed alterations or modifications during obesity have been recently reviewed by Matias and Di Marzo [81].

The nuclear peroxisome proliferator-activated receptor α

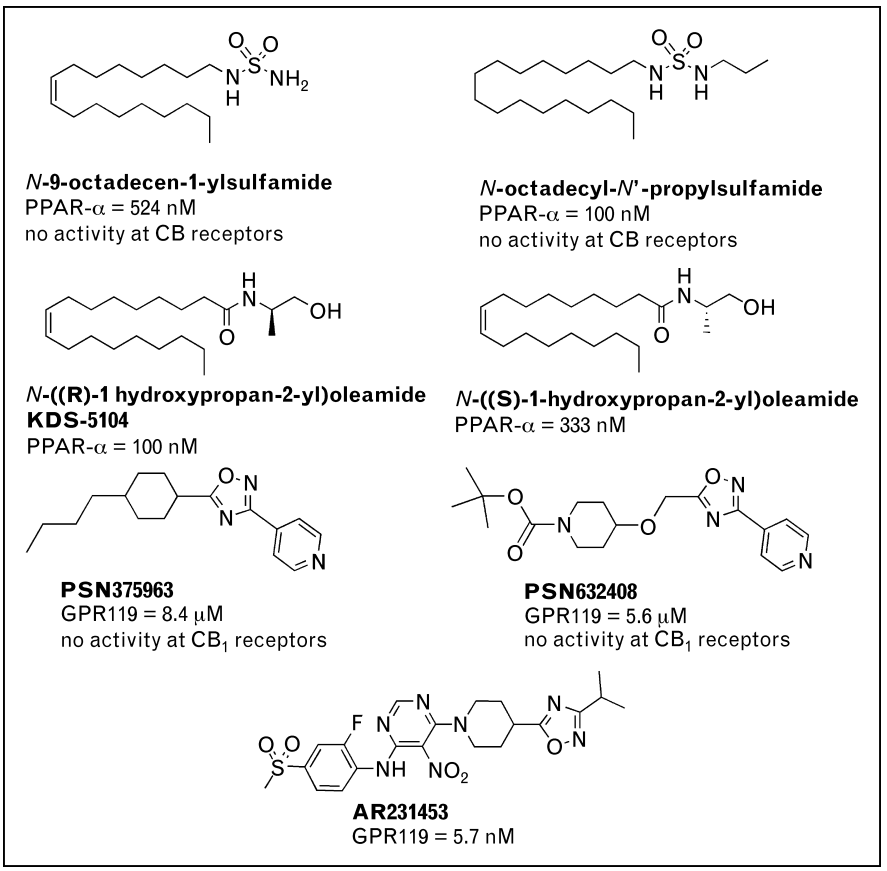
Oleoylethanolamide, a mono *cis*-unsaturated and shorter analogue of anandamide, is an endogenous fatty acid derivative involved in feeding and body mass regulation. In food-deprived rats (24 h) oleoylethanolamide suppressed food intake upon refeeding, an effect shared with *N*-palmitoylethanolamine but not with anandamide or oleic acid. Unlike anandamide, oleoylethanolamide does not bind to cannabinoid receptors [82], but like the endocannabinoid, it is metabolized by fatty acid amide hydrolase-1 [83]. Mice deficient for FAAH-1 exhibit a 40-fold increase in brain oleoylethanolamide levels [84]. The anorectic effect of oleoylethanolamide has a peripheral origin, since no effect on food intake was observed after direct administration of oleoylethanolamide in brain ventricles or following destruction of peripheral sensory fibers by capsaicin [85]. Levels of oleoylethanolamide in the intestine vary in relation to food consumption, since they are reduced during fasting and rise after refeeding; in other words, oleoylethanolamide levels give the opposite

pattern to that of anandamide level variations in response to food intake [73,86••,87•]. Oral administration of oleoylethanolamide gives a similar picture [88,89]. The peroxisome proliferator-activated receptor α (PPARα) is one of the molecular targets of oleoylethanolamide [90,91], mediating satiety, body weight maintenance, and lipolysis. This nuclear receptor, involved in the regulation of lipid metabolism, has become, together with other PPARs an attractive drug target [92] to treat dyslipidemia, diabetes, obesity and metabolic syndrome [93,94]. They are all ligand-activated transcription factors of the nuclear hormone receptor superfamily, sharing a high degree of structural homology, particularly in the DNA-binding domain and ligand and cofactor-binding domain, and act as lipid sensors [95]. Low-affinity PPARα activators such as fibrates are hypolipidemic agents that have been used as therapeutic agents for 40 years [96]. The interrelations between cannabinoids and PPARs were briefly reviewed by Sun *et al.* [97]; not only oleoylethanolamide but also *N*-palmitoylethanolamine, anandamide, virodhamine and noladin ether, as well as synthetic unrelated cannabinoid agonists such as WIN-55,212-2, are able to activate, at least partially, mouse PPAR-α (Fig. 1). In addition, other PPARs such as PPARγ are the targets of both anandamide and 2-arachidonoylglycerol [98] but also of Δ^9-tetrahydrocannabinol [99,100]. A combination therapy with rimonabant, a CB_1 cannabinoid antagonist/inverse agonist, and oleoylethanolamide has been reported to enhance the feeding suppression effect both in normal rats and in genetically obese Zucker rats, resulting in body weight reduction. The serum and liver lipid levels were reduced by the treatment. A parallel amelioration in the hepatic steatosis, through the control of the gene expression of stearoyl coenzyme A desaturase 1, a key enzyme in lipid biosynthesis and triglycerides secretion, was also obtained [101•], an effect similar to what was described for *N*-stearoylethanolamine [102]. The effects of oleoylethanolamide on ghrelin [59] and on fatty acid translocase (FAT/CD36), an integral membrane protein facilitating the free fatty acid uptake into cells [103], have also been described, although definitive answers for the responsible mechanisms remain to be defined.

The GPR119 receptor

GPR119, an orphan Gα(s) protein coupled receptor known to bind phospholipids [104], has recently been

Figure 3 Recently described ligands for the peroxisome proliferator activated receptor α (PPARα) and GPR119 receptor



The oxadiazoles PSN375963, PSN 632408, and AR231453 are GPR119 ligands [105••,106••]. The *N*-oleoylethanolamine derivatives are PPARα activators [107,108•].

deorphanized. Indeed, *N*-oleoylethanolamide binds and activates GPR119. In addition, small molecules showing hypophagic properties like PSN375963 and PSN632408 (Fig. 3 [105••,106••,107,108•]) also act as GPR119 agonists, without affecting PPARα and transient receptor potential vanilloid type 1 (TRPV1) receptors, raising the possibility of an alternative mechanism explaining the satiety mediated by *N*-oleoylethanolamide A [105••]. The expression and distribution of GPR119 in rodents is present in some abundance in the gastrointestinal tract, brain and pancreas. In this latter organ, GPR119 seems to be localized in the insulin-producing β-cells of the pancreatic islets where its mRNA levels were elevated in obese mice compared with lean animals [109]. Recently, Chu *et al.* [106••] suggested that when using GPR119-deficient mice – which possess a diabetic phenotype – GPR119 functions as a glucose-dependent insulinotropic receptor and may be suitable for the development of potent, orally active, small-molecule antihyperglycaemic agents. Thus, selective GPR119 agonists would represent, alone or in combination with PPARα agonists or CB_1 receptor antagonists, valuable therapeutic agents for the treatment of obesity and metabolic syndrome.

Although two molecular targets – PPARα and GPR119, which provide a rationale for the *N*-oleoylethanolamide effects on food intake – have been identified, less is known about this *N*-acylethanolamine catabolism in the gastrointestinal tract. Indeed, the administration of a potent FAAH-1 inhibitor, URB597, did not potentiate the oleoylethanolamide-induced hypophagia [110]. In fact, inhibition of FAAH-1 in the rat failed to affect the intestinal levels of the *N*-acylethanolamines anandamide, *N*-palmitoylethanolamine and *N*-oleoylethanolamide. In addition oleoylethanolamide and *N*-palmitoylethanolamine levels in the intestine were only slightly enhanced in FAAH-$1^{-/-}$ mice, and to a far lesser extent when compared with that observed in the brain and liver, suggesting that FAAH-1 does not play a key role in *N*-oleoylethanolamide-induced hypophagia. Further evidence in this regard is the fact that oleoylethanolamide produced a similar anorectic effect in wild-type and FAAH-1-deficient mice, suggesting that oleoylethanolamide metabolism in the intestine results from another enzyme. Candidate enzymes responsible for this activity are *N*-acylethanolamine acid amidase, which hydrolyses oleoylethanolamide and is expressed in the gastrointestinal tract [19], as well as ceramidases, as recently suggested [111]. These data should open the way for further studies aiming at characterizing oleoylethanolamide hydrolysis in the gastrointestinal tract. We believe that inhibitors of oleoylethanolamide metabolism acting on the metabolism of oleoylethanolamide in the gastrointestinal tract could provide useful tools to regulate food intake.

Conclusion

All these recent findings are cause for considerable excitement in the drug discovery field. Antagonists of the CB_1 cannabinoid receptors are now well developed, as testified by the number of compounds in clinical trials [112]. Less is known on the potential of mimicking oleoylethanolamide actions by activating its targets, namely PPARα and GPR119. Furthermore, many patents and papers reported the search for mixed PPARα–γ agonists or the use of combinations of the two agonists [113,114]. Analogues of oleoylethanolamide, including *N*-octadecyl-*N*'-propylsulfamide (Fig. 3) have just been released and elicit both activation of PPARα and feeding suppressant properties [107]. It is important to note that one of the compounds, *N*-octadecylsulfamide, mimics the effects of oleoylethanolamide on body weight but fails to activate PPARα. High throughput screening on GPR119 revealed new synthetic ligands such as PSN375963 and PSN632408 with hypophagic properties [105••]. Another recent example of a new GPR119 selective agonist is AR231453, a molecule that displays an enhanced glucose-dependent insulin release *in vivo* and improved oral glucose tolerance [106••].

Acknowledgements

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 779–780).

1 Devane WA, Hanus L, Breuer A, *et al.* Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 1992; 258: 1946–1949.

2 Lambert DM, Fowler CJ. The endocannabinoid system: drug targets, lead compounds, and potential therapeutic applications. J Med Chem 2005; 48:5059–5087.

3 Kogan NM, Mechoulam R. The chemistry of endocannabinoids. J Endocrinol Invest 2006; 29:3–14.

4 • Matias I, Di Marzo V. Endocannabinoids and the control of energy balance. Trends Endocrinol Metab 2007; 18:27–37.
A comprehensive review on the endocannabinoid actions at both central and peripheral levels. Includes a description of the outcome of the clinical trials on rimonabant, the CB1 cannabinoid antagonist.

5 Okamoto Y, Morishita J, Tsuboi K, *et al.* Molecular characterization of a phospholipase D generating anandamide and its congeners. J Biol Chem 2004; 279:5298–5305.

6 •• Jin XH, Okamoto Y, Morishita J, *et al.* Discovery and characterization of a Ca^{2+}-independent phosphatidylethanolamine *N*-acyltransferase generating the anandamide precursor and its congeners. J Biol Chem 2007; 282: 3614–3623.
A very nice paper describing the cloning and characterization of an *N*-acyltransferase activity, the enzyme responsible for the first step in anandamide synthesis.

7 •• Leung D, Saghatelian A, Simon GM, Cravatt BF. Inactivation of N-acyl phosphatidylethanolamine phospholipase D reveals multiple mechanisms for the biosynthesis of endocannabinoids. Biochemistry 2006; 45:4720–4726.
Proof of concept that NAPE phospholipase D is not the main enzyme involved in anandamide biosynthesis.

8 • Simon GM, Cravatt BF. Endocannabinoid biosynthesis proceeding through glycerophospho-N-acyl ethanolamine and a role for a/b-hydrolase 4 in this pathway. J Biol Chem 2006; 281:26465–26472.
A new pathway for the synthesis of *N*-acylethanolamines.

9 Liu J, Wang L, Harvey-White J, *et al.* A biosynthetic pathway for anandamide.
• Proc Natl Acad Sci USA 2006; 103:13345–13350.
A new pathway for the synthesis of *N*-acylethanolamines.

10 Bisogno T, Howell F, Williams G, *et al.* Cloning of the first sn1-DAG lipases points to the spatial and temporal regulation of endocannabinoid signaling in the brain. J Cell Biol 2003; 163:463–468.

11 Bisogno T, Ligresti A, Di Marzo V. The endocannabinoid signalling system: biochemical aspects. Pharmacol Biochem Behav 2005; 81:224–238.

12 Gonthier MP, Hoareau L, Festy F, *et al.* Identification of endocannabinoids
• and related compounds in human fat cells. Obesity 2007; 15:837–845.
Identification and quantification of the endocannabinoids and related compounds in human adipocytes.

13 Moore SA, Nomikos GG, Dickason-Chesterfield AK, *et al.* Identification of a high-affinity binding site involved in the transport of endocannabinoids. Proc Natl Acad Sci USA 2005; 102:17852–17857.

14 Alexander JP, Cravatt BF. The Putative endocannabinoid transport blocker LY2183240 is a potent inhibitor of FAAH and several other brain serine hydrolases. J Am Chem Soc 2006; 128:9699–9704.

15 Ortar G, Cascio MG, Moriello AS, Camalli M, Morera E, Nalli M, Di Marzo V. Carbamoyl tetrazoles as inhibitors of endocannabinoid inactivation: a critical revisitation. Eur J Med Chem 2007; 19 March [Epub ahead of print].

16 Cravatt BF, Giang DK, Mayfield SP, *et al.* Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. Nature 1996; 384:83–87.

17 Karlsson M, Contreras JA, Hellman U, *et al.* cDNA cloning, tissue distribution, and identification of the catalytic triad of monoglyceride lipase: evolutionary relationship to esterases, lysophospholipases, and haloperoxidases. J Biol Chem 1997; 272:27218–27223.

18 Dinh TP, Carpenter D, Leslie FM, *et al.* Brain monoglyceride lipase participating in endocannabinoid inactivation. Proc Natl Acad Sci USA 2002; 99:10819–10824.

19 Tsuboi K, Sun YX, Okamoto Y, *et al.* Molecular characterization of N-acylethanolamine-hydrolyzing acid amidase, a novel member of the choloylglycine hydrolase family with structural and functional similarity to acid ceramidase. J Biol Chem 2005; 280:11082–11092.

20 Wei BQ, Mikkelsen TS, McKinney MK, *et al.* A second fatty acid amide
• hydrolase with variable distribution among placental mammals. J Biol Chem 2006; 281:36569–36578.
This paper describes a second FAAH which has different substrate preferences and localization compared with the first FAAH.

21 Muccioli GG, Xu C, Cudaback E, *et al.* Identification of a novel endocannabinoid-hydrolyzing enzyme expressed by microglial cells. J Neurosci 2007; 27:2883–2889.

22 Dinh TP, Kathuria S, Piomelli D. RNA interference suggests a primary role for monoacylglycerol lipase in the degradation of the endocannabinoid 2-arachidonoylglycerol. Mol Pharmacol 2004; 66:1260–1264.

23 Vandevoorde S, Saha B, Mahadevan A, *et al.* Influence of the degree of unsaturation of the acyl side chain upon the interaction of analogues of 1-arachidonoylglycerol with monoacylglycerol lipase and fatty acid amide hydrolase. Biochem Biophys Res Commun 2005; 337:104–109.

24 Maccarrone M, Gasperi V, Fezza F, *et al.* Differential regulation of fatty acid amide hydrolase promoter in human immune cells and neuronal cells by leptin and progesterone. Eur J Biochem 2004; 271:4666–4676.

25 Engeli S, Bohnke J, Feldpausch M, *et al.* Activation of the peripheral endocannabinoid system in human obesity. Diabetes 2005; 54:2838–2843.

26 Bluher M, Engeli S, Kloting N, *et al.* Dysregulation of the peripheral and
• adipose tissue endocannabinoid system in human abdominal obesity. Diabetes 2006; 55:3053–3060.
Very interesting study demonstrating the variations in the endocannabinoid tone found in obese humans.

27 Sipe JC, Chiang K, Gerber AL, *et al.* A missense mutation in human fatty acid amide hydrolase associated with problem drug use. Proc Natl Acad Sci USA 2002; 99:8394–8399.

28 Sipe JC, Waalen J, Gerber A, Beutler E. Overweight and obesity associated with a missense polymorphism in fatty acid amide hydrolase (FAAH). Int J Obes 2005; 29:755–759.

29 Jensen DP, Andreasen CH, Andersen MK, *et al.* The functional Pro129Thr variant of the FAAH gene is not associated with various fat accumulation phenotypes in a population-based cohort of 5801 whites. J Mol Med 2007; 85:445–449.

30 Aberle J, Fedderwitz I, Klages N, *et al.* Genetic variation in two proteins of the
• endocannabinoid system and their influence on body mass index and metabolism under low fat diet. Horm Metab Res 2007; 39:395–397.
The influence of FAAH polymorphism on the effect of a 6-week diet is reported. Carriers of the P129T mutation in FAAH had a significantly greater decrease in triglycerides and total cholesterol compared with wild type.

31 Kirkham TC, Williams CM, Fezza F, Di Marzo V. 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 2002; 136:550–557.

32 Higgs S, Williams CM, Kirkham TC. Cannabinoid influences on palatability: microstructural analysis of sucrose drinking after D9-tetrahydrocannabinol, anandamide, 2-arachidonoyl glycerol and SR141716. Psychopharmacology 2003; 165:370–377.

33 Jamshidi N, Taylor DA. Anandamide administration into the ventromedial hypothalamus stimulates appetite in rats. Br J Pharmacol 2001; 134: 1151–1154.

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

35 Ravinet Trillou C, Delgorge C, Menet C, *et al.* CB1 cannabinoid receptor knockout in mice leads to leanness, resistance to diet-induced obesity and enhanced leptin sensitivity. Int J Obesity 2004; 28:640–648.

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

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

38 Hildebrandt AL, Kelly-Sullivan DM, Black SC. Antiobesity effects of chronic cannabinoid CB1 receptor antagonist treatment in diet-induced obese mice. Eur J Pharmacol 2003; 462:125–132.

39 Shearman LP, Rosko KM, Fleischer R, *et al.* Antidepressant-like and anorectic effects of the cannabinoid CB1 receptor inverse agonist AM251 in mice. Behav Pharmacol 2003; 14:573–582.

40 Werner NA, Koch JE. Effects of the cannabinoid antagonists AM281 and AM630 on deprivation-induced intake in Lewis rats. Brain Res 2003; 967: 290–292.

41 Lin LS, Lanza TJ Jr, Jewell JP, *et al.* Discovery of N-[(1S,2S)-3-(4-chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-methyl-2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}propanamide (MK-0364), a novel, acyclic cannabinoid-1 receptor inverse agonist for the treatment of obesity. J Med Chem 2006; 49:7584–7587.

42 Pavon FJ, Bilbao A, Hernandez-Folgado L, *et al.* Antiobesity effects of the novel in vivo neutral cannabinoid receptor antagonist 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-3-hexyl-1H-1,2,4-triazole: LH 21. Neuropharmacology 2006; 51:358–366.

43 Freedland CS, Poston JS, Porrino LJ. Effects of SR141716A, a central cannabinoid receptor antagonist, on food-maintained responding. Pharmacol Biochem Behav 2000; 67:265–270.

44 McLaughlin PJ, Winston K, Swezey L, *et al.* The cannabinoid CB1 antagonists SR 141716A and AM 251 suppress food intake and food-reinforced behavior in a variety of tasks in rats. Behav Pharmacol 2003; 14:583–588.

45 Colombo G, Agabio R, Diaz G, *et al.* Appetite suppression and weight loss after the cannabinoid antagonist SR 141716. Life Sci 1998; 63:L113–L117.

46 Bensaid M, Gary-Bobo M, Esclangon A, *et al.* 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 2003; 63: 908–914.

47 Gary-Bobo M, Elachouri G, Gallas JF, *et al.* Rimonabant reduces obesity-
•• associated hepatic steatosis and features of metabolic syndrome in obese Zucker fa/fa rats. Hepatology 2007; 46:122–129.
Study on the effects of the CB_1 blocker rimonabant on liver metabolism. Rimonabant was shown to exert a hepatoprotective effect in obese animals.

48 Poirier B, Bidouard JP, Cadrouvele C, *et al.* The antiobesity effect of rimonabant is associated with an improved serum lipid profile. Diabetes Obesity Metab 2005; 7:65–72.

49 Van Gaal LF, Rissanen AM, Scheen AJ, *et al.* 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.

50 Despres JP, Golay A, Sjoestroem L. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. New Engl J Med 2005; 353: 2121–2134.

51 Pi-Sunyer FX, Aronne LJ, Heshmati HM, *et al.,* for the RIO. 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.

52 Scheen AJ, Finer N, Hollander P, *et al.* Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. Lancet 2006; 368:1660–1672.

53 Henness S, Robinson DM, Lyseng-Williamson KA. Rimonabant. Drugs 2006; 66:2109–2119.

54 Bifulco M, Grimaldi C, Gazzerro P, *et al.* Rimonabant: just an antiobesity drug? Current evidence on its pleiotropic effects. Mol Pharmacol 2007; 71:1445–1456.

55 Patel PN, Pathak R. Rimonabant: a novel selective cannabinoid-1 receptor antagonist for treatment of obesity. Am J Health Syst Pharm 2007; 64:481–489.

56 • Lafontan M, Piazza PV, Girard J. Effects of CB1 antagonist on the control of metabolic functions in obese type 2 diabetic patients. Diabetes Metab 2007; 33:85–95.

Interesting review summarizing the recent findings on the effects of blocking the CB_1 receptor in patients with diabetes.

57 Matias I, Vergoni AV, Petrosino S, *et al.* Regulation of hypothalamic endocannabinoid levels by neuropeptides and hormones involved in food intake and metabolism: insulin and melanocortins. Neuropharmacology (in press).

58 Gamber KM, Macarthur H, Westfall TC. Cannabinoids augment the release of neuropeptide Y in the rat hypothalamus. Neuropharmacology 2005; 49:646–652.

59 Cani PD, Montoya ML, Neyrinck AM, *et al.* Potential modulation of plasma ghrelin and glucagon-like peptide-1 by anorexigenic cannabinoid compounds, SR141716A (rimonabant) and oleoylethanolamide. Br J Nutr 2004; 92:757–761.

60 Tucci SA, Rogers EK, Korbonits M, Kirkham TC. The cannabinoid CB1 receptor antagonist SR141716 blocks the orexigenic effects of intrahypothalamic ghrelin. Br J Pharmacol 2004; 143:520–523.

61 Rigamonti AE, Giordani C, Bonomo SM, *et al.* Early tolerance to the hypophagic effect of the cannabinoid receptor antagonist SR141716 does not impede blockade of an orexigenic stimulus. Eur J Pharmacol 2006; 542:116–120.

62 Hilairet S, Bouaboula M, Carriere D, *et al.* Hypersensitization of the orexin 1 receptor by the CB1 receptor: evidence for cross-talk blocked by the specific cb1 antagonist, SR141716. J Biol Chem 2003; 278:23731–23737.

63 Ellis J, Pediani JD, Canals M, *et al.* Orexin-1 receptor-cannabinoid CB1 receptor heterodimerization results in both ligand-dependent and -independent coordinated alterations of receptor localization and function. J Biol Chem 2006; 281:38812–38824.

64 Huang H, Acuna-Goycolea C, Li Y, *et al.* Cannabinoids excite hypothalamic melanin-concentrating hormone but inhibit hypocretin/orexin neurons: implications for cannabinoid actions on food intake and cognitive arousal. J Neurosci 2007; 27:4870–4881.

65 Kirkham TC, Williams CM. Synergistic effects of opioid and cannabinoid antagonists on food intake. Psychopharmacology 2001; 153:267–270.

66 Solinas M, Goldberg SR. Motivational effects of cannabinoids and opioids on food reinforcement depend on simultaneous activation of cannabinoid and opioid systems. Neuropsychopharmacology 2005; 30: 2035–2045.

67 Hermann H, Lutz B. Coexpression of the cannabinoid receptor type 1 with the corticotropin-releasing hormone receptor type 1 in distinct regions of the adult mouse forebrain. Neurosci Lett 2005; 375:13–18.

68 Verty AN, McFarlane JR, McGregor IS, Mallet PE. Evidence for an interaction between CB1 cannabinoid and melanocortin MCR-4 receptors in regulating food intake. Endocrinology 2004; 145:3224–3231.

69 Osei-Hyiaman D, DePetrillo M, Harvey-White J, *et al.* Cocaine- and amphetamine-related transcript is involved in the orexigenic effect of endogenous anandamide. Neuroendocrinology 2005; 81:273–282.

70 • Spoto B, Fezza F, Parlongo G, *et al.* Human adipose tissue binds and metabolizes the endocannabinoids anandamide and 2-arachidonoylglycerol. Biochimie 2006; 88:1889–1897.

Further proof of the presence of an active endocannabinoid system in adipose tissue in humans.

71 Gasperi V, Fezza F, Pasquariello N, *et al.* Endocannabinoids in adipocytes during differentiation and their role in glucose uptake. Cell Mol Life Sci 2007; 64:219–229.

72 Osei-Hyiaman D, DePetrillo M, Pacher P, *et al.* Endocannabinoid activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet-induced obesity. J Clin Invest 2005; 115:1298–1305.

73 Gomez R, Navarro M, Ferrer B, *et al.* A peripheral mechanism for CB1 cannabinoid receptor-dependent modulation of feeding. J Neurosci 2002; 22:9612–9617.

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

75 Juan-Pico P, Fuentes E, Bermudez-Silva FJ, *et al.* Cannabinoid receptors regulate Ca(2+) signals and insulin secretion in pancreatic beta-cell. Cell Calcium 2006; 39:155–162.

76 Bermudez-Silva FJ, Sanchez-Vera I, Suarez J, *et al.* Role of cannabinoid CB2 receptors in glucose homeostasis in rats. Eur J Pharmacol 2007; 565:207–211.

77 Matias I, Gonthier MP, Orlando P, *et al.* 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.

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

Comprehensive recent review on the endocannabinoid role in regulating energy metabolism.

79 • Cavuoto P, McAinch AJ, Hatzinikolas G, *et al.* Effects of cannabinoid receptors on skeletal muscle oxidative pathways. Mol Cell Endocrinol 2007; 267:63–69.

This paper suggests a role for the muscular tissues in the peripheral effects of CB_1 receptor activation.

80 Yan ZC, Liu DY, Zhang LL, *et al.* Exercise reduces adipose tissue via cannabinoid receptor type 1 which is regulated by peroxisome proliferator-activated receptor-delta. Biochem Biophys Res Commun 2007; 354:427–433.

81 Matias I, Di Marzo V. Endocannabinoid synthesis and degradation, and their regulation in the framework of energy balance. J Endocrinol Invest 2006; 29:15–26.

82 Lambert DM, DiPaolo FG, Sonveaux P, *et al.* Analogues and homologues of N-palmitoylethanolamide, a putative endogenous CB2 cannabinoid, as potential ligands for the cannabinoid receptors. Biochim Biophys Acta 1999; 1440:266–274.

83 Jonsson KO, Vandevoorde S, Lambert DM, *et al.* Effects of homologues and analogues of palmitoylethanolamide upon the inactivation of the endocannabinoid anandamide. Br J Pharmacol 2001; 133:1263–1275.

84 Cravatt BF, Demarest K, Patricelli MP, *et al.* Supersensitivity to anandamide and enhanced endogenous cannabinoid signaling in mice lacking fatty acid amide hydrolase. Proc Natl Acad Sci USA 2001; 98:9371–9376.

85 Rodriguez de Fonseca F, Navarro M, Gomez R, *et al.* An anorexic lipid mediator regulated by feeding. Nature 2001; 414:209–212.

86 •• Fu J, Astarita G, Gaetani S, *et al.* Food intake regulates oleoylethanolamide formation and degradation in the proximal small intestine. J Biol Chem 2007; 282:1518–1528.

N-oleoylethanolamine controls food intake by acting in the gastrointestinal tract, and food intake regulates *N*-oleoylethanolamine levels through regulation of the enzymes involved in its metabolism.

87 • Petersen G, Sorensen C, Schmid PC, *et al.* Intestinal levels of anandamide and oleoylethanolamide in food-deprived rats are regulated through their precursors. Biochim Biophys Acta 2006; 1761:143–150.

The levels of anandamide and *N*-oleoylethanolamine are inversely regulated by food intake.

88 Oveisi F, Gaetani S, Eng KT, Piomelli D. Oleoylethanolamide inhibits food intake in free-feeding rats after oral administration. Pharmacol Res 2004; 49:461–466.

89 Nielsen MJ, Petersen G, Astrup A, Hansen HS. Food intake is inhibited by oral oleoylethanolamide. J Lipid Res 2004; 45:1027–1029.

90 Fu J, Gaetani S, Oveisi F, *et al.* Oleylethanolamide regulates feeding and body weight through activation of the nuclear receptor PPAR-α. Nature 2003; 425: 90–93.

91 Guzman M, Lo Verme J, Fu J, *et al.* Oleoylethanolamide stimulates lipolysis by activating the nuclear receptor peroxisome proliferator-activated receptor α (PPAR-α). J Biol Chem 2004; 279:27849–27854.

92 Staels B, Fruchart JC. Therapeutic roles of peroxisome proliferator-activated receptor agonists. Diabetes 2005; 54:2460–2470.

93 Berger JP, Akiyama TE, Meinke PT. PPARs: therapeutic targets for metabolic disease. Trends Pharmacol Sci 2005; 26:244–251.

94 Fievet C, Fruchart JC, Staels B. PPARalpha and PPARgamma dual agonists for the treatment of type 2 diabetes and the metabolic syndrome. Curr Opin Pharmacol 2006; 6:606–614.

95 Michalik L, Auwerx J, Berger JP, *et al.* International Union of Pharmacology. LXI: Peroxisome proliferator-activated receptors. Pharmacol Rev 2006; 58:726–741.

96 Backes JM, Gibson CA, Ruisinger JF, Moriarty PM. Fibrates: what have we learned in the past 40 years? Pharmacotherapy 2007; 27:412–424.

97 Sun Y, Alexander SP, Kendall DA, Bennett AJ. Cannabinoids and PPARalpha signalling. Biochem Soc Trans 2006; 34:1095–1097.

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

99 O'Sullivan SE, Tarling EJ, Bennett AJ, *et al.* Novel time-dependent vascular actions of Delta9-tetrahydrocannabinol mediated by peroxisome proliferator-activated receptor gamma. Biochem Biophys Res Commun 2005; 337:824–831.

100 O'Sullivan SE, Kendall DA, Randall MD. Further characterization of the time-dependent vascular effects of delta9-tetrahydrocannabinol. J Pharmacol Exp Ther 2006; 317:428–438.

101 • Serrano A, del Arco I, Javier Pavon F, *et al.* The cannabinoid CB1 receptor antagonist SR141716A (rimonabant) enhances the metabolic benefits of long-term treatment with oleoylethanolamide in Zucker rats. Neuropharmacology 2007; 24 March [Epub ahead of print].

This study suggests therapeutic potential for using a combined therapy comprising CB_1 receptor antagonists and oleoylethanolamide-like derivatives.

102 Terrazzino S, Berto F, Dalle CM, *et al.* Stearoylethanolamide exerts anorexic effects in mice via down-regulation of liver stearoyl-coenzyme A desaturase-1 mRNA expression. FASEB J 2004; 18:1580–1582.

103 Yang Y, Chen M, Loux TJ, Harmon CM. Regulation of FAT/CD36 mRNA gene expression by long chain fatty acids in the differentiated 3T3-L1 cells. Pediatr Surg Int 2007; 23:675–683.

104 Soga T, Ohishi T, Matsui T, *et al.* Lysophosphatidylcholine enhances glucose-dependent insulin secretion via an orphan G-protein-coupled receptor. Biochem Biophys Res Commun 2005; 326:744–751.

105 •• Overton HA, Babbs AJ, Doel SM, *et al.* Deorphanization of a G protein-coupled receptor for oleoylethanolamide and its use in the discovery of small-molecule hypophagic agents. Cell Metab 2006; 3:167–175.

Very important paper suggesting that oleoylethanolamide possesses drugable molecular targets besides PPARα. Two synthetic ligands that activate GPR119 are also described.

106 •• Chu ZL, Jones RM, He H, *et al.* A role for beta-cell-expressed G protein-coupled receptor 119 in glycemic control by enhancing glucose-dependent insulin release. Endocrinology 2007; 148:2601–2609.

GPR119 is expressed in the pancreas where it can regulate glyceamia. This paper suggests that the receptor could be an interesting target for treating patients with diabetes.

107 Cano C, Pavon J, Serrano A, *et al.* Novel sulfamide analogs of oleoylethanolamide showing in vivo satiety inducing actions and PPARalpha activation. J Med Chem 2007; 50:389–393.

108 • Astarita G, Di Giacomo B, Gaetani S, *et al.* Pharmacological characterization of hydrolysis-resistant analogs of oleoylethanolamide with potent anorexiant properties. J Pharmacol Exp Ther 2006; 318:563–570.

Describes the pharmacological properties of *N*-(S)-1-hydroxypropan-2-yl)oleamide, a stable analogue of oleoylethanolamide that activates PPARα and regulates feeding in rodents.

109 Sakamoto Y, Inoue H, Kawakami S, *et al.* Expression and distribution of Gpr119 in the pancreatic islets of mice and rats: predominant localization in pancreatic polypeptide-secreting PP-cells. Biochem Biophys Res Commun 2006; 351:474–480.

110 Fegley D, Gaetani S, Duranti A, *et al.* Characterization of the fatty acid amide hydrolase inhibitor cyclohexyl carbamic acid 3′-carbamoyl-biphenyl-3-yl ester (URB597): effects on anandamide and oleoylethanolamide deactivation. J Pharmacol Exp Ther 2005; 313:352–358.

111 Hansen HS, Petersen G, Artmann A, Larsen PJ. Inhibitors of anorexic lipid hydrolysis for the treatment of eating disorders. Int. Pat. Appl. WO200700 6319; 2007.

112 Muccioli GG, Lambert DM. Latest advances in cannabinoid receptor antagonists and inverse agonists. Exp Opinion Ther Patents 2006; 16: 1405–1423.

113 Cha DR, Zhang X, Zhang Y, *et al.* PPAR {alpha}/{gamma} dual agonist tesaglitazar attenuates diabetic nephropathy in db/db mice. Diabetes 2007; 29 May [Epub ahead of print].

114 Bajaj M, Suraamornkul S, Hardies LJ, *et al.* Effects of peroxisome proliferator-activated receptor (PPAR)-alpha and PPAR-gamma agonists on glucose and lipid metabolism in patients with type 2 diabetes mellitus. Diabetologia 2007; 50:1723–1731.