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The endocannabinoid system in the adipose organ

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Abstract

The endocannabinoid system is found in most, if not all, mammalian organs and is involved in a variety of physiological functions, ranging from the control of synaptic plasticity in the brain to the modulation of smooth muscle motility in the gastrointestinal tract. This signaling complex consists of G protein-coupled cannabinoid receptors, endogenous ligands for those receptors (endocannabinoids) and enzymes/transporters responsible for the formation and deactivation of these ligands. There are two subtypes of cannabinoid receptors, CB_1 and CB_2, and two major endocannabinoids, arachidonoylethanolamide (anandamide) and 2-arachidonoyl-*sn*-glycerol (2-AG), which are produced upon demand through cleavage of distinct phospholipid precursors. All molecular components of the endocannabinoid system are represented in the adipose organ, where endocannabinoid signals are thought to regulate critical homeostatic processes, including adipogenesis, lipogenesis and thermogenesis. Importantly, obesity was found to be associated with excess endocannabinoid activity in visceral fat depots, and the therapeutic potential of normalizing such activity by blocking CB_1 receptors has been the focus of substantial preclinical and clinical research. Results have been mixed thus far, mostly owing to the emergence of psychiatric side effects rooted in the protective functions served by brain endocannabinoids in mood and affect regulation. Further studies about the roles played by the endocannabinoid system in the adipose organ will offer new insights into the pathogenesis of obesity and might help identify new ways to leverage this signaling complex for therapeutic benefit.

Keywords

2-arachidonoyl-*sn*-glycerol (2-AG); adipogenesis; anandamide; cannabinoid (CB) receptors; endocannabinoid (ECB); lipogenesis; lipolysis; metabolic disorders; obesity; oleoylethanolamide (OEA); thermogenesis; trans-differentiation

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Conflict of interest

The authors declare that they have no conflict of interest.

1. Introduction

Δ^9-tetrahydrocannabinol (THC) is a terpenophenolic constituent of cannabis and the active agent responsible for the majority of the plant's pharmacological properties [1-3]. THC produces its effects by binding to two quasi-ubiquitous G protein-coupled receptors, CB_1 and CB_2 [4,5]. CB_1 cannabinoid receptors mediate most of the central and peripheral actions of THC, while CB_2 receptors contribute to other less-well understood effects such as those exerted on the immune system [6-8]. The indiscriminate hijacking of these receptors by THC, especially when used at high doses, contrasts with the controlled recruitment produced by its endogenous lipid-derived ligands – the endocannabinoids arachidonoylethanolamide (anandamide) and 2-arachidonoyl-*sn*-glycerol (2-AG) [2,9-11] – whose activities are tightly regulated by a set of enzymes and transporters that cooperate to ensure that cannabinoid receptors are recruited only when and where their activation is needed [12-14]. Collectively, these molecules constitute the endocannabinoid system, a signaling complex that serves a vast array of modulatory functions in mammalian physiology. In this mini-review, we provide a brief overview of current knowledge about the presence and role of the endocannabinoid system in the adipose organ.

2. Endocannabinoids and their receptors

As mentioned above, the endocannabinoid system is comprised of two cell-surface receptors (CB_1 and CB_2), two lipid-derived endocannabinoid molecules (anandamide and 2-AG), and several intracellular proteins involved in the formation, transport and deactivation of such molecules.

2.1 Cannabinoid receptors in the adipose organ

CB_1 and CB_2 receptors exhibit 48% identity in amino acid sequence and signal through the transducing G proteins, G_1 and G_o [6,7]. CB_1 (encoded in humans by the *CNR1* gene) is abundantly expressed in the central nervous system (CNS) where it is primarily, albeit not exclusively, localized to axon terminals of γ-amino-butyric acid (GABA)-ergic interneurons and glutamatergic projection neurons [15]. Two important consequences of neuronal CB_1 receptor activation are the reduction of neurotransmitter release (*via* inhibition of Ca^{2+} channel activity) and the suppression of membrane excitability (*via* increase of K+ channel activity) [6,16,17]. Non-neuronal cells of the CNS, such as astrocytes and microglia, also express CB_1 [18-20]. Moreover, its widespread occurrence outside the CNS – e.g., in the peripheral nervous system, vasculature, small intestine, liver, pancreas and skeletal muscle [21] – has been linked to the diverse influences exerted by endocannabinoid messengers on homeostasis [21,22]: for example, in the small intestine CB_1 receptors are involved in feeding regulation and smooth muscle contractility [23] while in the liver they contribute to the control of lipogenesis and fibrogenesis [24,25].

The presence of CB_1 receptors in adipocytes of both white and brown adipose tissues (abbreviated henceforth as WAT and BAT, respectively) is well established [26-28]. In vitro studies suggest that CB_1 expression in white adipocytes may coincide with the differentiation of these cells from committed preadipocytes [26,29,30], raising the possibility that the endocannabinoid system might contribute to this developmental process.

There is also functional evidence that noradrenergic nerve fibers and resident macrophages interspersed in WAT and BAT parenchyma might also contain CB_1 [31,32], though this remains to be conclusively demonstrated.

The CB_2 receptor subtype (encoded in humans by the *CNR2* gene) is mainly found in cellular constituents of the innate and adaptive immune systems – including monocyte-derived cells and lymphocytes – where it exerts a broad spectrum of modulatory effects on cytokine release, apoptosis and cell migration [33]. Low levels of CB_2 expression have been measured in both visceral and subcutaneous adipose tissues of mice [28] and biopsies of human adipose tissue, possibly reflecting a restricted localization to resident macrophages, pre-adipose cells or vascular elements [34]. It is still uncertain whether adipocytes contain CB_2, with some evidence supporting and other negating this possibility [35-37]. Filling this knowledge gap may shed light on the positive association reported, in children, between body-mass index and expression of the hypofunctional CB_2 variant CB_2-Q63R [38].

2.2 Endocannabinoid messengers in the adipose organ

Anandamide and 2-AG are the two best-characterized endocannabinoid molecules found in mammalian tissues [2,14]. As shown in Figure 1A, anandamide formation starts with the transfer of an arachidonate group from the *sn*-1 position of 1,2-diarachidonoyl-phosphatidylcholine to the free amino group of phosphatidylethanolamine (PE), which generates the anandamide precursor *N*-arachidonoyl-PE [12,39]. This reaction occurs predominantly upon demand – for example, *via* ligation of certain transmitter or hormone receptors [40,41] – and is catalyzed by the calcium-dependent *N*-acyl transferase activity of cytosolic type-ε phospholipase A_2 (encoded by *PLA2G4E*) [42]. Hydrolytic cleavage of membrane-bound *N*-arachidonoyl-PE by a unique zinc-containing phospholipase D (*NAPEPLD*) [43,44] releases anandamide, which diffuses out of the cell and into the external milieu [40,45]. Anandamide is deactivated through a two-step process in which the compound is first internalized by cells by an as-yet-uncharacterized facilitated-diffusion mechanism [46,47], followed by intracellular hydrolysis catalyzed by the serine amidase fatty acid amide hydrolase (*FAAH*) [48,49] (Figure 1A).

Like anandamide, 2-AG is also generated upon demand (Figure 1B). The membrane phospholipid that serves as its precursor, phosphatidylinositol-4,5-bisphosphate (PIP_2), is hydrolyzed by a receptor-operated phospholipase C (*PLC*), probably PLCβ and/or PLCε [50,51], to produce 1,2-diacylglycerol (DAG), which is then cleaved by the α or β isoform of diacylglycerol lipase (*DGL*) to generate 2-AG [13,45,52]. In the postsynaptic spine of glutamate-sensitive neurons of the brain, PLC and DGL-α are physically linked to type-5 metabotropic glutamate receptors in a multimolecular complex (the 'endocannabinoid signalosome') for efficient, on-demand formation of 2-AG [53]. In contrast to classical neurotransmitters such as glutamate or GABA, 2-AG travels backwards across the synaptic cleft from the postsynaptic spine (which houses the signalosome) to the axon terminal (where the majority of CB_1 receptors are localized) to mediate a retrograde signaling process that produces a variety of short- and long-term changes in synaptic efficiency [2,53]. The effects of 2-AG are terminated by the lipid hydrolases, monoacylglyceride lipase (*MGL*) and, to a lesser extent, α/β-hydrolase domain-6 (*ABHD-6*) (Figure 1B) [54,55].

The adipose organ of small mammals and humans contains the entire complement of proteins needed to produce and degrade endocannabinoid molecules [28,56,57]. In fact, the 2-AG-hydrolyzing enzyme MGL was first purified and molecularly cloned from mouse WAT, where its role in the last step of hormone-dependent lipolysis – i.e., the hydrolysis of triacylglycerol-derived monoacylglycerols into fatty acid and glycerol – has been long recognized [58]. The presence of other endocannabinoid-metabolizing enzymes has been documented in various depots of rodent and human WAT [28,59-61]. Moreover, in vivo microdialysis studies have shown that anandamide and 2-AG can be released within the parenchyma of human abdominal fat [62]. Similar to WAT, the BAT of small mammals such as mice [56] and marmots (*Marmota flaviventris*) [63] also contains endocannabinoids and their metabolizing enzymes.

As discussed above, the endocannabinoids are primarily generated upon demand through receptor- or activity-dependent mechanisms. What physiological stimuli control their mobilization in the adipose organ? In addition to the developmental signals mentioned in section 2.1 [64], experiments in mice suggest that cold exposure and β_3 adrenergic receptor activation promote anandamide and 2-AG accumulation in WAT and enhance expression of the 2-AG-producing enzyme DGL-α [56]. The functional significance of cold-stimulated endocannabinoid production by adipose cells is discussed in the following section.

3. Physiological roles

3.1 The endocannabinoids as paracrine messengers in the adipose organ

In the CNS, a primary role of postsynaptically produced endocannabinoids is to control the release of excitatory and inhibitory neurotransmitters from axon terminals [1,2]. A similar negative-feedback mechanism may operate in white and brown cellular components of the adipose organ. As mentioned above, studies have shown that cold exposure increases endocannabinoid mobilization in WAT, presumably *via* norepinephrine-mediated activation of β_3 adrenergic receptors [56]. Moreover, there is evidence that CB_1 receptors are present on sympathetic terminals innervating the adipose organ and that their activation inhibits norepinephrine release [65-67]. A plausible interpretation of these findings is that adipocyte-derived endocannabinoids serve as negative regulators of sympathetic outflow [57] to slow down lipolysis and counter the conversion of adipocytes from a fat-storing into a heat-producing phenotype (discussed in section 3.2). This hypothesis is consistent with the broad roles played by the endocannabinoids as paracrine/autocrine mediators of energy conservation in multiple organ systems [68]. In addition to curbing autonomic outflow *via* their paracrine action on sympathetic nerve terminals, the endocannabinoids are also thought to modulate in an autocrine manner three processes that are critical to WAT and BAT function: adipogenesis, lipogenesis and heat production. In closing this section, it is worth noting that CB_1 receptor signaling in adipose tissue might contribute, in ways that remain unclear, to the cognitive and emotional deficits produced in mice by diet-induced obesity [69].

3.2 Endocannabinoid signaling in WAT: control of adipogenesis and lipogenesis

The endocannabinoid system has emerged an important regulator of adipogenesis and lipogenesis in WAT (Figure 2). Adipogenesis is the differentiation process through which preadipocytes mature into adipocytes under the control of hormonal signals such as insulin, while lipogenesis is the metabolic process through which fatty acids are synthesized from acetyl-CoA and are esterified into triglycerides [70]. Adipogenic stimuli induce terminal differentiation in committed preadipocytes by recruiting the ligand-operated transcription factor, peroxisome proliferator-activated receptor-γ (PPAR-γ) [70]. Pharmacological stimulation of CB_1 receptors in cultures of mouse 3T3 adipocytes enhances PPAR-γ expression, accelerates adipocyte proliferation and promotes triglyceride accumulation in lipid droplets [30,71]. CB_1 activation also increases glucose uptake in primary cultures of human white adipocytes [34] and heightens lipoprotein lipase activity [57], two events that cooperate in promoting the uptake and storage of non-esterified fatty acids by white adipocytes. Conversely, differentiation of mouse 3T3 cells is accompanied by an increase in CB_1 receptor binding and other markers of endocannabinoid activity [64]. These two sets of findings are suggestive of a role for autocrine endocannabinoid signaling in adipogenesis and lipogenesis [30,72].

Another proposed function for white-adipose endocannabinoids is to counter mitochondrial generation and the consequent browning of WAT (Figure 2). ‘Browning’ refers to the conversion of mature fat-storing white adipocytes, which contain relatively few mitochondria, into heat-producing mitochondria-enriched ‘beige’ or ‘brite’ (brown-in-white) adipocytes [73]. These heterogeneous phenotypes are thought to arise either by trans-differentiation of mature white adipocytes or by de novo differentiation of precursor cells (for review, see [74,75]). Pharmacological stimulation of CB_1 receptors in primary cultures of mouse or human white adipocytes lowers the phosphorylation state of 5’-AMP-activated protein kinase (AMPK), disabling this cellular energy sensor [76] and consequently suppressing expression of PGC-1α, master transcriptional co-activator of mitochondrial biogenesis [77,78]. Conversely, CB_1 receptor blockade in cultures of SV40-immortalized mouse adipocytes suppresses PGC-1α expression and counters the development of a thermogenic phenotype [79]. Similarly, genetically modified mice that lack CB_1 in adipocytes exhibit a spontaneous browning of WAT, particularly in subcutaneous fat depots, a phenomenon that is associated with enhanced energy expenditure, decreased body weight, reduced total adiposity and improved insulin sensitivity [66].

The presence of CB_2 in WAT remains uncertain [35-38], though resident macrophages appear to contain it at detectable levels [80]. Its roles, if any, are also controversial. For example, administration of the CB_2-selective agonist JWH-133 was found to potentiate inflammation in WAT of diet-induced obese mice [80], whereas beneficial effects on fat mass and adipocyte size were reported in the same model after administration of the less selective CB_2 agonist JWH-015 [81].

3.3 Endocannabinoid signaling in BAT: control of thermogenesis

CB_1 receptors are prominently expressed in rodent and human BAT [27], where their density increases following cold exposure [27]. This points to a role for CB_1 in non-shivering

thermogenesis [73], the metabolic process that generates heat in response to cold and other environmental stimuli [82]. Pharmacological studies support this possibility (Figure 3). Systemic administration of THC lowers the expression of uncoupling protein-1 (UCP-1) in rat BAT [83]: since the main function of UCP-1 is to dissipate the proton gradient generated by oxidative phosphorylation, its decreased activity is expected to suppress thermogenesis [84]. Conversely, incubation with the CB_1 inverse agonist rimonabant heightens oxygen consumption and elevates UCP-1 expression in cultures of brown T37i adipocytes, while co-incubation of the same cells with rimonabant plus norepinephrine causes a synergistic increase in phosphorylation of the lipolytic enzyme, hormone-sensitive lipase [85]. Consistent with these *in vitro* results, systemic administration of rimonabant or AM6545, a peripherally restricted neutral CB_1 antagonist, stimulates whole-body energy expenditure, heightens expression of genes involved in BAT thermogenesis and decreases lipid droplet size in brown adipocytes [85].

3.4 Central endocannabinoid control of WAT and BAT function

Endocannabinoid signals are critical contributors to the hypothalamic regulation of adipose physiology. This topic has been thoroughly reviewed [72,86] and only two relevant examples will be highlighted here. Quarta and collaborators found that genetically modified mice in which CB_1 was selectively deleted in neurons, but not in other cell types, are lean and resistant to diet-induced obesity [67]. A strikingly similar metabolic phenotype was observed in transgenic mice overexpressing the 2-AG-hydrolyzing enzyme MGL in calcium-calmodulin kinase II-containing neurons [87]. In addition to displaying reduced 2-AG levels in forebrain, these mice are lean and resistant to diet-induced obesity. Moreover, they exhibit elevated energy cost of activity, increased UCP-1 levels in BAT and hypersensitivity to β_3-adrenergic-stimulated thermogenesis [87]. The converging phenotypes of these two mouse models underscore the global influence exerted by endocannabinoid signals in the regulation of adipose-organ function and body-wide energy balance.

4. The endocannabinoid system in the adipose organ: a safe target to treat obesity?

A large body of evidence indicates that obesity – a major risk factor for the development of type-2 diabetes, cardiovascular disease and liver steatosis – is associated with central and peripheral hyperactivity of the endocannabinoid system, which can be effectively (albeit not safely) corrected by administration of globally active CB_1 receptor blockers. Excellent reviews of this field of research are available [88-92] but is important to point out in the present context that signs of excess endocannabinoid activity are clearly detectable both in the circulation and in visceral compartments of the adipose organ, whose pathogenic role in obesity is well recognized [73]. Circulating levels of 2-AG are significantly elevated in persons with obesity and are correlated with body mass index (BMI), visceral fat mass and fasting insulin and triglyceride concentrations [93,94]. A one-year lifestyle modification program normalized 2-AG levels [95]. In addition, Sarzani and collaborators showed that visceral fat of overweight and dysmetabolic patients contains higher levels of CB_1 mRNA compared to normal-weight subjects, and that CB_1 expression in this fat depot is positively correlated with local anandamide levels, perirenal and total visceral adipose tissue area, and

BMI [96,97]. Reinforcing these findings, a cross-sectional study in lean and obese persons suggests that obesity may be accompanied by a relative increase in the number of CB_1 receptors found in visceral compared to subcutaneous white fat depots [98].

The results outlined above may have important therapeutic implications. In obese animals and humans, CB_1 inverse agonists and neutral antagonists produce sustained weight loss along with significant improvements in lipid profile and insulin resistance (for review, see [99]). In a series of randomized placebo-controlled clinical trials, the CB_1 inverse agonist rimonabant was shown to lower body weight and mitigate cardiovascular risk factors in persons with obesity and type-2 diabetes [100-103]. Rimonabant was approved for the treatment of obesity in some Countries but was withdrawn shortly thereafter due to the emergence of dose-dependent psychiatric side effects [99]. These included anxiety, depression and suicidal ideation and thus resulted, in all likelihood, from the interference of CNS-penetrant CB_1 blockers with the protective control exerted by central endocannabinoids on affect, mood and the response to stress (for review, see [104]).

A promising alternative strategy, which is currently under preclinical investigation, is to target CB_1 receptors in the adipose and other peripheral organs involved in metabolic dysfunction (e.g., pancreas, liver) [37,105,106]. The effects of two peripherally restricted compounds, AM6545 and JD5037, have been studied in detail [105,107]. Both agents have low brain penetrance, high affinity and selectivity for CB_1 receptors and no overt central effects. They differ in one important property, however: AM6545 is a neutral antagonist (i.e., it has no activity in the absence of an agonist) whereas JD5037 is an inverse agonist (i.e., it produces a receptor response opposite to that of an agonist) [107,108]. AM6545 significantly reduces body-weight gain in diet-induced obese mice, though not as effectively as does the inverse agonist rimonabant [105]. In the same model, JD5037 is as effective as a globally active inverse agonist at decreasing food intake and body weight gain. The compound was also shown to improve lipid profile, glucose handling, insulin sensitivity and hepatic steatosis [107,108]. If the preclinical evidence outlined above is confirmed in the clinic, peripherally restricted CB_1 blockers might have a strong positive impact on the treatment of obesity and other metabolic disorders.

5. Paracannabinoid signals in adipose organ physiology

Mammalian tissues produce a family of lipid molecules that are biogenetically related to the endocannabinoids, but do not productively interact with cannabinoid receptors. In the adipose organ, the best understood member of this ‘paracannabinoid’ family is the anandamide analog, oleoylethanolamide (OEA) (Figure 4). OEA is an endogenous agonist of the ligand-operated transcription factor PPAR-α and a potent small-intestinal regulator of feeding behavior [23,109-111]. As seen with anandamide [56], OEA production in white adipose tissue is stimulated by cold exposure and β-adrenergic receptor activation [112]. Importantly, however, activation of PPAR-α by OEA causes effects that are functionally opposite to those produced by anandamide acting at CB_1. OEA accelerates lipolysis in cultures of rat white adipocytes and attenuates body-weight gain and hyperlipidemia in obese mice and rats [113,114]. Even though the anti-obesity properties of OEA have

been documented in a randomized, placebo-controlled trial [115-117], the physiological significance and pathological implications of this signaling lipid are still understudied.

6. Conclusions

There is strong preclinical and clinical evidence that endocannabinoid signaling at CB_1 receptors is a critical regulator of adipose organ physiology and a potential target for anti-obesity medications. Important knowledge gaps remain, including the role of endocannabinoid signals in WAT and BAT development and their interaction with paracannabinoid messengers such as OEA. Despite these unanswered questions, it is clear that the therapeutic potential of endocannabinoid modulation calls for further basic and clinical investigation.

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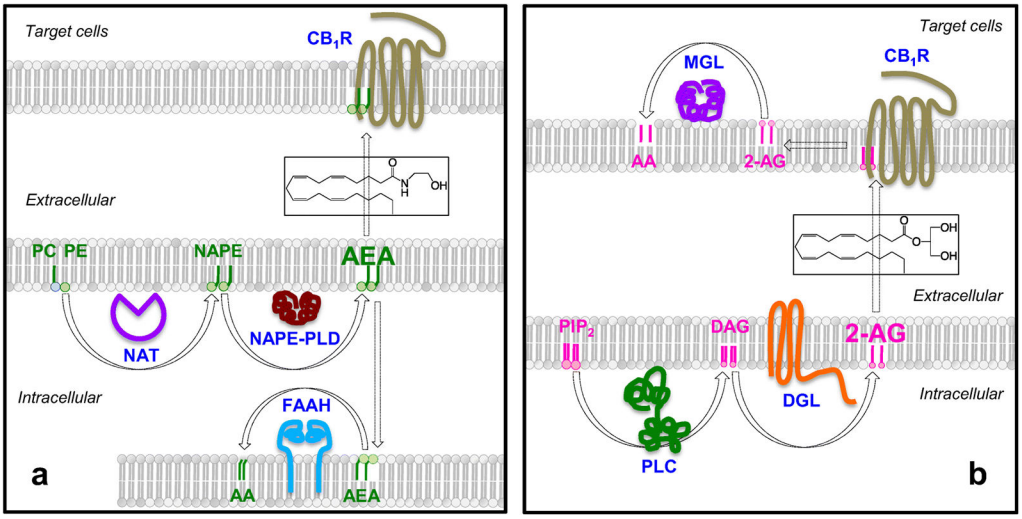

Figure 1. Molecular components of the endocannabinoid system.

(A) Anandamide is produced by hydrolysis of the phospholipid precursor, *N*-arachidonoyl-phosphatidylethanolamine (*N*-arachidonoyl-PE), catalyzed by a unique zinc-containing phospholipase D (PLD). *N*-arachidonoyl-PE is produced through a two-step reaction in which an arachidonate group is transferred from the *sn*-2 position of a phospholipid to the *sn*-1 position of lysophosphatidylcholine (PC), producing 1,2-diarachidonoyl-PC. The *sn*-1 arachidonoyl chain of 1,2-diarachidonoyl-PC is then transferred to the free amino group of PE generating *N*-arachidonoyl-PE. Anandamide is degraded by the intracellular serine amidase, fatty acid amide hydrolase (FAAH). (B) Receptor-operated phospholipase C (PLC) converts phosphatidylinositol-4,5-bisphosphate (PIP_2) into 1,2-diacylglycerol (DAG). DAG is hydrolyzed by diacylglycerol lipase (DGL) forming 2-AG. 2-AG is subjected to hydrolytic cleavage catalyzed by monoacylglycerol lipase (MGL) or, to a lesser extent, α/β hydrolase domain-containing protein 6 (ABHD-6).

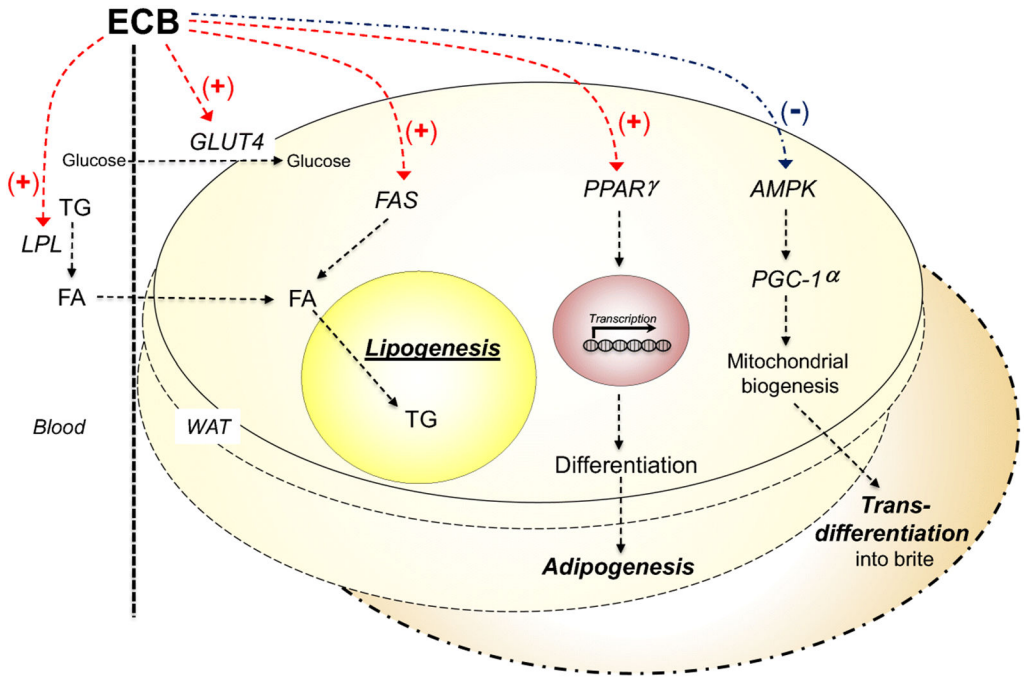

Figure 2. Endocannabinoid signals in WAT physiology

In WAT, CB_1 receptor activation increases glucose uptake (mediated by the insulin-regulated glucose transporter 4, GLUT4) and fatty acid biosynthesis (catalyzed by fatty acid synthase, FAS). In addition, it enhances transcription of genes involved in adipocyte differentiation such as the ligand-operated transcription factor, PPARγ, and impairs mitochondrial biogenesis and WAT browning by inhibiting the 5'-AMP-activated protein kinase (AMPK) - PGC-1α pathway.

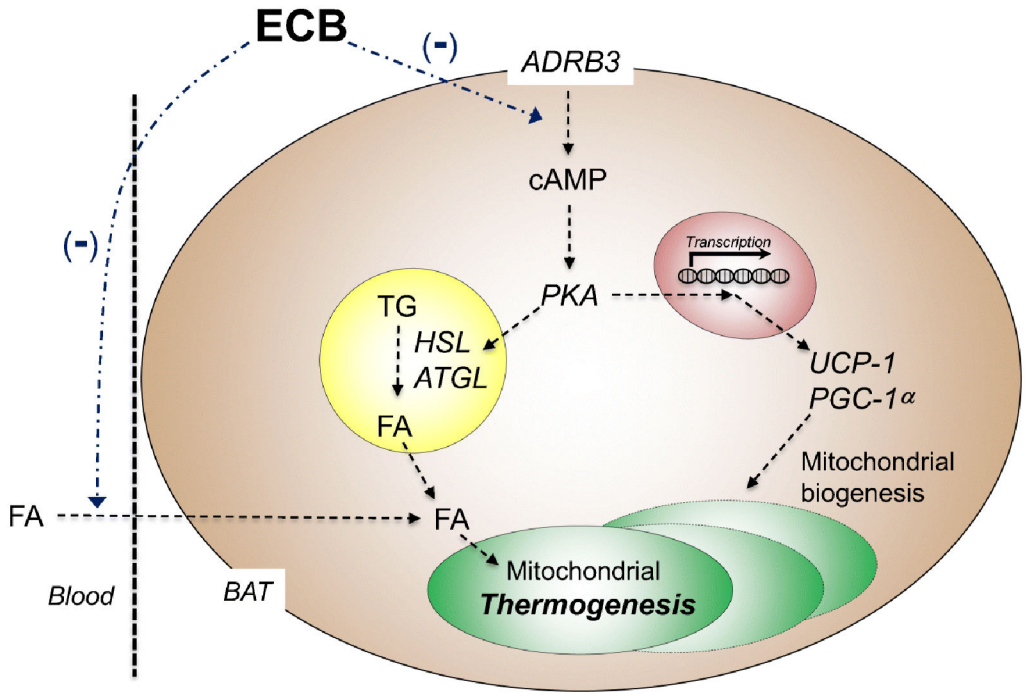

Figure 3. Endocannabinoid signals in BAT physiology

Activation of β_3 adrenergic receptors (ADRB3) in BAT initiates canonical cAMP - protein kinase A (PKA) signaling. PKA phosphorylates and activates hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL) to liberate fatty acids (FA) from lipid droplets. In addition, FA activate UCP-1 in the mitochondrial inner membrane, which dissipates the proton gradient and uncouples the electron transport chain from ATP synthesis, generating heat. Either central or peripheral blockade of CB_1 receptors heightens thermogenesis by dampening local endocannabinoid activity and consequently boosting sympathetic outflow to the adipose organ.

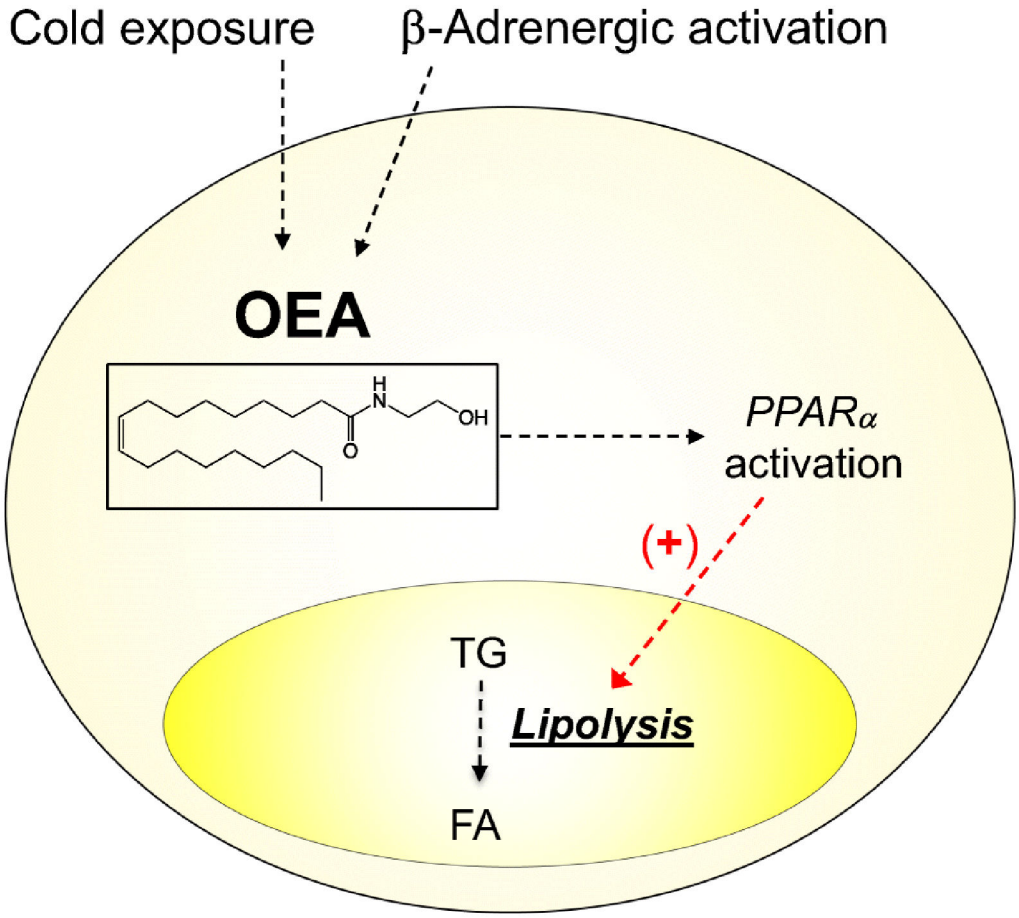

Figure 4. Paracannabinoid signals in the adipose organ.

OEA is produced and degraded though an enzyme pathway that overlaps with anandamide's but starts from a different phospholipid precursor (N-oleoyl-PE instead of N-arachidonoyl-PE). Unlike anandamide, however, OEA does not interact productively with CB_1 receptors. In fact, its actions are opposite to those of anandamide and are mediated by activation of the ligand-operated transcription factor, PPAR-α.