Current Diabetes Reports (2019) 19: 117
https://doi.org/10.1007/s11892-019-1248-9

OBESITY (KM GADDE, SECTION EDITOR)

The Expanded Endocannabinoid System/Endocannabinoidome as a Potential Target for Treating Diabetes Mellitus

Alain Veilleux[1,2,3] · Vincenzo Di Marzo[1,2,3,4,5] · Cristoforo Silvestri[3,4,5]

Published online: 4 November 2019

Abstract

Purpose of Review The endocannabinoid (eCB) system, i.e. the receptors that respond to the psychoactive component of cannabis, their endogenous ligands and the ligand metabolic enzymes, is part of a larger family of lipid signals termed the endocannabinoidome (eCBome). We summarize recent discoveries of the roles that the eCBome plays within peripheral tissues in diabetes, and how it is being targeted, in an effort to develop novel therapeutics for the treatment of this increasingly prevalent disease.

Recent Findings As with the eCB system, many eCBome members regulate several physiological processes, including energy intake and storage, glucose and lipid metabolism and pancreatic health, which contribute to the development of type 2 diabetes (T2D). Preclinical studies increasingly support the notion that targeting the eCBome may beneficially affect T2D.

Summary The eCBome is implicated in T2D at several levels and in a variety of tissues, making this complex lipid signaling system a potential source of many potential therapeutics for the treatments for T2D.

Keywords Endocannabinoidome · Bioactive lipids · Peripheral tissues · Glucose · Insulin

Introduction: The Endocannabinoid System and its Subsequent Expansion to the "Endocannabinoidome"

The discovery of two G protein-coupled receptors, the cannabinoid receptor type-1 (CB1) and − 2 (CB2) [1, 2], for the cannabis-derived natural product, Δ^9-tetrahydrocannabinol (THC), responsible for most of the psychotropic, euphoric and appetite-stimulating actions (via CB1 receptors) and immune-modulatory effects (via CB2 receptors) of marijuana, opened the way to the identification of the *endocannabinoids* (eCBs). These are two arachidonic acid-derived molecules, i.e. arachidonoylethanolamide (AEA or anandamide) and 2-arachidonoyl-glycerol (2-AG), capable of binding with high affinity to, and stimulating with good efficacy, both CB1 and CB2 receptors [3, 4]. The subsequent identification of anabolic and catabolic routes and enzymes (Fig. 1) for the regulation of AEA and 2-AG tissue concentrations, and hence of CB1 and CB2 activity, as well as of eCB biosynthetic precursors and degradation products, led to the definition of *the endocannabinoid system* as the ensemble of all these proteins and small lipid molecules.

Initially, and up to the turn of the century, the eCB system was composed of: 1) CB1 and CB2, 2) AEA and 2-AG with the respective biosynthetic precursors, e.g. the *N*-arachidonoyl-phosphatidylethanolamines (NArPEs) and the 1-acyl-*sn*-2-arachidonoyl-glycerols (AcArGs), 3) three biosynthetic enzymes capable of converting NArPEs and AcArGs into AEA and 2-AG, i.e. a *N*-acyl-phosphatidylethanolamine-specific phospholipase D-like (NAPE-PLD) and two sn-1 selective diacylglycerol lipases, (DAGLs), DAGLα and β, respectively

This article is part of the Topical Collection on *Obesity*

✉ Cristoforo Silvestri
cristoforo.silvestri@criucpq.ulaval.ca

Alain Veilleux
Alain.Veilleux@fsaa.ulaval.ca

Vincenzo Di Marzo
vincenzo.dimarzo@criucpq.ulaval.ca

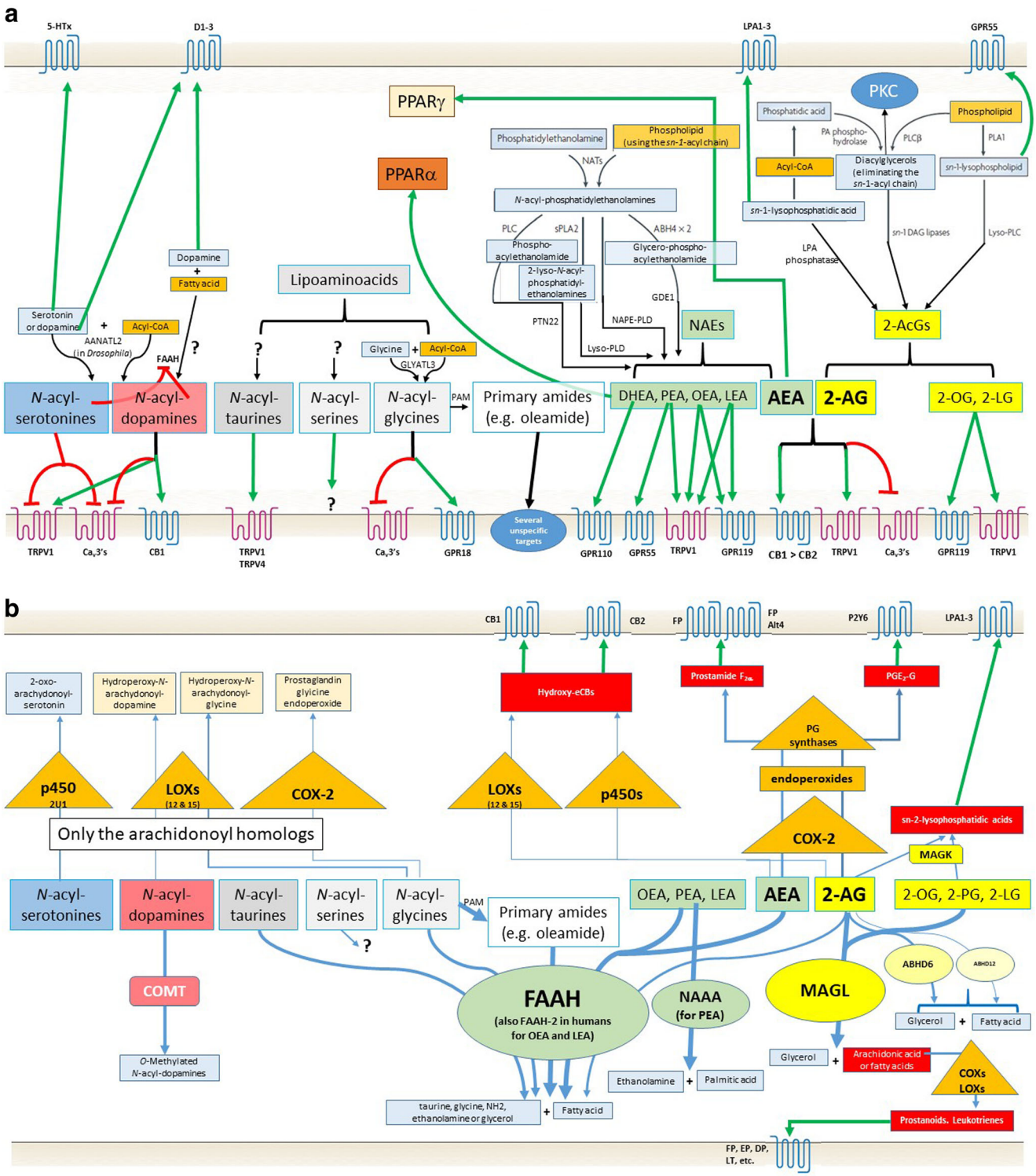
1 École de nutrition, Université Laval, Québec, QC, Canada

2 Institut sur la nutrition et les aliments fonctionnels, Université Laval, Québec, QC, Canada

3 Canadian Excellence Research Chair on the Microbiome-Endocannabinoidome Axis in Metabolic Health, Québec, Canada

4 Institut de cardiologie et de pneumologie de Québec, Université Laval, Québec, QC, Canada

5 Department de médecine, Université Laval, Québec, QC, Canada



and 4) two hydrolases inactivating AEA and 2-AG, i.e. fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively [5–8]. However, it was soon realized that: 1) AEA and 2-AG congeners, i.e. the *N*-acylethanolamines (NAEs) and 2-mono-acyl-glycerol (2-MAGs), respectively, were biosynthesised using NAPE-PLD and DAGLs from precursors similar to those of the two eCBs, and inactivated to the respective fatty acids and ethanolamine or glycerol by FAAH and MAGL; 2) these lipids were much less active or even inactive, in most cases, at CB1 and CB2 receptors, and instead capable of modulating the activity of other molecular targets; 3) NAEs and 2-MAGs, including AEA and 2-AG, can

◀ **Fig. 1 The endocannabinoidome, an expanded endocannabinoid system**. (**A**) The endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are often accompanied in tissues by their congeners, the *N*-acylethanolamines (NAEs), such as *N*-palmitoyl-, *N*-oleoyl and *N*-linoleoyl-ethanolamine (PEA, OEA and LEA), and the 2-acyl-glycerols (2-AcGs), such as 2-oleoyl and 2-linoleoyl-glycerol (2-OG and 2-LG). Congeners share with the two endocannabinoids redundant biosynthetic pathways and enzymes and, in part, receptors other than CB1 and CB2, such as the transient receptor channels of type 1 (TRPV1), the peroxisome proliferator-activated nuclear receptors (PPAR) α and γ, which are activated, and the T-type Ca^{2+} ($Ca_{v.3}$) channels, which are inhibited. The congeners also have other receptors, such as orphan GPCRs like GPR55, GPR110, or GPR119. The possible biosynthetic precursors for 2-AG also have their own targets, such as protein kinase C (PKC), for the *sn*-1-acyl-2-arachidonoyl-glycerols; GPR55, for the *sn*-1-lyso-2-arachidonoyl-phosphatidylinositols; and the lysophosphatidic acid receptors 1–3 (LPA1–3) for the *sn*-1-lyso-2-arachidonoyl-phosphatidic acids. Other long chain fatty acid amides, such as primary amides (including the sleep inducing factor oleamide), the "lipoamino acids" (the most studied ones being *N*-acyl-serines, −glycines and –taurines) and some *N*-acyl-neurotransmitters (*N*-acyl-dopamines and –serotonins) have also been identified. They are promiscuous in their targets, which include orphan GPCRs, TRP channels and $Ca_{v.3}$ channels. *N*-arachidonoyl-dopamine also activates CB1. Distinct biosynthetic pathways exist for different lipoamino acids and *N*-acyl-neurotransmitters. The latter derive from the corresponding neurotransmitters, whose receptors are also shown. (**B**) The endocannabinoids, their congeners and the various long chain fatty acid amides often share inactivating enzymes. Congeners are inactivated by the same hydrolytic enzymes, which, however, may have different substrate selectivity: 1) fatty acid amide hydrolase (FAAH) for all NAEs; 2) FAAH-2 (so far found only in human tissues), with preference for OEA and LEA; 3) *N*-acylethanolamine acid amidohydrolase (NAAA), with preference for saturated NAEs such as PEA; 4) monoacylglycerol lipase (MAGL), specific for all long chain 2-AcGs, especially if unsaturated; and 5) α,β-hydrolases 6 and 12 (ABHD6 and ABHD12), which also have other ester substrates. FAAH is also used for the inactivation of *N*-acyl-taurines and some lipoamino acids (namely the *N*-acyl-glycines and -taurines). Finally, some oxidizing enzymes of the arachidonate cascade, such as cyclooxygenase-2 (COX-2), and various lipoxygenases (LOX) recognize the arachidonoyl-containing congeners of most of these mediators. Importantly, several metabolic products, such as the prostaglandin ethanolamides (prostamides) and prostaglandin glycerol esters (PGGEs) have their own receptors, whereas usually the LOX and cytochrome p450 oxygenase (p450) derivatives of endocannabinoids still activate CB1 and CB2 receptors. *Arrows* indicate metabolic processes or activation, *blunt arrows* indicate inhibition. In (**B**) *arrow thickness* and *character size* indicate the importance of the pathways and enzymes. (**A,B**) Along with THC, many non-euphoric plant cannabinoids interact with, among others, endocannabinoidome receptors and enzymes, which underlie in part their therapeutic effects. Other abbreviations: AANATL2, arylalkylamine N-acyltransferase-like 2, isoform A; ABHD4, α/β-hydrolase 4; CBDA, cannabidiolic acid; CBDV, cannabidivarin; COMT, catechol-O-methyltransferase; D1, dopamine receptor 1; DPs, prostaglandin D2 receptors; EPs, prostaglandin E2 receptors; 5-HT, 5-hydroxytryptamine; GDE1, glycerophosphodiester phosphodiesterase 1; GLYATL3, glycine *N*-acyltransferase-like protein 3; MAGK, monoacylglycerol kinase; NAPE-PLD, *N*-acyl-phosphatidylethanolamine-specific phospholipase D; NATs, *N*-acyltransferases (including phospholipase A2 group IVE and phospholipase A/acyltransferase 1); PAM, peptidyl-glycine α-amidating monooxygenase; P2Y6, P2Y purinoceptor 6; PLA1A, phospholipase A1 member A; PLC, phospholipase C; PGE2-G, prostaglandin E2-glycerol; PTPN22, tyrosine-protein phosphatase non-receptor type 22; sPLA2, soluble phospholipase A2; THCA, Δ^9-tetrahydrocannolic acid; THCV, Δ^9-tetrahydrocannabivarin

be biosynthesized and also degraded via alternative pathways and enzymes; and 4) the two eCBs, like their congeners and several other lipid mediators, are quite promiscuous in their pharmacological activity in as much as they modulate the activity of other receptors (Fig.1; recently reviewed in [9]). These findings, together with the identification of other long chain fatty acid derivatives, including primary fatty acid amides and several *N*-acylated amino acids and neurotransmitters, with molecular targets and inactivating enzymes often in common with eCBs, led to the definition of the "expanded eCB system" or *endocannabinoidome* (eCBome), potentially including hundreds of lipid mediators, more than 20 biosynthetic or inactivating enzymes and more than 20 molecular targets, such as many previously identified nuclear receptors, ligand-activated ion channels and orphan GPCRs (Fig.1; recently reviewed in [9]).

The presence of such a complex signaling system comprising the eCBs, their many metabolic enzymes and targets together, and several eCB-related lipid mediators, often sharing with the former compounds metabolic enzymes and receptors, considerably complicates the development of selective pharmacological and genetic tools to be used for both the understanding of the function in the control of energy metabolism of the eCBome and its exploitation towards new therapies against metabolic disorders. Nevertheless, as we review in this article, our knowledge of the role of the eCB system, and even of the more complicated eCBome, in metabolic control, is quite advanced, and several strategies for the development of new therapeutic drugs based on such knowledge are already available.

Epidemiological Evidence of a Dysregulated Endocannabinoidome in Diabetes Mellitus

Increased eCB system tone, especially through central and peripheral CB1 signaling, enhances food intake, endorses highly palatable food intake and promotes energy storage via activation of peripheral anabolic pathways. As a result, higher eCB levels contribute to body fat accumulation, particularly in the visceral depots, and have been related to the development of obesity-associated metabolic abnormalities, an effect prevented by peripheral CB1 receptor blockade in animal models. Human cross-sectional data definitively support increased levels of eCBs, i.e. anandamide and/or 2-AG, both in plasma of obese subjects [10–18]. Of particular interest is the relatively strong association of 2-AG, over anandamide, with visceral adiposity, insulin resistance and dyslipidemia [10, 13–16, 19, 20], which is independent of total adiposity [10, 16]. Higher eCBs levels were also evidenced in adipose tissue, especially in the visceral depots, of obese individuals [10, 11, 15]. Only few studies have addressed levels of eCBome mediators in obesity and related complications. The PPARα agonists, palmitoylethanolamide (PEA) and oleoylethanolamide (OEA) show modest positive association

with adiposity [13], while they were negatively related to insulin resistance indexes, especially when normalized to the level of their corresponding eCB AEA (i.e. PEA/AEA and OEA/AEA) [17]. Patients with type 2 diabetes (T2D) exhibit higher circulating concentrations of eCBs, as well as of the AEA congeners PEA, OEA and linoleoylethanolamide (LEA), than people without diabetes with similar adiposity [21, 22]. These observations are further supported by decreased circulating anandamide and 2-AG levels in different interventions aiming at negative energy balance and weight loss, i.e. dietary intervention [12, 19] and bariatric surgery [23], which are associated to amelioration of insulin resistance and dyslipidemia. Yet, further data are needed to obtain a complete overview of peripheral eCBome dysregulation in obesity and T2D, whilst actual epidemiological evidence clearly establishes the link between increased eCB system tone, weight gain and visceral adiposity, and also strongly suggests that eCB system dysregulation can directly impact glucose homeostasis independently of its role on energy balance and fat accumulation (review in [24]).

Peripheral eCBome Regulation of Glucose Metabolism

CB1 was initially thought be exclusively expressed within the central nervous system, but was later identified at lower expression levels, which are subsequently increased under conditions of obesity and insulin resistance, in peripheral tissues including adipose tissue [25, 26], muscle [27], the liver [25], the pancreas [28] and intestinal tract [29]. Within adipocytes, CB1 overactivation leads to decreased mitochondrial activity, altered adipokine production, and increased glucose uptake along with increased lipid accumulation [30]. In humans, markers of insulin resistance correlate with upregulated CB1 expression in both visceral and subcutaneous white adipose tissue, independent of BMI, indicating that insulin resistance, and not obesity per se associates with upregulated CB1 expression [26]. In the same study, CB1 inhibition reduced lipolysis rates in adipose tissue ex vivo supporting the notion that CB1 activity, by modulating circulating levels of adipose-derived free fatty acids, can impact whole-body insulin sensitivity. The key role of CB1 in the adipose tissue in T2D was highlighted using an inducible, adipocyte specific CB1 knockout model, which not only attenuated the development of diet-induced obesity and metabolic complications including insulin resistance, but also reversed them in mice that were already obese [31].

White adipose tissues express other eCBome receptors as well, including G protein-coupled Receptor 55 (GPR55) [32] and transient receptor potential cation channel subfamily V member 1 (TRPV1) [33]. Similar to CB1, GPR55 expression is increased in adipose tissues of obese individuals, and even more in those with T2D. However the opposite was observed in adipose tissue from *ob*/*ob* mice or mice on a high-fat diet [32]. Indeed, *Gpr55*$^{-/-}$ mice spontaneously develop increase adiposity and insulin resistance in adipose tissue in association with decreased energy expenditure [34, 35•]. In line with this, GPR55 activation resulted in increased insulin signaling in adipocytes in vitro, while antagonism upregulated lipogenic gene expression and increased fat accumulation [35•]. However, profound metabolic effects have not been observed in other *Gpr55*$^{-/-}$ mouse studies, perhaps due to strain or age differences (reviewed in [36]). Thus, given the frequent discordance between human and mouse data, the role adipose tissue GPR55 plays in obesity and associated metabolic complications remains to be fully established.

Unlike CB1, expression of TRPV1 (a cation channel acting as a receptor for several NAEs) in the white adipose tissue is reduced in mouse models of obesity and diabetes and in obese men, and activation of TRPV1 inhibits, rather than stimulating, the development of obesity and insulin resistance [33, 37]. Further, *Trpv1*$^{-/-}$ mice are sensitized to high fat diets, becoming more obese and insulin resistant than controls, in part due to reduced glucose metabolism in different adipose tissue depots, but not in skeletal muscle or liver [38].

White adipose tissue depots may be the major source of circulating endocannabinoids during the consumption of high-fat diets associated with obesity [39] in line with epidemiological observations (see above). Fat-derived eCBs can signal directly to muscle to inhibit insulin signaling [40], which is improved by CB1 antagonism in both insulin-sensitive and resistant muscle explants [41]. Further, CB1 exhibits pleiotropy also in muscle cells, inhibiting mitochondrial biogenesis and oxidative metabolism activity [30]. Thus, even though the impact of obesity on muscle-specific CB1 expression and its alteration under conditions of insulin resistance are confounding, having been reported to either increase or decrease depending on the experimental model [30], CB1 clearly plays a role in regulating muscle metabolism and glucose homeostasis. Of course, the white adipose tissue also produces eCBome lipid members that do not activate CB1. Adipocyte-specific knockout of NAE synthesizing-*Napepld* did not alter AEA levels in adipose tissue but significantly decreased OEA, PEA and stearoylethanolamide (SEA), inducing obesity, glucose intolerance and insulin resistance, which was associated with decreased insulin signaling in muscle and liver, but not adipose tissue [42••]. Interestingly, the effects on glucose metabolism were associated with an altered gut microbiome, implicating commensal microbes as being important for eCBome regulation of glucose homeostasis [42••]. Muscle also expresses the OEA receptor GPR55, which appears to have the opposite effects of CB1; *Gpr55*$^{-/-}$ mice have decreased skeletal muscle insulin sensitivity and, in vitro, GPR55-dependent signaling stimulates insulin pathways in muscle cells [35•]. Interestingly, CB1 and GPR55 physically interact (at least in vitro) [43], with complex functional consequences; CB1 inhibits GPR55, while GPR55 enhances CB1, activity. However, this functional interaction is altered in the presence of CB1 ligands making the situation complex, as,

for instance, AEA, which has been suggested to also activate GPR55, is able to restore the activity of this receptor. It remains to be determined if these interactions occur in vivo, and if they are impacted under obesity and/or during insulin resistance, when both are upregulated in adipose tissue and at the same time exposed to an altered eCBome tone.

Recently, circulating levels of 2-AG and its precursor and metabolic by-product arachidonic acid (AA), but not AEA, were positively associated with nonalcoholic fatty liver disease (NAFLD), which is strongly associated with T2D [44]. In animal models of NAFLD, CB1 and the levels of 2-AG and/or AEA are increased significantly [45], and the liver is a major site of action of eCBs with respect to their metabolic action [30]. CB1 activity inhibits mitochondrial biogenesis and beta oxidation [46], upregulates lipogenesis [45], and dysregulates glucose homeostasis at both the levels of glucose uptake and gluconeogenesis [47, 48]. Hepatocyte-specific knockout of CB1 does not confer resistance to diet-induced obesity, but does inhibit the development of NAFLD and insulin resistance [48, 49]. Global CB1 knockout mice in which CB1 is transgenically expressed specifically within hepatocytes highlight the critical role of hepatocyte CB1 in regulating whole-body glucose homeostasis. These mice are the mirror image of the aforementioned hepatocyte specific CB1 knockout mice in that, under conditions of diet-induced obesity, they remain lean but develop both hepatic and systemic insulin resistance [48]. The regulation of whole-body glucose homeostasis by CB1 in the liver is not limited to CB1 in hepatocytes, however, as knockout of CB1 in resident macrophages of the liver (Kupffer cells) similarly improved glucose tolerance and insulin sensitivity without affecting hepatosteatosis in mice on a high fat diet [50]. PPARα is another eCBome receptor critical to liver lipid homeostasis, generally promoting lipid metabolism. Administration of the PPARα NAE ligand, OEA, to rats on a high fat diet inhibited the development of NAFLD, upregulating PPARα-dependent lipid metabolism [51]. The expression of another OEA receptor, G protein-coupled receptor 119 (GPR119), in hepatocytes is somewhat controversial. However, a GPR119 agonist inhibited lipogenic gene expression in hepatocytes of high fat diet-fed mice, which also developed less fatty liver [52]. Taken together, eCBome regulation of liver lipid metabolism is differentially regulated by various eCBome members, which may have subsequent effects on whole-body glucose homeostasis.

Together with the development of peripheral insulin resistance, T2D involves the loss of β-cell function and, ultimately, pancreatic β-cell mass. Insulin secretion by β cells is tightly coupled to blood glucose levels but this process is finely regulated according to the physiological situation by a number of mediators such as incretin, neurotransmitters and eCBome mediators [53, 54]. The endocrine pancreas has a functional eCBome with the expression of receptors, i.e. CB1, CB2, TRPV1 and GPR55, anabolic and catabolic enzymes, i.e. NAPE-PLD, DAGLα, FAAH and MAGL, as well as on demand eCB biosynthesis upon glucose exposure [55–57]. While there are several discrepancies between models, anandamide usually decreases pancreatic responsiveness by promoting basal insulin secretion and dampening glucose-induce insulin secretion [56–59]. CB1 blockade normalized basal and glucose-induced insulin secretion in hyperinsulinemic and obese mice, which in turn normalizes glucose homeostasis [59, 60]. In contrast, activation of GPR55 leads to reduced islet inflammation and concomitant increase in glucose-induced insulin secretion [61, 62]. More recently, *N*-acyl-taurines, eCBome mediators binding, among others, TRPV1, were also shown to negatively regulate *β*-cell function [63]. *N*-oleoyl taurine and *N*-palmitoyl taurine enhanced the basal and glucose-induced secretion of mature insulin, but not insulin synthesis, leading to its depletion and β-cell dysfunction. The impact of eCBs on insulin production may, however, be surpassed by their roles in maintaining *β*-cell mass. Increased eCB system activity promotes apoptosis and inhibits proliferation of *β* cells [55]. Accordingly, chronic CB1 inhibition was shown to protect against *β*-cell loss in obesity and diabetes and to contribute to the attenuation of diabetes and insulin resistance [28]. In sum, eCBome mediators appear to variedly acutely regulate insulin secretion, but in an obese state, chronically elevated local and circulating eCBs such as AEA and 2-AG appear to impede β-cell function, promote inflammation and lead to β-cell apoptosis.

The Emerging Metabolic Function of the eCBome in the Gastrointestinal Tract

Disturbed gastrointestinal tract motility is a frequent clinical problem in patients with T2D [64]. Increases in the levels of eCBome mediators AEA, PEA and OEA, as found in obesity and T2D, inhibit gastric emptying [65] and intestinal motility [66] through CB1 and, possibly, GPR55 signaling [67, 68]. Such deceleration of upper gut motility may increase the satiety signal arising from the stomach and the duodenum, but it may also delay small intestine nutrient absorption and contribute to normalizing postprandial circulating nutrient spikes [69]. The role of the eCBome in nutrient sensing also strongly contributes to the regulation of satiety. In fact, intraduodenal production of OEA, and potentially other NAEs, by the NAPE-PLD step-limiting enzyme is sufficient to increase meal satiety, suggesting a local anorexigenic action of OEA administration [70, 71]. Food-stimulated OEA production in enterocytes regulates feeding via the activation of PPARα, which is known to 1) promote the expression of proteins involved in lipid metabolism, 2) repress inducible nitric oxide synthase, an enzyme that generates NO, which may act as an appetite-stimulating signal, and 3) to initiate the vagus nerve-mediated hindbrain satiety signal [70, 72, 73]. Several NAEs, i.e. OEA and LEA, as well as 2-oleoylglycerol (2-OG), an

intermediate of lipid digestion, can also activate GPR119 receptors and promote incretin release from the small intestine enteroendocrine cells [74–76]. Accordingly, plasma levels of GLP-1 and GIP, the two main incretin hormones, raise following a luminal delivery of 2-OG in healthy subjects and contribute to increased satiety, reduced gastrointestinal tract motility, enhanced energy expenditure and glucose-induced insulin secretion [75]. Thus, GPR119, PPARα and their eCBome ligands are part of an enteric fat sensing mechanism playing a crucial role in energy balance and metabolism [77]. Intriguingly, chronic high fat feeding disrupted feeding-induced mobilization of OEA in the small intestine, indicative of a blunted inhibitory feedback response to fat intake leading to overfeeding and subsequent weight gain [78].

In addition, several eCBome mediators are also involved in the modulation of key intestinal functions which are altered in obesity and T2D. Indeed, aberrant enteric lipid metabolism in presence of insulin resistance, i.e. exacerbated lipoprotein secretion in response to dietary fat, is associated with increased AEA and docohexanoylethanolamide (DHEA)-induced PPARγ transcriptional activity [79]. Moreover, the barrier function, which relies largely on intestinal paracellular permeability, is challenged by several eCBome mediators and targets with opposing roles. On the one hand, enteric CB1 activation by anandamide and 2-AG increased paracellular permeability [80, 81], but, on the other hand, TRPV1 and PPARα activation by non-saturated long chain eCBome mediators and by OEA and PEA, respectively, decreased paracellular permeability [82•]. Intestinal epithelium leakage of pro-inflammatory bacterial-derived molecules (i.e. lipopolysaccharides) promotes the establishment of an inflammatory state in intestinal submucosa layer, a hallmark of obesity and T2D. Moreover, most eCBome targets, including CB1, CB2, PPARα, PPARγ and GPR55, are involved in inflammatory pathways. Indeed, CB1 activation by AEA directly promotes inflammation but also play an important immunomodulatory role in gut [83, 84]. In contrast, most eCBome mediators, and especially PEA and OEA, exert a beneficial action via PPARα and GPR55, alleviating chemical or cytokine-induced inflammation [82•, 85, 86]. In sum, a complex balance between CB1 and other eCBome signaling pathways seems therefore involved in intestinal mucosa barrier integrity, inflammatory state and metabolism.

Potential Therapeutic Applications of Targeting the eCBome for the Treatment of T2D

The number and redundancy of action of eCBome members make targeting this system an attractive option for the treatment of many illnesses, including T2D, although it poses challenges with respect to the ability to limit undesirable off-target effects. The fact that most eCBome members have wide tissue and cell type distributions compounds this issue, resulting in a potential requirement for tissue-specific targeting to minimize undesirable results. A perfect example of this is rimonabant (SR141716), the first and only marketed CB1 antagonist/reverse agonist for the treatment of obesity and related metabolic perturbations. Rimonabant significantly improved metabolic parameters, including glucose tolerance [87–90], but was removed from the market due to centrally mediated side effects related to depression and anxiety [91], which appear to be due not only to its ability to pass the blood brain barrier but also due to its activity as an inverse agonist at CB1 (which would allow it to act also in those tissues or cells where eCB tone is not perniciously elevated). Given the involvement of peripherally expressed CB1 in various aspects of the metabolic syndrome, the focus switched to peripherally restricted antagonists/inverse agonists, which do not inhibit centrally expressed CB1, or neutral/silent antagonists which are inactive in the absence of endogenous agonists (reviewed in [92, 93]). Several peripherally restricted CB1 antagonists counteract weight gain and several associated metabolic perturbations, including dysregulation of glucose homeostasis and hyperinsulinemia, in various murine models of obesity; these include JD5037 [94, 95] and the neutral antagonists LH-21 [96] and AM6545 [97, 98]. These effects appear to be a result of inhibition of CB1 in both adipose tissue and the liver [94, 95, 98]. Fewer studies have been performed with brain-penetrant neutral antagonists; however, AM4113, which exhibits similar selectivity for CB1 over CB2 as rimonabant, similarly transiently reduced food intake but sustained weight loss in a 14-day trail, although with decreased fasting glucose levels similar to pair fed controls [99]. Targeting CB2 to treat diabetes, in contrast, has been much less investigated, due to the less established and still controversial role of this eCB receptor in the control of energy metabolism [100, 101]. Nevertheless, the CB2-specific agonist JWH133 improved glucose homeostasis in chow-fed rats [58], while in high-fat diet- or streptozotocin-induced type 2 and 1 diabetic mice another agonist, SER601, improved insulin sensitivity, attributed to improved beta cell function, though without affecting glucose homeostasis [102].

Epidemiological studies of cannabis (marijuana) for which the eCBome is eponymously named found that chronic use is associated with leanness and lower levels of insulin resistance and diabetes [103, 104]. Cannabis use downregulates CB1 activity, and this has been proposed as a mechanism for the above-mentioned counterintuitive associations [105]. However, cannabis contains many cannabinoids that have complex pharmacological actions distinct from that of its principal psychoactive component THC. Δ^9-Tetrahydrocannabivarin (THCV) is such a cannabinoid, which is a CB1 antagonist and a CB2 and TRPV1 agonist (reviewed in [106]). THCV improved glucose handling in both a diet-induced and genetic (*ob*/*ob*) model of obesity [107]. In a clinical trial, THCV decreased fasting glucose levels along with apparent improved beta cell function and increased circulating levels of the insulin-sensitizing adipokine, adiponectin [108].

As noted above, eCBome mediator activity is not limited to CB1/2 receptors, and incudes other receptors that are of relevance to T2D. Of these, PPARα and PPARγ are possibly the best studied (each having several clinically approved drugs developed) and their roles have been extensively reviewed elsewhere (see [109]) and will not be discussed here. GPR55 has been (somewhat controversially) referred to as the third cannabinoid receptor [110]. Acute activation of GPR55 in chow fed mice by several agonists, including OEA, AM251, 0–1602 and abnormal cannabidiol (abn-CBD) increased insulin release and decreased glucose clearance in a glucose tolerance test, with abn-CBD being the most potent [111]. In streptozotocin-induced type 1 diabetic mice, chronic abn-CBD decreased circulating glucose, increased circulating insulin and improved glucose tolerance and insulin sensitivity [61]. In the same study, the authors also tested the GPR119 agonist AS-1269574 with similar results, and interestingly the effects of both abn-CBD and AS-1269574 on glucose and insulin were diminished in GLP1 receptor knockout mice indicating that both compounds act in part by increasing GLP1 activity [61]. Indeed increased GLP1, along with direct stimulation of insulin release, is believed to be one of the main modes of action by which agonists of GPR119, one of the most studied eCBome receptor targets for the treatment of T2D (reviewed in [112, 113]), exert their antidiabetic effects [114]. Several such agonists have moved forward to clinical trials based on their efficacy at countering glucose dyshomeostasis in various preclinical models, although none have gone past phase 2 trials to date, thus casting some doubt on the ability of preclinical results to translate to clinical ones (reviewed extensively in [112, 113]). Of note, the eCBome member 2-OG, while not as potent a GPR119 ligand as OEA or LEA, is present in the intestines in vastly higher concentrations than any NAEs and thus is more likely to activate intestinal GPR119, and also activates TRPV1 [9]. Indeed, 2-OG provided as a single bolus or derived from a dietary precursor increased plasma GLP1 and glucose-dependent insulinotropic polypeptide (GIP) levels in healthy [115] and diabetic humans [116], respectively. And, at the time of writing, there is a human study recruiting participants to determine the effects of 2-OG on glucose sensitivity [117].

Unlike the eCBome receptors discussed above, TRPV1 is a channel receptor, which responds to noxious heat and the 'spicy' component of chili peppers, capsaicin. This compound improves glucose homeostasis and insulin sensitivity in several murine models of diabetes [37, 118–121]. In humans, hot chili peppers consumed with a meal improved insulin sensitivity in overweight individuals [122] and in women with gestational diabetes [102]. However, in another recent human trial, chronic capsaicin exposure increased circulating insulin levels without affecting measures of insulin sensitivity [123]. The antidiabetic activity of capsaicin is believed to be due to TRPV1 activation. However, TRPV1 is immediately desensitized after activation [124], and desensitization in sensory nerve cells improves glucose tolerance in the absence of apparent amelioration of insulin resistance in Zucker rats [125]. Indeed, TRPV1 antagonists may also hold promise for the treatment of T2D, as the TRPV1 antagonist BCTC stimulated insulin release and improved glucose tolerance in Zucker obese rats [125], and another TRPV1 antagonist, XEN-D0501, is currently in phase 2 clinical trials for T2D [126].

The gut microbiome is implicated in several aspects of host health, particularly metabolic health, including the pathogenesis of diabetes [127, 128]. This complex endogenous ecosystem is, therefore, considered a valid therapeutic target which can be modified through the diet by either probiotics or prebiotics for the treatment of diabetes (recently reviewed in [129]). Gut microbiota regulate eCBome tone at both the receptor and enzyme levels in colon and adipose tissue [130], and gut microbiota changes in diabetic *db*/*db* mice are associated with increased AEA and decreased 2-AG in fat [131]. Further, bacterial-derived lipopolysaccharide-induced metabolic endotoxaemia and insulin resistance is partially mediated by CB1 [84]. Modification of the microbiome with prebiotics in obese *ob*/*ob* mice decreased CB1 expression and AEA levels in adipose tissue, modifying gut permeability, adipogenesis and lipid metabolism [130]. Finally, treatment with the mucin-feeding bacterium *Akkermansia muciniphila* increased the intestinal levels of the acylglycerols 2-AG, 2-OG and 2-palmitoylglycerol (2-PG) in association with a reduction in diet-induced hyperglycaemia and insulin resistance [132], and is currently under investigation in a clinical trial in which insulin resistance is a primary outcome measure [133].

Conclusions

Despite the failure of rimonabant, the eCB system, and its expansion, the eCBome, remain an attractive target for the treatment of a variety of metabolic disorders, T2D included. This is evidenced by the variety of novel approaches to target CB1 activity, from the development of neutral and/or peripherally restricted antagonists, to using non-psychoactive cannabis-derived cannabinoids and, more recently, to targeting the gut microbiome, the latter of which also appears to modify the wider eCBome. Given the redundancy and overlap found within the eCBome, and their involvement in various aspects of T2D, development of multi-target drugs that manipulate several aspects of the eCBome may prove to be more efficacious than those that are highly specific. Indeed, the recent success of cannabis-based medicines in preclinical and clinical studies, including THCV for the treatment of T2D [107, 108], may in part be due to their complex pharmacology as pertains to the eCBome [106, 134]. Likewise, nutritional interventions, such as the use of functional foods delivering long chain fatty acids, including dietary n-3 polyunsaturated fatty

acids [135, 136], capable of affecting the tissue concentrations of various eCBome mediators at once in a manner that may result in metabolic benefits, needs to be further explored. Of course, as also exemplified by the indiscriminate targeting of CB1 by rimonabant, special attention will have to be paid to the potential for serious side effects due to the expression of eCBome members in a wide array of tissues. Thus, while targeting the eCBome undoubtedly poses challenges, our incremental understanding of its complexities and multifaceted involvement in various pathologies will undoubtedly be facilitated through the use of various "omics" technologies, which will, in our view, make it the source of many future therapeutic strategies for various diseases, including T2D.

Compliance with Ethical Standards

Conflict of Interest Alain Veilleux declares no conflict of interest.
Vincenzo Di Marzo reports grants from GW Pharmaceuticals.
Cristoforo Silvestri reports he was a previous employee of GW Pharmaceuticals.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Abbreviations AcArGs, 1-acyl-sn-2-arachidonoyl-glycerols; 2-AG, 2-arachidonoyl-glycerol; 2-MAG, 2-mono-acyl-glycerol; 2-OG, 2-oleoylglycerol; 2-PG, 2-palmitoylglycerol; abn-CBD, abnormal cannabidiol; AA, arachidonic acid; AEA, arachidonoylethanolamide; CB1/2, cannabinoid receptor type-1/2; THC, D9-tetrahydrocannabinol; THCV, D9-Tetrahydrocannabivarin; DAGL, diacylglycerol lipase; DHEA, docohexanoylethanolamide; eCB, endocannabinoid; eCBome, endocannabinoidome; FAAH, fatty acid amide hydrolase; GPR119, G protein-coupled Receptor 119; GPR55, G protein-coupled Receptor 55; GIP, glucose-dependent insulinotropic polypeptide; LEA, linoleoylethanolamide; MAGL, monoacylglycerol lipase; NAE, N-acylethanolamine; NAPE-PLD, N-acyl-phosphatidylethanolamine-specific phospholipase D-like; NArPEs, N-arachidonoyl-phosphatidylethanolamines; NAFLD, nonalcoholic fatty liver disease; OEA, oleoylethanolamide; PEA, palmitoylethanolamide; SEA, stearoylethanolamide; TRPV1, transient receptor potential cation channel subfamily V member 1

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Matsuda LA, Young AC. Structure of a cannabinoid receptor and functional expression of the cloned eDNA. 1990;346:4.
2. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature. 1993;365:61–5.
3. Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science. 1992;258:1946–9.
4. Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem Pharmacol. 1995;50:83–90.
5. Dinh TP, Carpenter D, Leslie FM, Freund TF, Katona I, Sensi SL, et al. Brain monoglyceride lipase participating in endocannabinoid inactivation. Proc Natl Acad Sci U S A. 2002;99:10819–24.
6. Cravatt BF, Giang DK, Mayfield SP, Boger DL, Lerner RA, Gilula NB. Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. Nature. 1996;384:83–7.
7. Bisogno T, Howell F, Williams G, Minassi A, Cascio MG, Ligresti A, 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;163:463–8.
8. Okamoto Y, Morishita J, Tsuboi K, Tonai T, Ueda N. Molecular characterization of a phospholipase D generating anandamide and its congeners. J Biol Chem. 2004;279:5298–305.
9. Di Marzo V. New approaches and challenges to targeting the endocannabinoid system. Nat Rev Drug Discov. 2018;17:623–39.
10. Blüher M, Engeli S, Klöting N, Berndt J, Fasshauer M, Bátkai S, et al. Dysregulation of the peripheral and adipose tissue endocannabinoid system in human abdominal obesity. Diabetes. 2006;55:3053–60.
11. Engeli S, Böhnke J, Feldpausch M, Gorzelniak K, Janke J, Bátkai S, et al. Activation of the peripheral endocannabinoid system in human obesity. Diabetes. 2005;54:2838–43.
12. van Eyk HJ, van Schinkel LD, Kantae V, Dronkers CEA, Westenberg JJM, de Roos A, et al. Caloric restriction lowers endocannabinoid tonus and improves cardiac function in type 2 diabetes. Nutr Diabetes [Internet]. 2018 [cited 2019 May 8];8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5851430/
13. Fanelli F, Mezzullo M, Repaci A, Belluomo I, Ibarra Gasparini D, Di Dalmazi G, et al. Profiling plasma N-Acylethanolamine levels and their ratios as a biomarker of obesity and dysmetabolism. Mol Metab. 2018;14:82–94.
14. Fanelli F, Mezzullo M, Belluomo I, Di Lallo VD, Baccini M, Ibarra Gasparini D, et al. Plasma 2-arachidonoylglycerol is a biomarker of age and menopause related insulin resistance and dyslipidemia in lean but not in obese men and women. Mol Metab. 2017;6:406–15.
15. Matias I, Gonthier M-P, Orlando P, Martiadis V, De Petrocellis L, Cervino C, et al. Regulation, function, and dysregulation of endocannabinoids in models of adipose and β-pancreatic cells and in obesity and hyperglycemia. J Clin Endocrinol Metab. 2006;91:3171–80.
16. Côté M, Matias I, Lemieux I, Petrosino S, Alméras N, Després J-P, et al. Circulating endocannabinoid levels, abdominal adiposity and related cardiometabolic risk factors in obese men. Int J Obes (Lond). 2007;31:692–9.
17. de Martins CJM, Genelhu V, MMG P, BMJ C, Mangia RF, Aveta T, et al. Circulating endocannabinoids and the polymorphism 385C>A in fatty acid amide hydrolase (FAAH) gene May identify the obesity phenotype related to Cardiometabolic risk: A study conducted in a Brazilian population of complex interethnic admixture. PLoS One. 2015;10:e0142728.
18. Little TJ, Cvijanovic N, DiPatrizio NV, Argueta DA, Rayner CK, Feinle-Bisset C, et al. Plasma endocannabinoid levels in lean, overweight, and obese humans: relationships to intestinal permeability markers, inflammation, and incretin secretion. Am J Physiol Endocrinol Metab. 2018;315:E489–95.
19. Di Marzo V, Côté M, Matias I, Lemieux I, Arsenault BJ, Cartier A, et al. Changes in plasma endocannabinoid levels in viscerally obese men following a 1 year lifestyle modification programme and waist circumference reduction: associations with changes in metabolic risk factors. Diabetologia. 2008;52:213.
20. Abdulnour J, Yasari S, Rabasa-Lhoret R, Faraj M, Petrosino S, Piscitelli F, et al. Circulating endocannabinoids in insulin sensitive

vs. insulin resistant obese postmenopausal women. A MONET group study. Obesity. 2014;22:211–6.
21. Matias I, Petrosino S, Racioppi A, Capasso R, Izzo AA, Di Marzo V. Dysregulation of peripheral endocannabinoid levels in hyperglycemia and obesity: effect of high fat diets. Mol Cell Endocrinol. 2008;286:S66–78.
22. Grapov D, Adams SH, Pedersen TL, Garvey WT, Newman JW. Type 2 diabetes associated changes in the plasma non-esterified fatty acids, oxylipins and endocannabinoids. PLoS One. 2012;7:e48852.
23. Mallipedhi A, Prior SL, Dunseath G, Bracken RM, Barry J, Caplin S, et al. Changes in Plasma Levels of N-Arachidonoyl Ethanolamine and N-Palmitoylethanolamine following Bariatric Surgery in Morbidly Obese Females with Impaired Glucose Homeostasis. J Diabetes Res [Internet]. 2015 [cited 2019 May 8];2015. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4385619/
24. Gruden G, Barutta F, Kunos G, Pacher P. Role of the endocannabinoid system in diabetes and diabetic complications. Br J Pharmacol. 2016;173:1116–27.
25. Jourdan T, Djaouti L, Demizieux L, Gresti J, Vergès B, Degrace P. CB1 antagonism exerts specific molecular effects on visceral and subcutaneous fat and reverses liver steatosis in diet-induced obese mice. Diabetes. 2010;59:926–34.
26. Sidibeh CO, Pereira MJ, Lau Börjesson J, Kamble PG, Skrtic S, Katsogiannos P, et al. Role of cannabinoid receptor 1 in human adipose tissue for lipolysis regulation and insulin resistance. Endocrine. 2017;55:839–52.
27. Pagotto U, Marsicano G, Cota D, Lutz B, Pasquali R. The emerging role of the endocannabinoid system in endocrine regulation and energy balance. Endocr Rev. 2006;27:73–100.
28. Jourdan T, Godlewski G, Cinar R, Bertola A, Szanda G, Liu J, et al. Activation of the Nlrp3 inflammasome in infiltrating macrophages by endocannabinoids mediates beta cell loss in type 2 diabetes. Nat Med. 2013;19:1132–40.
29. Pertwee RG. Cannabinoids and the gastrointestinal tract. Gut. 2001;48:859–67.
30. Silvestri C, Di Marzo V. The endocannabinoid system in energy Homeostasis and the Etiopathology of metabolic disorders. Cell Metab. 2013;17:475–90.
31. Ruiz de Azua I, Mancini G, Srivastava RK, Rey AA, Cardinal P, Tedesco L, et al. Adipocyte cannabinoid receptor CB1 regulates energy homeostasis and alternatively activated macrophages. J Clin Invest. 127:4148–62.
32. Moreno-Navarrete JM, Catalán V, Whyte L, Díaz-Arteaga A, Vázquez-Martínez R, Rotellar F, et al. The l-α-Lysophosphatidylinositol/GPR55 system and its potential role in human obesity. Diabetes. 2012;61:281–91.
33. Zhang LL, Yan Liu D, Ma LQ, Luo ZD, Cao TB, Zhong J, et al. Activation of transient receptor potential Vanilloid Type-1 channel prevents Adipogenesis and obesity. Circ Res. 2007;100:1063–70.
34. Meadows A, Lee JH, Wu C-S, Wei Q, Pradhan G, Yafi M, et al. Deletion of G-protein-coupled receptor 55 promotes obesity by reducing physical activity. Int J Obes. 2016;40:417–24.
35.• Lipina C, Walsh SK, Mitchell SE, Speakman JR, Wainwright CL, Hundal HS. GPR55 deficiency is associated with increased adiposity and impaired insulin signaling in peripheral metabolic tissues. FASEB J. 2019;33:1299–312 **Findings from this study demonstrate that GPR55, a widely expressed OEA and PEA receptor, is a positive regulator of adipogenesis and insulin action in skeletal muscle, adipose tissue and liver**.
36. Alhouayek M, Masquelier J, Muccioli GG. Lysophosphatidylinositols, from cell membrane constituents to GPR55 ligands. Trends Pharmacol Sci. 2018;39:586–604.
37. Kang J-H, Tsuyoshi G, Han I-S, Kawada T, Kim YM, Yu R. Dietary capsaicin reduces obesity-induced insulin resistance and hepatic steatosis in obese mice fed a high-fat diet. Obesity. 2010;18:780–7.
38. Lee E, Jung DY, Kim JH, Patel PR, Hu X, Lee Y, et al. Transient receptor potential vanilloid type-1 channel regulates diet-induced obesity, insulin resistance, and leptin resistance. FASEB J. 2015;29:3182–92.
39. Kuipers EN, Kantae V, Maarse BCE, van den Berg SM, van Eenige R, Nahon KJ, et al. High Fat Diet Increases Circulating Endocannabinoids Accompanied by Increased Synthesis Enzymes in Adipose Tissue. Front Physiol [Internet]. 2019 [cited 2019 May 15];9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6335353/
40. Eckardt K, Sell H, Taube A, Koenen M, Platzbecker B, Cramer A, et al. Cannabinoid type 1 receptors in human skeletal muscle cells participate in the negative crosstalk between fat and muscle. Diabetologia. 2009;52:664–74.
41. Lindborg KA, Teachey MK, Jacob S, Henriksen EJ. Effects of in vitro antagonism of endocannabinoid-1 receptors on the glucose transport system in normal and insulin-resistant rat skeletal muscle. Diabetes Obes Metab. 2010;12:722–30.
42.•• Geurts L, Everard A, Van Hul M, Essaghir A, Duparc T, Matamoros S, et al. Adipose tissue NAPE-PLD controls fat mass development by altering the browning process and gut microbiota. Nature Communications [Internet]. 2015 [cited 2018 Aug 3];6. Available from: http://www.nature.com/articles/ncomms7495. **This study simultaneously demonstrates the complexity of NAPE-PLD enzyme activity in the regulation of eCBome mediator levels within adipocytes and its critical role in regulating adipose tissue physiology, obesity and whole-body glucose metabolism. Significantly, it also identifies the gut μB as a key factor in mediating the development of this phenotype, highlighting the importance of an adipose tissue eCBome - gut μB axis to metabolic health.**
43. Kargl J, Balenga N, Parzmair GP, Brown AJ, Heinemann A, Waldhoer M. The cannabinoid receptor CB1 modulates the signaling properties of the Lysophosphatidylinositol receptor GPR55. J Biol Chem. 2012;287:44234–48.
44. Zelber-Sagi S, Azar S, Nemirovski A, Webb M, Halpern Z, Shibolet O, et al. Serum levels of endocannabinoids are independently associated with nonalcoholic fatty liver disease. Obesity. 2017;25:94–101.
45. Osei-Hyiaman D, DePetrillo M, Pacher P, Liu J, Radaeva S, Bátkai S, et al. Endocannabinoid activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet-induced obesity. J Clin Invest. 2005;115:1298–305.
46. Tedesco L, Valerio A, Dossena M, Cardile A, Ragni M, Pagano C, et al. Cannabinoid receptor stimulation impairs mitochondrial biogenesis in mouse White adipose tissue, muscle, and liver. Diabetes. 2010;59:2826–36.
47. Chanda D, Kim D-K, Li T, Kim Y-H, Koo S-H, Lee C-H, et al. Cannabinoid receptor type 1 (CB1R) signaling regulates hepatic gluconeogenesis via induction of endoplasmic reticulum-bound transcription factor cAMP-responsive element-binding protein H (CREBH) in primary hepatocytes. J Biol Chem. 2011;286:27971–9.
48. Liu J, Zhou L, Xiong K, Godlewski G, Mukhopadhyay B, Tam J, et al. Hepatic Cannabinoid Receptor-1 Mediates Diet-Induced Insulin Resistance via Inhibition of Insulin Signaling and Clearance in Mice. Gastroenterology. 2012;142:1218–1228.e1.
49. Osei-Hyiaman D, Liu J, Zhou L, Godlewski G, Harvey-White J, Jeong W, et al. Hepatic CB1 receptor is required for development of diet-induced steatosis, dyslipidemia, and insulin and leptin resistance in mice. J Clin Invest. 2008;118:3160–9.
50. Jourdan T, Nicoloro SM, Zhou Z, Shen Y, Liu J, Coffey NJ, et al. Decreasing CB1 receptor signaling in Kupffer cells improves insulin sensitivity in obese mice. Molecular Metabolism. 2017;6:1517–28.

51. Li L, Li L, Chen L, Lin X, Xu Y, Ren J, et al. Effect of oleoylethanolamide on diet-induced nonalcoholic fatty liver in rats. J Pharmacol Sci. 2015;127:244–50.
52. Yang JW, Kim HS, Im JH, Kim JW, Jun DW, Lim SC, et al. GPR119: a promising target for nonalcoholic fatty liver disease. FASEB J. 2016;30:324–35.
53. Hiriart M, Velasco M, Larqué C, Diaz-Garcia CM. Metabolic syndrome and ionic channels in pancreatic beta cells. Vitam Horm. 2014;95:87–114.
54. González-Mariscal I, Egan JM. Endocannabinoids in the islets of Langerhans: the ugly, the bad, and the good facts. Am J Physiol Endocrinol Metab. 2018;315:E174–9.
55. Kim W, Doyle ME, Liu Z, Lao Q, Shin Y-K, Carlson OD, et al. Cannabinoids inhibit insulin receptor signaling in pancreatic β-cells. Diabetes. 2011;60:1198–209.
56. Li C, Vilches-Flores A, Zhao M, Amiel SA, Jones PM, Persaud SJ. Expression and function of monoacylglycerol lipase in mouse β-cells and human islets of Langerhans. Cell Physiol Biochem. 2012;30:347–58.
57. Malenczyk K, Keimpema E, Piscitelli F, Calvigioni D, Björklund P, Mackie K, et al. Fetal endocannabinoids orchestrate the organization of pancreatic islet microarchitecture. Proc Natl Acad Sci U S A. 2015;112:E6185–94.
58. Bermudez-Silva FJ, Sanchez-Vera I, Suárez J, Serrano A, Fuentes E, Juan-Pico P, et al. Role of cannabinoid CB2 receptors in glucose homeostasis in rats. Eur J Pharmacol. 2007;565:207–11.
59. González-Mariscal I, Krzysik-Walker SM, Doyle ME, Liu Q-R, Cimbro R, Santa-Cruz Calvo S, et al. Human CB1 receptor isoforms, present in hepatocytes and β-cells, are involved in regulating metabolism. Sci Rep. 2016;6:33302.
60. Duvivier VF, Delafoy-Plasse L, Delion V, Lechevalier P, Le Bail J-C, Guillot E, et al. Beneficial effect of a chronic treatment with rimonabant on pancreatic function and beta-cell morphology in Zucker fatty rats. Eur J Pharmacol. 2009;616:314–20.
61. McKillop AM, Moran BM, Abdel-Wahab YHA, Gormley NM, Flatt PR. Metabolic effects of orally administered small-molecule agonists of GPR55 and GPR119 in multiple low-dose streptozotocin-induced diabetic and incretin-receptor-knockout mice. Diabetologia. 2016;59:2674–85.
62. Romero-Zerbo SY, Rafacho A, Díaz-Arteaga A, Suárez J, Quesada I, Imbernon M, et al. A role for the putative cannabinoid receptor GPR55 in the islets of Langerhans. J Endocrinol. 2011;211:177–85.
63. Aichler M, Borgmann D, Krumsiek J, Buck A, MacDonald PE, Fox JEM, et al. N-acyl Taurines and Acylcarnitines Cause an Imbalance in Insulin Synthesis and Secretion Provoking β Cell Dysfunction in Type 2 Diabetes. Cell Metab. 2017;25:1334–1347.e4.
64. Koch KL. Diabetic gastropathy: gastric neuromuscular dysfunction in diabetes mellitus: a review of symptoms, pathophysiology, and treatment. Dig Dis Sci. 1999;44:1061–75.
65. Di Marzo V, Capasso R, Matias I, Aviello G, Petrosino S, Borrelli F, et al. The role of endocannabinoids in the regulation of gastric emptying: alterations in mice fed a high-fat diet. Br J Pharmacol. 2008;153:1272–80.
66. Capasso R, Orlando P, Pagano E, Aveta T, Buono L, Borrelli F, et al. Palmitoylethanolamide normalizes intestinal motility in a model of post-inflammatory accelerated transit: involvement of CB_1 receptors and TRPV1 channels. Br J Pharmacol. 2014;171:4026–37.
67. Cluny NL, Keenan CM, Duncan M, Fox A, Lutz B, Sharkey KA. Naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone (SAB378), a peripherally restricted cannabinoid CB1/CB2 receptor agonist, inhibits gastrointestinal motility but has no effect on experimental colitis in mice. J Pharmacol Exp Ther. 2010;334:973–80.
68. Lin X-H, Yuece B, Li Y-Y, Feng Y-J, Feng J-Y, Yu L-Y, et al. A novel CB receptor GPR55 and its ligands are involved in regulation of gut movement in rodents. Neurogastroenterol Motil. 2011;23:862–e342.
69. Troy-Fioramonti S, Demizieux L, Gresti J, Muller T, Vergès B, Degrace P. Acute activation of cannabinoid receptors by anandamide reduces gastrointestinal motility and improves postprandial glycemia in mice. Diabetes. 2015;64:808–18.
70. Fu J, Kim J, Oveisi F, Astarita G, Piomelli D. Targeted enhancement of oleoylethanolamide production in proximal small intestine induces across-meal satiety in rats. Am J Physiol Regul Integr Comp Physiol. 2008;295:R45–50.
71. Everard A, Plovier H, Rastelli M, Van Hul M, de Wouters d'Oplinter A, Geurts L, et al. Intestinal epithelial N-acylphosphatidylethanolamine phospholipase D links dietary fat to metabolic adaptations in obesity and steatosis. Nat Commun. 2019;10:457.
72. Stricker-Krongrad A, Beck B, Burlet C. Nitric oxide mediates hyperphagia of obese Zucker rats: relation to specific changes in the microstructure of feeding behavior. Life Sci. 1996;58:PL9–15.
73. Hankir MK, Seyfried F, Hintschich CA, Diep T-A, Kleberg K, Kranz M, et al. Gastric bypass surgery recruits a gut PPAR-α-striatal D1R pathway to reduce fat appetite in obese rats. Cell Metab. 2017;25:335–44.
74. Overton HA, Babbs AJ, Doel SM, Fyfe MCT, Gardner LS, Griffin G, 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;3:167–75.
75. Hansen KB, Rosenkilde MM, Knop FK, Wellner N, Diep TA, Rehfeld JF, et al. 2-Oleoyl glycerol is a GPR119 agonist and signals GLP-1 release in humans. J Clin Endocrinol Metab. 2011;96:E1409–17.
76. Lauffer LM, Iakoubov R, Brubaker PL. GPR119 is essential for oleoylethanolamide-induced glucagon-like peptide-1 secretion from the intestinal enteroendocrine L-cell. Diabetes. 2009;58:1058–66.
77. Schwartz GJ, Fu J, Astarita G, Li X, Gaetani S, Campolongo P, et al. The lipid messenger OEA links dietary fat intake to satiety. Cell Metab. 2008;8:281–8.
78. Igarashi M, DiPatrizio NV, Narayanaswami V, Piomelli D. Feeding-induced oleoylethanolamide mobilization is disrupted in the gut of diet-induced obese rodents. Biochim Biophys Acta. 1851;2015:1218–26.
79. Duszka K, Oresic M, Le May C, König J, Wahli W. PPARγ modulates long chain fatty acid processing in the intestinal epithelium. Int J Mol Sci. 2017;18.
80. Karwad MA, Couch DG, Theophilidou E, Sarmad S, Barrett DA, Larvin M, et al. The role of CB1 in intestinal permeability and inflammation. FASEB J. 2017;31:3267–77.
81. Alhamoruni A, Wright KL, Larvin M, O'Sullivan SE. Cannabinoids mediate opposing effects on inflammation-induced intestinal permeability. Br J Pharmacol. 2012;165:2598–610.
82•. Karwad MA, Macpherson T, Wang B, Theophilidou E, Sarmad S, Barrett DA, et al. Oleoylethanolamine and palmitoylethanolamine modulate intestinal permeability in vitro via TRPV1 and PPARα. FASEB J. 2017;31:469–81 **This *in* vitro study identifies a potential endogenous role for the eCBome mediators OEA and PEA in regulating intestinal permeability associated with inflammation. Both OEA, via TRPV1, and PEA, via PPARA, decrease cytokine-induced transepithelial permeability**.
83. Acharya N, Penukonda S, Shcheglova T, Hagymasi AT, Basu S, Srivastava PK. Endocannabinoid system acts as a regulator of immune homeostasis in the gut. Proc Natl Acad Sci U S A. 2017;114:5005–10.

84. Grunewald ZI, Lee S, Kirkland R, Ross M, de La Serre CB. Cannabinoid receptor type-1 partially mediates metabolic endotoxemia-induced inflammation and insulin resistance. Physiol Behav. 2019;199:282–91.
85. Couch DG, Tasker C, Theophilidou E, Lund JN, O'Sullivan SE. Cannabidiol and palmitoylethanolamide are anti-inflammatory in the acutely inflamed human colon. Clin Sci. 2017;131:2611–26.
86. Esposito G, Capoccia E, Turco F, Palumbo I, Lu J, Steardo A, et al. Palmitoylethanolamide improves colon inflammation through an enteric glia/toll like receptor 4-dependent PPAR-α activation. Gut. 2014;63:1300–12.
87. Després J-P, Golay A, Sjöström L. Effects of Rimonabant on metabolic risk factors in overweight patients with dyslipidemia. N Engl J Med. 2005;14.
88. Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rössner S, RIO-Europe Study Group. 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;365:1389–97.
89. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J. RIO-North America Study Group. 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;295:761–75.
90. Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF, RIO-Diabetes Study Group. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. Lancet. 2006;368:1660–72.
91. Sam AH, Salem V, Ghatei MA. Rimonabant: From RIO to Ban. J Obes [Internet]. 2011 [cited 2019 May 11];2011. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136184/
92. Silvestri C, Marzo VD. Second generation CB1 receptor blockers and other inhibitors of peripheral endocannabinoid overactivity and the rationale of their use against metabolic disorders. Expert Opin Investig Drugs. 2012;21:1309–22.
93. Tam J, Hinden L, Drori A, Udi S, Azar S, Baraghithy S. The therapeutic potential of targeting the peripheral endocannabinoid/CB1 receptor system. Eur J Intern Med. 2018;49:23–9.
94. Cinar R, Godlewski G, Liu J, Tam J, Jourdan T, Mukhopadhyay B, et al. Hepatic cannabinoid-1 receptors mediate diet-induced insulin resistance by increasing de novo synthesis of long-chain ceramides. Hepatology. 2014;59:143–53.
95. Tam J, Cinar R, Liu J, Godlewski G, Wesley D, Jourdan T, et al. Peripheral cannabinoid-1 receptor inverse agonism reduces obesity by reversing leptin resistance. Cell Metab. 2012;16:167–79.
96. Romero-Zerbo SY, Ruz-Maldonado I, Espinosa-Jiménez V, Rafacho A, Gómez-Conde AI, Sánchez-Salido L, et al. The cannabinoid ligand LH-21 reduces anxiety and improves glucose handling in diet-induced obese pre-diabetic mice. Sci Rep. 2017;7:3946.
97. Tam J, Vemuri VK, Liu J, Bátkai S, Mukhopadhyay B, Godlewski G, et al. Peripheral CB1 cannabinoid receptor blockade improves cardiometabolic risk in mouse models of obesity. J Clin Invest. 2010;120:2953–66.
98. Ma H, Zhang G, Mou C, Fu X, Chen Y. Peripheral CB1 Receptor Neutral Antagonist, AM6545, Ameliorates Hypometabolic Obesity and Improves Adipokine Secretion in Monosodium Glutamate Induced Obese Mice. Front Pharmacol [Internet]. 2018 [cited 2019 May 12];9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5869198/
99. Cluny NL, Chambers AP, Vemuri VK, Wood JT, Eller LK, Freni C, et al. The neutral cannabinoid CB1 receptor antagonist A M4113 regulates body weight through changes in energy intake in the rat. Pharmacol Biochem Behav. 2011;97:537–43.
100. Agudo J, Martin M, Roca C, Molas M, Bura AS, Zimmer A, et al. Deficiency of CB2 cannabinoid receptor in mice improves insulin sensitivity but increases food intake and obesity with age. Diabetologia. 2010;53:2629–40.
101. Deveaux V, Cadoudal T, Ichigotani Y, Teixeira-Clerc F, Louvet A, Manin S, et al. Cannabinoid CB2 receptor potentiates obesity-associated inflammation, Insulin Resistance and Hepatic Steatosis. PLOS ONE. 2009;4:e5844.
102. Zhang X, Gao S, Niu J, Li P, Deng J, Xu S, et al. Cannabinoid 2 receptor agonist improves systemic sensitivity to insulin in high-fat diet/Streptozotocin-induced diabetic mice. CPB. 2016;40:1175–85.
103. Imtiaz S, Rehm J. The relationship between cannabis use and diabetes: results from the National Epidemiologic Survey on alcohol and related conditions III. Drug Alcohol Rev. 2018;37:897–902.
104. Penner EA, Buettner H, Mittleman MA. The impact of marijuana use on glucose, insulin, and insulin resistance among US adults. Am J Med. 2013;126:583–9.
105. Clark T, Jessica Jones, Hall A, Tabner S, Kmiec R. Theoretical Explanation for Reduced Body Mass Index and Obesity Rates in Cannabis Users. 2018 [cited 2019 Jan 8]; Available from: http://www.preprints.org/manuscript/201807.0197/v1
106. Roger Pertwee, Maria Grazia Cascio. Chapter 6: Known Pharmacological Actions of Delta-9-Tetrahydrocannabinol and of Four Other Chemical Constituents of Cannabis that Activate Cannabinoid Receptors. In: Roger Pertwee, editor. Handbook of Cannabis [Internet]. First Edition. Oxford University Press; 2014. p. 115–136. Available from: https://www.oxfordscholarship.com/view/10.1093/acprof:oso/9780199662685.001.0001/acprof-9780199662685-chapter-6
107. Wargent ET, Zaibi MS, Silvestri C, Hislop DC, Stocker CJ, Stott CG, et al. The cannabinoid Δ9-tetrahydrocannabivarin (THCV) ameliorates insulin sensitivity in two mouse models of obesity. Nutr Diabetes. 2013;3:e68.
108. Jadoon KA, Ratcliffe SH, Barrett DA, Thomas EL, Stott C, Bell JD, et al. Efficacy and safety of Cannabidiol and Tetrahydrocannabivarin on glycemic and lipid parameters in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled, Parallel Group Pilot Study. Diabetes Care. 2016;39:1777–86.
109. Gross B, Pawlak M, Lefebvre P, Staels B. PPARs in obesity-induced T2DM, dyslipidaemia and NAFLD. Nat Rev Endocrinol. 2017;13:36–49.
110. Moriconi A, Cerbara I, Maccarrone M, Topai A. GPR55: current knowledge and future perspectives of a purported "Type-3" cannabinoid receptor. Curr Med Chem. 2010;17:1411–29.
111. McKillop AM, Moran BM, Abdel-Wahab YHA, Flatt PR. Evaluation of the insulin releasing and antihyperglycaemic activities of GPR55 lipid agonists using clonal beta-cells, isolated pancreatic islets and mice. Br J Pharmacol. 2013;170:978–90.
112. Yang JW, Kim HS, Choi Y-W, Kim Y-M, Kang KW. Therapeutic application of GPR119 ligands in metabolic disorders. Diabetes Obes Metab. 2018;20:257–69.
113. Ritter K, Buning C, Halland N, Pöverlein C, Schwink L. G protein-coupled receptor 119 (GPR119) agonists for the treatment of diabetes: recent Progress and prevailing challenges. J Med Chem. 2016;59:3579–92.
114. Ohishi T, Yoshida S. The therapeutic potential of GPR119 agonists for type 2 diabetes. Expert Opin Investig Drugs. 2012;21:321–8.
115. Hansen KB, Rosenkilde MM, Knop FK, Wellner N, Diep TA, Rehfeld JF, et al. 2-Oleoyl glycerol is a GPR119 agonist and signals GLP-1 release in humans. J Clin Endocrinol Metab. 2011;96:E1409–17.
116. Mandøe MJ, Hansen KB, Windeløv JA, Knop FK, Rehfeld JF, Rosenkilde MM, et al. Comparing olive oil and C4-dietary oil, a

prodrug for the GPR119 agonist, 2-oleoyl glycerol, less energy intake of the latter is needed to stimulate incretin hormone secretion in overweight subjects with type 2 diabetes. Nutr Diabetes. 2018;8:2.
117. Effect of Dietary Oils as G-protein-coupled Receptor Agonists on Glucose Tolerance - Full Text View - ClinicalTrials.gov [Internet]. [cited 2019 May 13]. Available from: https://clinicaltrials.gov/ct2/show/NCT03774095
118. Song J-X, Ren H, Gao Y-F, Lee C-Y, Li S-F, Zhang F, et al. Dietary Capsaicin Improves Glucose Homeostasis and Alters the Gut Microbiota in Obese Diabetic ob/ob Mice. Frontiers in Physiology [Internet]. 2017 [cited 2018 Jul 25];8. Available from: http://journal.frontiersin.org/article/10.3389/fphys.2017.00602/full
119. Kang J-H, Tsuyoshi G, Le Ngoc H, Kim H-M, Tu TH, Noh H-J, et al. Dietary capsaicin attenuates metabolic dysregulation in genetically obese diabetic mice. J Med Food. 2011;14:310–5.
120. Kang C, Wang B, Kaliannan K, Wang X, Lang H, Hui S, et al. Gut Microbiota Mediates the Protective Effects of Dietary Capsaicin against Chronic Low-Grade Inflammation and Associated Obesity Induced by High-Fat Diet. mBio. 2017;8:e00470–17.
121. Wang P, Yan Z, Zhong J, Chen J, Ni Y, Li L, et al. Transient receptor potential Vanilloid 1 activation enhances gut glucagon-like Peptide-1 secretion and improves glucose Homeostasis. Diabetes. 2012;61:2155–65.
122. Kroff J, Hume DJ, Pienaar P, Tucker R, Lambert EV, Rae DE. The metabolic effects of a commercially available chicken peri-peri (African bird's eye chilli) meal in overweight individuals. Br J Nutr. 2017;117:635–44.
123. Urbina SL, Roberts MD, Kephart WC, Villa KB, Santos EN, Olivencia AM, et al. Effects of twelve weeks of capsaicinoid supplementation on body composition, appetite and self-reported caloric intake in overweight individuals. Appetite. 2017;113:264–73.
124. Touska F, Marsakova L, Teisinger J, Vlachova V. A "cute" desensitization of TRPV1. Curr Pharm Biotechnol. 2011;12:122–9.
125. Gram DX, Hansen AJ. Inhibition of the activity of the capsaicin receptor in the treatment of obesity or obesity-related diseases and disorders [Internet]. 2011 [cited 2019 May 14]. Available from: https://patents.google.com/patent/US7879866B2/en
126. Clinical Trials Register [Internet]. [cited 2019 May 14]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-003843-12/DK#E
127. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. 2012;490:55–60.
128. Karlsson FH, Tremaroli V, Nookaew I, Bergström G, Behre CJ, Fagerberg B, et al. Gut metagenome in European women with normal, impaired and diabetic glucose control. Nature. 2013;498:99–103.
129. Kim YA, Keogh JB, Clifton PM. Probiotics, prebiotics, synbiotics and insulin sensitivity. Nutr Res Rev. 2018;31:35–51.
130. Muccioli GG, Naslain D, Bäckhed F, Reigstad CS, Lambert DM, Delzenne NM, et al. The endocannabinoid system links gut microbiota to adipogenesis. Molecular Systems Biology [Internet]. 2010 [cited 2018 Aug 3];6. Available from: http://msb.embopress.org/cgi/doi/10.1038/msb.2010.46
131. Geurts L, Lazarevic V, Derrien M, Everard A, Van Roye M, Knauf C, et al. Altered Gut Microbiota and Endocannabinoid System Tone in Obese and Diabetic Leptin-Resistant Mice: Impact on Apelin Regulation in Adipose Tissue. Front Microbiol [Internet]. 2011 [cited 2018 Aug 3];2. Available from: https://www.frontiersin.org/articles/10.3389/fmicb.2011.00149/full
132. Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, et al. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. PNAS. 2013;110:9066–71.
133. Evaluation of the Effects Associated With the Administration of Akkermansia Muciniphila on Parameters of Metabolic Syndrome - Full Text View - ClinicalTrials.gov [Internet]. [cited 2019 May 14]. Available from: https://clinicaltrials.gov/ct2/show/NCT02637115
134. Brodie JS, Di Marzo V, Guy GW. Polypharmacology shakes hands with complex Aetiopathology. Trends Pharmacol Sci. 2015;36:802–21.
135. Piscitelli F, Carta G, Bisogno T, Murru E, Cordeddu L, Berge K, et al. Effect of dietary krill oil supplementation on the endocannabinoidome of metabolically relevant tissues from high-fat-fed mice. Nutr Metab (Lond). 2011;8:51.
136. Demizieux L, Piscitelli F, Troy-Fioramonti S, Iannotti FA, Borrino S, Gresti J, et al. Early low-fat diet enriched with linolenic acid reduces liver endocannabinoid tone and improves late glycemic control after a high-fat diet challenge in mice. Diabetes. 2016;65:1824–37.