British Journal of Pharmacology

British Journal of Pharmacology (2017) **174** 1464–1483 1464

Themed Section: Principles of Pharmacological Research of Nutraceuticals

REVIEW ARTICLE

Cannabimimetic phytochemicals in the diet – an evolutionary link to food selection and metabolic stress adaptation?*

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Received 6 July 2016; **Revised** 5 November 2016; **Accepted** 13 November 2016

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*Paper dedicated to Prof. em. Dr. Dr. hc Otto Sticher on the occasion of his 80th birthday.

The endocannabinoid system (ECS) is a major lipid signalling network that plays important pro-homeostatic (allostatic) roles not only in the nervous system but also in peripheral organs. There is increasing evidence that there is a dietary component in the modulation of the ECS. Cannabinoid receptors in hominids co-evolved with diet, and the ECS constitutes a feedback loop for food selection and energy metabolism. Here, it is postulated that the mismatch of ancient lipid genes of hunter-gatherers and pastoralists with the high-carbohydrate diet introduced by agriculture could be compensated for via dietary modulation of the ECS. In addition to the fatty acid precursors of endocannabinoids, the potential role of dietary cannabimimetic phytochemicals in agriculturist nutrition is discussed. Dietary secondary metabolites from vegetables and spices able to enhance the activity of cannabinoid-type 2 (CB_2) receptors may provide adaptive metabolic advantages and counteract inflammation. In contrast, chronic CB_1 receptor activation in hedonic obese individuals may enhance pathophysiological processes related to hyperlipidaemia, diabetes, hepatorenal inflammation and cardiometabolic risk. Food able to modulate the CB_1/CB_2 receptor activation ratio may thus play a role in the nutrition transition of Western high-calorie diets. In this review, the interplay between diet and the ECS is highlighted from an evolutionary perspective. The emerging potential of cannabimimetic food as a nutraceutical strategy is critically discussed.

LINKED ARTICLES

This article is part of a themed section on Principles of Pharmacological Research of Nutraceuticals. To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v174.11/issuetoc

Abbreviations

2-AG, 2-arachidonoyl glycerol; AA, arachidonic acid; AEA, *N*-arachidonoylethanolamine, anandamide; apoE, apolipoprotein E; BAT, brown adipose tissue; BCP, β-caryophyllene; CNR1, gene encoding CB_1 receptors; DHA, docosahexaenoic acid; DIM, 3,3′-diindolylmethane; EC, endocannabinoid; ECS, endocannabinoid system; EPA, eicosapentanoic acid; FAAH, fatty acid amide hydrolase; NAE, N-acylethanolamine; PEA, palmitoylethanolamide; PUFA, polyunsaturated fatty acid; SNP, single nucleotide polymorphism; T2DM, diabetes mellitus type 2; THC, Δ^9-tetrahydrocannabinol; TRPV1, transient receptor potential vanilloid 1

DOI:10.1111/bph.13676

Tables of Links

TARGETS	
GPCRs[a]	**Enzymes**[e]
AMY_1 receptor	ALDH2
CB_1 receptor	COX-2
CB_2 receptor	FAAH (FAAH1)
GPR55	MAGL (MGL)
Ligand-gated ion channels[b]	PLA_2
$GABA_A$ receptor	
NMDA receptor	
Voltage-gated ion channels[c]	
TRPV1	
Nuclear hormone receptors[d]	
PPARγ	

LIGANDS	
2-AG	EPA
AA (arachidonic acid)	GLP-1
AEA	PEA
DHA	THC

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.*, 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 ([a,b,c,d,e]Alexander *et al.*, 2015a,b,c,d,e).

The endocannabinoid system (ECS) is an ancient panorgan eicosanoid signalling network in which arachidonic acid (AA) derived lipids act in concert with particular receptors and enzymes resulting in the complex modulation of numerous central and peripheral physiological and pathophysiological processes (Pertwee, 2005, 2009; Di Marzo, 2008a; Pacher and Mechoulam, 2011; DiPatrizio and Piomelli, 2015). The ECS comprises classical GPCR cannabinoid receptors (CB_1 and CB_2) and potentially also the orphan receptor GPR55 (Pertwee, 2007; Ryberg *et al.*, 2007), which are differentially activated by the endocannabinoids (ECs) 2-arachidonoyl glycerol (2-AG) and *N*-arachidonoylethanolamine (anandamide, AEA) (Devane *et al.*, 1992; Mechoulam *et al.*, 1995; Sugiura *et al.*, 1995; Hanus, 2009). AEA and 2-AG, which are generated from discrete phospholipid precursors at the inner cellular membrane leaflet, also modulate different ion channels and nuclear receptors, like, for example, transient receptor potential vanilloid 1 (TRPV1), $GABA_A$ receptors and PPAR-γ (O'Sullivan, 2007; Ross, 2009; De Petrocellis and Di Marzo, 2010; Pertwee, 2010; Sigel *et al.*, 2011). Importantly, the enzymes degrading the ECs AEA and 2-AG, namely, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), but also α-β hydrolases-6 (ABHD6) have been shown to regulate local and paracrine EC concentrations (Di Marzo, 2008a; Marrs *et al.*, 2010). In inflamed tissue, COX-2 catalyses the oxygenation of both AA and ECs, leading to an additional control of tissue EC concentration during inflammation (Hermanson *et al.*, 2014). Finally, there is an as yet unidentified facilitated EC cellular reuptake mechanism in certain neuronal cell types and immune cells that can be selectively inhibited and may thus present another level of biological regulation (Nicolussi and Gertsch, 2015). CB_1 receptors are involved in the control of behaviour (e.g. motivation, reward, memory processing and habituation to stress) and are thus expressed widely in the CNS where they act as major neuronal circuit breakers, generating a negative retrograde feedback at both glutamatergic and GABAergic synapses in the CNS (Freund *et al.*, 2003; Kano, 2014). CB_1 receptors are not only among the most frequent GPCR species in the brain, but functional CB_1 receptors are also expressed peripherally and overall probably evolved under the selection pressure of fundamental physiological stress stimuli (Bowles *et al.*, 2015; Morena *et al.*, 2016). These include physical activity, famine, the fight or flight response, traumata and microbial infections. The peripheral signal transduction pathways of CB_1 receptors are still poorly understood. Activation of the ECS is associated with the major stress response (i.e. via the hypothalamic pituitary adrenal axis) or just physical activity (Tantimonaco *et al.*, 2014). While the glucocorticoid receptor regulates expression of the CNR1 gene encoding CB_1 receptors (Hillard, 2014), ECs modulate stress factors in the brain (McEwen *et al.*, 2015). This regulation appears to be dynamic and not static. For instance, studies in rodents indicate that acute glucocorticoid administration enhances the activity of ECs whereas chronic exposure to glucocorticoids down-regulates the ECS (McPartland *et al.*, 2014). In healthy mammals, CB_1 receptor signalling may facilitate their survival after excessive physical activity, stress and trauma by restoring homeostasis, suppressing negative memories and reducing anxiety at the level of the CNS (Ruehle *et al.*, 2012), as well as reactivating appetite and catabolic processes at the peripheral level (Watkins and Kim, 2015). The CB_1 receptor-mediated neuronal responses are linked to central reward and motivation (Hernandez and Cheer, 2015), and hedonically positive sensory properties of food lead to activation of CB_1 receptor-mediated reward circuits, which control food selection in rodents (DiPatrizio and Simansky, 2008; Deshmukh and Sharma, 2012; Hernandez and Cheer, 2012; Thompson *et al.*, 2016). The selection of palatable food (i.e. lipid and sugar craving) is already present in newborns. It has been shown that milk suckling in newborns is partly mediated via CB_1 receptor activation (Mechoulam *et al.*, 2006). Accordingly, CB_1 receptors are present in taste buds, and their activation enhances neural responses to sweet foods (DiPatrizio and Piomelli, 2012). Milk

is also a significant source of AA, which can trigger EC biosynthesis in the brain (Berger *et al.*, 2001), thus having potentially broad physiological effects. ECs are not only involved in the initiation of suckling and, therefore, in the feeding and growth of the offspring but also impact behaviour (Manduca *et al.*, 2012). The amount of 2-AG in human milk is in the range of 7–20 nM, that is, close to receptor-active concentrations and about 100 times higher than AEA (Di Marzo *et al.*, 1998). Distinct dairy fat compositions have been shown to modulate the levels of ECs in plasma in a yet poorly understood manner (Pintus *et al.*, 2013; Dunn *et al.*, 2014). It remains unclear whether fat intake in humans is directly linked to ECS-mediated pathophysiological effects (i.e. via chronic CB_1 receptor activation). For instance, carnivores and pastoralists ingest ECs and significant amounts of the EC precursor AA from raw meat or dairy products without adverse effects. While the ingestion of ECs may not lead to systemic physiological effects beyond the gastrointestinal (GI) tract because they are locally metabolized (Di Marzo *et al.*, 1998), the modulation of the EC concentrations by bioavailable polyunsaturated fatty acids (PUFAs) like AA is well described and will be discussed below.

Experiments with genetically modified mice have shown that central CB_1 receptors can exert paradoxical effects on food intake, depending on whether they are localized to presynaptic terminals of excitatory or inhibitory neurons (Bellocchio *et al.*, 2010). In order to better understand this apparent hormetic complexity, the functioning of the ECS needs be put into context with evolution, that is, the environmental selection pressures and dietary habits, which are very different among different mammals, but also between distinct human populations (e.g. hunter-gatherers versus Western societies or upon the introduction of agriculture). Comparisons with great apes and the fossil and archaeological records suggest that among the most important changes in diet was an increase in plant carbohydrates during human evolution (Aiello and Wells, 2002). Generally, in the context of high-calorie diets as found in plant starch farming societies, chronic CB_1 receptor activation is associated with increased obesity, an unfavourable lipid profile, insulin resistance, exacerbation of inflammation in the liver and kidney (Di Marzo, 2008b; Gruden *et al.*, 2016) and cardiometabolic risk (Janero, 2012).In contrast, CB_2 receptors, which show 68% homology to CB_1 receptors in the transmembrane region, appear to be primarily expressed in the periphery in immune cells like monocytes/macrophages where they negatively modulate inflammatory stress, for example, via attenuation of Toll-like receptor-induced signal transduction pathways (Tomar *et al.*, 2015). In the liver and kidney, CB_2 receptor activation is clearly protective (Pacher and Mechoulam, 2011). Many other cell types seem to express low amounts of CB_2 receptors, although they may not be present functionally at the cell surface (Kleyer *et al.*, 2012). CB_2 receptors have been shown to protect tissues from fibrotic processes, possibly also by modulating macrophage polarization (Pacher and Mechoulam, 2011; Gertsch, 2016). Intriguingly, CB_2 receptors have more recently been shown to stimulate a number of positive metabolic processes leading to antidiabetic effects and cardiometabolic protection (*vide infra*). As proposed here, one role of CB_2 receptors in diet-driven metabolic processes could be to antagonize the pathophysiological metabolic effects mediated by CB_1 receptors, at least in a high-calorie and pro-inflammatory dietary context. Although CB_2 receptors in the brain are clearly expressed in microglia cells (Maresz *et al.*, 2005), the presence or physiological relevance of functional CB_2 receptors in subsets of neurons is still debated. Importantly, both CB receptors play pro-homeostatic physiological roles, which may however differ in distinct animal species. The metabolic effects of the overall EC concentrations in tissues are clearly complex as these lipids are promiscuous in their action (Di Marzo and De Petrocellis, 2012) and in addition to CB receptors also target different channels and nuclear receptors (*vide supra*). For instance, AEA also activates the PPARs (O'Sullivan, 2007), a family of transcription factors that regulate energy balance by promoting either energy deposition or energy dissipation (Medina-Gomez *et al.*, 2007). Under normal physiological conditions, PPARγ is mainly expressed in adipose tissue together with CB_1 receptors where it regulates diverse functions such as the development of fat cells and their capacity to store lipids. Since there are numerous PPAR modulators (e.g. PPARγ activators) in vegetable diets (Wang *et al.*, 2014; Li *et al.*, 2015), PPAR-active phytochemicals in diet may play a co-regulatory role in modulating the ECS. From an evolutionary perspective, depending on dietary habits, the role of the ECS in energy metabolism could be distinctly different between herbivores, carnivores and omnivores. The ECS is also a regulator of intestinal function and the brain-gut axis. It generally inhibits neural activity in pathways involved in the physiological regulation of the GI tract, including visceral sensation, pain, motility but also different forms of inflammation (Izzo, 2007; Izzo *et al.*, 2015; Sharkey and Wiley, 2016). The dysregulation of the ECS has been implicated in numerous human diseases, and its pharmacological modulation is a very promising strategy to prevent or treat inflammatory, neurodegenerative, cardiovascular, metabolic disorders, ischaemia damage, as well as pain and maybe certain types of cancer (Di Marzo, 2008a; Pacher, 2009; Maccarrone *et al.*, 2015).

Although several comprehensive reviews on the connection between diet and the ECS have been published (Matias *et al.*, 2006; Osei-Hyiaman *et al.*, 2006; Carr *et al.*, 2008; Di Marzo *et al.*, 2009; DiPatrizio and Piomelli, 2012; Bisogno and Maccarrone, 2014; Kleberg *et al.*, 2014), little emphasis has been put on the evolutionary context and the differential roles CB_1 and CB_2 receptors might play in food selection and metabolic stress. One exception is the excellent review by DiPatrizio and Piomelli (2012) providing open questions on the role of the CB_1 receptors in energy needs and maintaining metabolic balance in mammals. Here, an evolutionary perspective on the link between diet and the ECS is provided, with emphasis on the changes introduced by agriculture and potential health implications of a 'cannabimimetic diet'.

Cannabimimetics in the plant kingdom and vegetable food

Secondary metabolism in plants is an enormously rich source of chemically diverse molecules (Firn and Jones, 2003; Koch *et al.*, 2005), and it is therefore not surprising to find numerous biologically active natural products in plants, including food plants (Nilius and Appendino, 2013; Atanasov *et al.*, 2015, Russo, 2016). From a phylogenetic perspective,

secondary metabolite ligands of mammalian receptors do already occur in the plant kingdom. Apart from peptides, virtually all neurotransmitters and hormones have already been 'invented' by plants and fungi (Murch, 2006), pointing towards receptor evolution driven by chemical environmental selection pressures (i.e. ligand-based selection of mutations based on function). Nevertheless, chemical diversity in plants is shaped by environmental conditions and predation pressure, leading to vitamin-like (i.e. essential), nonspecific (Gertsch, 2016) or even xenohormetic secondary metabolites (Lamming *et al.*, 2004; Howitz and Sinclair, 2008) in the Animalia food pyramid. Neurotransmitters, modulators and hormones naturally have very short half-lives and are not generally orally bioavailable due to the metabolic enzymes present in most tissues, including the GI tract. Noteworthy, ECs are present widely in lower plants, including mosses and ferns but not in flowering plants that serve as food for mammals (Gachet *et al.*, 2017). However, based on the chemotype diversity and substrate plasticity of secondary metabolism, numerous 'similars' are being produced from related chemical scaffolds, mimicking or modulating the action of mammalian receptor ligands or enzyme substrates (Appendino *et al.*, 2014). If such phytochemicals by chance have a better metabolic stability than an endogenous ligand, they are likely to exert targeted pharmacological effects. Through diet, such effects can be chronic. In the context of this short review and perspective, Δ^9-tetrahydrocannabinol (THC) from *Cannabis sativa* L. mimics the effects of 2-AG and AEA by activating cannabinoid receptors, a coincidence that has led to the medicinal and recreational use and cultivation of this plant species and ultimately the discovery of the ECS (Mechoulam, 2002). Nutritious cannabis seeds lacking phytocannabinoids have played a role as food and have been cultivated since millennia (Chen *et al.*, 2012). Although the ECS has been elucidated thanks to research on phytocannabinoids from cannabis, there are food-derived natural products that are able to indirectly modulate this system, at least in the periphery. Given the apparent prominent modulatory role of the ECS in energy metabolism, the elucidation of ECS active dietary factors beyond common nutrients could serve as basis to search for a covariance between genes and diet.

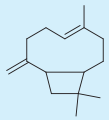
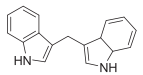
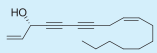
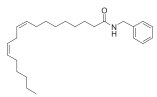
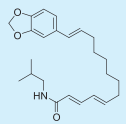
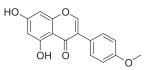
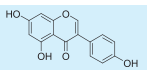
In order to identify secondary metabolite signatures in plants that potentially modulate ECS proteins, we are currently screening global plant extract libraries within the frameworks of MedPlant.EU and the Swiss NCCR TransCure. Different widespread (canonical) triterpenoids have already been shown to inhibit metabolic enzymes of the major EC 2-AG (King *et al.*, 2009; Bento *et al.*, 2011b; Chicca *et al.*, 2012; Parkkari *et al.*, 2014), ubiquitous plant flavonoids were found to inhibit FAAH, the metabolic enzyme degrading AEA and other *N*-acylethanolamines (NAEs) (Thors *et al.*, 2007; 2008; 2010) and to weakly modulate CB receptors (Khedr *et al.*, 2016) (Table 1). Intriguingly, the ubiquitous plant sesquiterpene β-caryophyllene (BCP) has been shown to exert potent CB_2 receptor-mediated cannabimimetic effects in mice (Gertsch, 2008; Gertsch *et al.*, 2008; Bento *et al.*, 2011a; Horváth *et al.*, 2012; Cheng *et al.*, 2014; Klauke *et al.*, 2014) and *N*-alkylamides from maca (*Lepidium meyenii* Walp.) and black pepper (*Piper nigrum* L.) show cannabimimetic effects *in vitro* and *in vivo* respectively (Hajdu *et al.*, 2014; Nicolussi *et al.*, 2014). The polyacetylene falcarinol (carotatoxin) present in carrots and other vegetables was shown to inhibit CB_1 receptor activation by AEA *in vitro* (Leonti *et al.*, 2010). Several isoprenylated analogues of the naturally occurring plant stilbenoid trans-resveratrol bind to both CB_1 and CB_2 receptors with low affinity (Brents *et al.*, 2012). The widespread dietary triterpnoids oleanolic acid (present in olive oil) and ursolic acid (Table 1) have been shown to inhibit ABDH12 (Parkkari *et al.*, 2014), an enzyme that controls 2-AG levels in immune cells. Thus, different dietary phytochemicals have already been shown to directly or indirectly modulate the ECS (here referred to as cannabimimetics) (Gertsch *et al.*, 2010; Russo, 2016). The emerging question is whether such phytochemicals in spices and food are bioavailable and exert physiological effects *in vivo* and how diet modulates the ECS and *vice versa*? Currently, the best evidence of a dietary link to ECS modulation stems from studies on PUFAs, that is, the indirect effects of Ω6 and Ω3 fatty acids on EC production and/or ECS proteins (*vide infra*). Yet the more recent discovery of CB_2 receptor-selective cannabimimetics in spices may play a widely unrecognized physiological role, coinciding with the emerging evidence that certain spices and vegetables in the diet can reduce the risk of metabolic syndrome and diabetes mellitus type 2 (T2DM) and associated risk factors (Sikand *et al.*, 2015).

The endocannabinoid food-medicine continuum in the context of life-style

Bioactive phytochemicals form the molecular basis of the food-medicine continuum, which has its origin in the co-evolution of diet and biochemical processes underlying animal physiology (Etkin and Ross, 1982; Johns, 1990; Moerman, 1996; Heinrich and Prieto, 2008). Just like essential fatty acids and vitamins have evolved from the constant animal–plant interactions in time and space, there are probably numerous yet poorly understood dietary biochemical modulations that shape our fitness. Almost certainly, many of these plant–animal interactions remain to be discovered. Based on the concept of phytochemical network pharmacology (Hopkins, 2008; Gertsch, 2011), weak yet constant modulatory effects on different nodes of the ECS (even below detection *in vitro*) may suffice to exert significant physiological effects over time. Such effects are of particular relevance for dietary interventions. As illustrated by recent genetic association studies with CB receptors (*vide infra*), dietary selection pressures might also explain some of the pronounced species differences observed with ligands targeting cannabinoid receptors, in particular CB_2 receptors (McPartland *et al.*, 2007). The development of the ECS reflects convergent, divergent and parallel evolution involving duplications and mutations of EC receptors, resulting in gene extinctions or new structures/functions (McPartland *et al.*, 2006). Given the importance of the constant flux of phytochemicals from vegetable food, some of these later adaptive events may have been associated with dietary changes, such as the introduction of agriculture and the differential use of spices rich in cannabimimetics (*vide infra*). For instance, a recent study has shown that the continuous consumption of Ω3 PUFAs by the Inuit in Greenland causes dietary genetic and

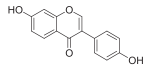
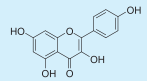
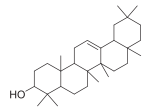
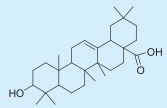
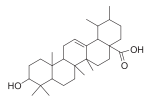
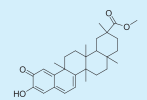
Table 1

Phytochemicals in diet that may modulate the ECS

Plant secondary metabolite	Chemical structure	Dietary origin	Target/effect	Potency (IC_{50}, K_i)/ efficacy	*In vivo* evidence	Selected references
BCP		Most widespread, numerous food plants, spices	CB_2 receptoragonist	~200 nM/ partial (*in vitro*), full (*in vivo*)	strong	Gertsch *et al.*, 2008; Horváth *et al.*, 2012; Klauke *et al.*, 2014
DIM		Brassicaceae vegetables	CB_2 receptor agonist	~1 μM/partial	missing	Yin *et al.*, 2009
Falcarinol		Apiaceae, carrots (*Daucus carrota*), ginseng	CB_1 receptor inverse agonist	~200 nM/full	missing (indirect)	Leonti *et al.*, 2010
Macamide		Macca (*Lepidium meyenii*)	AEA reuptake inhibitor (CB_1 binding)	~200 nM/partial	missing	Hajdu *et al.*, 2014
Guineensine		*Piper* spp., black pepper	AEA reuptake inhibitor	~200 nM/full	good	Nicolussi *et al.*, 2014
Biochanin A		Soybeans (*Glycine max*), chickpeas (*Cicer arietinum*)	FAAH1 inhibitor	0.5–2 μM/full	some	Thors *et al.*, 2010
Genistein		Fava beans (*Vicia faba*), lupin (*Lupinus* spp.), soy	FAAH inhibitor/AEA uptake inhibitor	1–3 μM/full	missing	Thors *et al.*, 2007; Thors *et al.*, 2010

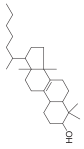
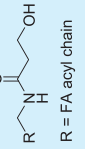
continues

Table 1 (Continued)

Plant secondary metabolite	Chemical structure	Dietary origin	Target/effect	Potency (IC_{50}, K_i)/ efficacy	*In vivo* evidence	Selected references
Daidzein		Fava beans (*Vicia faba*), lupin (*Lupinus* spp.), soy	FAAH inhibitor/AEA uptake inhibitor	2–4 μM/full	missing	Thors *et al.*, 2007; Thors *et al.*, 2010
Kaempferol		Widespread in food plants	FAAH inhibitor	2–4 μM	missing	Thors *et al.*, 2008
β-amyrin		Widespread in vegetables	MAGL/ABHD6/ ABHD12 inhibitor	~1 μM/partial	some	Bento *et al.*, 2011b; Chicca *et al.*, 2012
Oleanolic acid		Relatively widespread in food plants (olive oil)	ABHD12 inhibitor	~1.5 μM/full	some	Parkkari *et al.*, 2014
Ursolic acid		Widespread in food plants	ABHD12 inhibitor	~2 μM/partial	missing	Parkkari *et al.*, 2014
Pristimerin		Scarce in food, Celastraceae	MAGL inhibitor	100 nM/full reversible	missing	King *et al.*, 2009

continues

Table 1 (Continued)

Plant secondary metabolite	Chemical structure	Dietary origin	Target/effect	Potency (IC_{50}, K_i)/ efficacy	*In vivo* evidence	Selected references
Euphol		Scarce in food	MAGL inhibitor	300 nM/ full reversible	missing	King *et al.*, 2009
NAEs	 R = FA acyl chain	Present in higher plants, widespread in fresh food plants	FAAH and NAAA inhibitors	nM metabolized *in vivo*	some	Gachet *et al.*, 2017; Petrosino and Di Marzo, 2017

physiological adaptations reflected by mutations in desaturase genes (Fumagalli *et al.*, 2015). Therefore, dietary habits can change physiology within a relatively short time span (~10 000 years) via both genetic and epigenetic mechanisms. Despite the fact that some ECS genes show evidence of adaptive evolution, the system is under strong purifying selection (McPartland *et al.*, 2007), suggesting that diet could indeed be a major factor in this process.

As reviewed by Leonard *et al.* (2010), research in human evolutionary biology has shown that many of the key features that distinguish humans from other primates (e.g. our large brain size) also have implications for our distinctive nutritional needs (Aiello and Wheeler, 1995; Leonard and Robertson, 1997; Leonard, 2002). To accommodate the metabolic demands of our large brains, humans consume diets that are very dense in energy and nutrients. For instance, there are intriguing differences in lipid consumption between humans and monkeys (*vide infra*) revealing that humans strictly prefer lipid-rich foods (Montmayeur and le Coutre, 2010). CB_1 receptor activation is associated with increased energy intake and decrease energy expenditure by controlling the activity of neural pathways involved in the sensing and hedonic processing of fatty foods (DiPatrizio and Piomelli, 2012). Consequently, the ECS is a lipid signalling network that has implications for lipid intake. In the gut, ECs may promote fat intake by activating CB_1 receptors on vagal fibres and enteric neurons (Izzo and Sharkey, 2010). Kirkham (2009) further emphasized the central role of the ECS to process lipid food stimuli that exert an influence over consumption via innate and learned appetites, generating the complex psychological experiences of hunger, lipid craving and delight independently of energy status. As pointed out by Leonard *et al.* (2010), in contrast to the levels seen in human populations, monkeys obtain only a small share of calories from dietary fat. Popovich *et al.* (1997) estimated that lowland gorillas derive only approximately 3% of their energy from dietary fats. The need for an energy-rich diet in Paleolithic and Neolithic times has shaped our ability to detect and metabolize high-fat foods. Food preferences are based on lipid sensory inputs (Sclafani, 2001; Gaillard *et al.*, 2008; Le Coutre and Schmitt, 2008) and that our brains have the ability to assess the energy content of foods with remarkable accuracy (Toepel *et al.*, 2009). Additionally, compared with monkeys, humans have an enhanced capacity to digest and metabolize higher fat diets. Our GI tract has an expanded small intestine and reduced colon, consistent with the consumption of a high-quality diet consisting of large amounts of animal food (Milton, 1987). Since natural fat intake differs widely between animal species, the translation from animal studies to humans needs to be interpreted with care. In contrast to most non-carnivorous animals, humans ingest significant amounts of AA through animal products like meat, dairy products and eggs (an estimated 0.1–0.6 $g \cdot day^{-1}$). In contrast to the fish and algae-derived Ω3 PUFAs docosahexaenoic acid (DHA) and eicosapentanoic acid (EPA), which tend to lower EC levels, the intake of AA has been shown by different studies to be associated with increased EC levels in different tissues (reviewed in McPartland *et al.*, 2014). The consumption of Ω3 and Ω6 essential fatty acids in Western diets (USA) has changed markedly with industrialization, with an increase in γ-linoleic acid (LA)

availability from an estimated 3% to about 8% of energy supply (Blasbalg *et al.*, 2011). Higher food plants (Angiosperms), which constitute most of mammalian vegetable diet, do not generally synthesize AA but the precursor LA that is essential for AA biosynthesis in animals. Although high AA intake has been associated with pro-oxidative and inflammatory systemic responses (Ferretti *et al.*, 1997; Ling *et al.*, 2012) and some evidence suggests that the consumption of a diet high in AA is associated with the development of leptin resistance and obesity (Cheng *et al.*, 2015), the role of this Ω6 PUFA is pleiotropic and complex (playing distinct positive and negative roles in different circumstances). Recent data suggest that there is even a possibility of chronic AA administration having a reducing anti-inflammatory effect on the kidney (Katakura *et al.*, 2015). Moreover, no evidence is available from randomized, controlled intervention studies among healthy, noninfant humans to show that addition of the AA precursor LA to the diet increases the concentration of inflammatory markers (Johnson and Fritsche, 2012). Biochemically, dietary AA is incorporated into membrane phospholipids from where it is released by a PLA_2-mediated enzymatic hydrolysis or exists as triacylglycerol. Free AA (arachidonate) can either be tissue and/or inflammation-dependently metabolized into prostaglandins, leukotrienes, thromboxanes, prostacyclin or ECs. 2-AG is a significant precursor (store) of AA in brain that is regulated via 2-AG hydrolysis (Nomura *et al.*, 2011). Overall, AA intake is of fundamental importance for human brain development where AA and DHA constitute the major PUFAs in the CNS. The vital importance of AA was shown by a FADS1 KO study in which AA supplementation prevented the lethal phenotype (Fan *et al.*, 2012). To assure there are sufficient amounts of AA in the brain, rather than generating AA *de novo* from LA, our organs seem to preferentially take it from diet. Dietary AA seems to be efficiently taken up and transported into different organ tissues, including the liver and brain by poorly understood mechanisms. It has been shown that orally ingested labelled arachidonate is directly incorporated into phospholipids of the brain and other organs (Likhodii and Cunnane, 1999). A recent LC–MS/MS study revealed that plasma concentrations of AA in human, young healthy individuals are in the range of 2.5–8 μM and inversely correlate with cortisol levels (Gachet *et al.*, 2015; Gachet and Gertsch, 2016). In streptozotocin-induced diabetes animal models, AA was found to be depleted and Δ5-desaturation inhibition described as a fundamental feature of diabetes (Holman *et al.*, 1983). A more recent study showed that a lower AA/dihomo-γ-linolenic acid ratio is associated with metabolic abnormalities in obese individuals (Zhao *et al.*, 2016). The current literature on human studies with Ω3 PUFA enriched diets (e.g. krill, *Euphausia superba* Dana oil) on the effects of the ECS is somewhat unclear and may reflect differences between human populations. In obese individuals, the Ω6/Ω3 PUFA ratio in plasma generally correlates with a decrease in EC levels (Banni *et al.*, 2011). It has been suggested that early dietary interventions based on Ω3 PUFAs may represent an alternative strategy to drugs for reducing endocannabinoid tone and improving metabolic parameters in the metabolic syndrome (Demizieux *et al.*, 2016). For example, krill diet let to a concomitant reduction of triglyceridaemia and EC levels and was associated with a decreased waist/hip and visceral fat/skeletal muscle mass ratio (Berge *et al.*, 2013). In this study, it was suggested that treatments with krill formulations may produce different effects on plasma EC levels depending on different cohorts of subjects, duration of treatments (4 vs. 24 weeks) and dosage (2 vs. 4 $g \cdot day^{-1}$). Most likely, the effects of PUFAs on the human ECS strictly depend on the lifestyle. Accordingly, hunter-gatherers and pastoralist societies such as the ones in the Sub-Saharan region do not show increased obesity or T2DM, despite their constant high intake of Ω6 PUFA (AA). Generally, a lower ratio of Ω6/Ω3 PUFAs is desirable in reducing the risk of many of the chronic diseases of high prevalence in industrialized societies or societies with high-carbohydrate intake (Simopoulos, 2002; Wang and Chan, 2015).

Finch and Stanford (2004) have shown that the evolution of key 'meat-adaptive' genes in hominid evolution, such as apolipoprotein E (apoE), are critical for the promotion of the enhanced lipid metabolism necessary for subsisting on diets with greater levels of animal material. A beneficial interplay between apoE and CB_1 receptor activation has been proposed (Zhao *et al.*, 2010; Bartelt *et al.*, 2011). In agreement with the concept of genetic adaptation to diet, the CB_1 (CNR1) single nucleotide polymorphism (SNP) 1359 G/A (p.Thr453Thr; rs1049353), a common polymorphism in Caucasians, has been reported to be associated with less fat intake (fatty acids and cholesterol) but more carbohydrate intake in obese females (de Luis *et al.*, 2016). The latter association is interesting as it could suggest that CB_1 receptors originally served to motivate lipid intake from meat are under dietary pressure in Western societies. Moreover, carriers of this SNP have a better lipid profile and a lower body mass index (Storr *et al.*, 2010; de Luis *et al.*, 2015). In contrast, in a small group of 60 diabetic individuals a lack of association of G1359A polymorphism with obesity, cardiovascular risk factors was reported (de Luis *et al.*, 2010). However, subjects with C385C genotype of FAAH1 showed an improvement in insulin and homeostatic model assessment-R levels with a high PUFA hypocaloric diet after losing weight for 3 months (de Luis *et al.*, 2013). In women with obesity, an overall association of the mutant-type group G1359A and A1359A with a better cardiovascular profile (triglyceride, high-density lipoprotein cholesterol, insulin and homeostasis model assessment levels) than the SNP lacking group was reported (de Luis *et al.*, 2011). These emerging human genetic data may suggest a possible purifying selection of genes in the ECS with respect to dietary habits.

If chronic CB_1 receptor activation in humans would cause consistent hyperphagia independently of lifestyle, beyond the well-documented acute appetite-stimulating effects, and/or foster insulin resistance or T2DM, then this should be clearly observed in the human populations that regularly smoke high THC cannabis for recreational purposes. THC is a potent partial human CB_1 receptor agonist but only a very inefficient human CB_2 receptor agonist, at least *in vitro*. Indeed, acute cannabis use is classically associated with snacking behaviour (munchies). Studies generally suggest that acute cannabis use stimulates appetite, also in the therapeutic context of hypohagia in AIDS and cancer patients (Whiting *et al.*, 2015). Nevertheless, as for large epidemiological studies in the general population, findings consistently indicate that cannabis users tend to have rather lower body

mass indices than nonusers (Hayatbakhsh *et al.*, 2010). The reason for this discrepancy between animal studies and humans and the overall unclear picture could be that cannabis consumers have a differential stress response from the rest of the population, and above all, they are not generally obese. Perceived stress, emotional eating, anhedonia, depression, dietary restraint and disinhibition are risk factors for obesity. Consequently, neuropsychological effects counteracting stress through cannabis consumption may mask the molecular mechanisms studied in mice. Although in one human study chronic cannabis smoking was associated with visceral adiposity and adipose tissue insulin resistance (Muniyappa *et al.*, 2013), there is no explicit evidence that cannabis smoking causes insulin resistance or T2DM (Alshaarawy and Anthony, 2015). Nevertheless, a recent study has shown that increased years of cannabis or cigarette smoking are important factors in metabolic health (Yankey *et al.*, 2016), concluding that each year increase in marijuana use was significantly associated (maybe not causative) with increased odds of metabolic syndrome and hypertension. From a mechanistic point of view, the best evidence for the negative metabolic effects mediated via CB_1 receptors stems from animal experiments. Chronic CB_1 receptor activation in mice clearly causes obesity-related insulin resistance; this is probably mediated by hepatic CB_1 receptor-induced inhibition of insulin signalling and clearance (Liu *et al.*, 2012; Picone and Kendall, 2015). Moreover, peripherally restricted CB_1 receptor antagonists retain efficacy in reducing weight and improving metabolic abnormalities in mouse models of obesity (Kunos and Tam, 2011).

The function of CB_1 receptors may make sense in the context of hunter-gatherer nutrition where fat is the primary nutrient and physical activity is high, but might have led to a conflict with high-carbohydrate intake in professional agriculturist nutrition. An emerging question is whether different lifestyles determine the role of the ECS in allostasis. Diets of hunter-gatherers show substantial variation in their carbohydrate content. However, the range of energy intake from carbohydrates in the diets of most hunter-gatherer societies is markedly lower from the amounts currently recommended for healthy Western humans (Ströhle and Hahn, 2011). In line with the extreme carbohydrate craving in humans, who have more copies of the salivary amylase genes than primates and thus more efficiently digest starch (Perry *et al.*, 2007), the onset of agriculture was probably one of the most dramatic and important developments in human history (Diamond, 2002). Carbohydrate farming incited the most important dietary transition, which is still ongoing to the present day of post-agriculturist nutrition (i.e. based on refined sugars). The generation and excess use of sugars could be seen in analogy to the detrimental impact of the first distilled alcohol on humans. The sudden availability of excess sugars in combination with fats in diet may have led to a collision of genes that evolved to cope with high energy demands due to constant physical activity (Neel, 1962). Excessive consumption of high-energy, palatable food without physical activity contributes to obesity, which results in the metabolic syndrome, heart disease and T2DM (Mazier *et al.*, 2015). In obese individuals, increased EC levels are also found in the liver, adipose tissue, pancreas and skeletal muscle, where they contribute to hepatic steatosis and insulin resistance, adipocyte hypertrophy and inflammation, reduced glucose uptake and oxygen consumption in the muscle and reduced beta cell function (Silvestri *et al.*, 2011; Cristino *et al.*, 2014a,b). Thus, CB_1 receptors may have evolved as pro-homeostatic (i.e. allostatic) receptors in the context of survival challenges (food restriction, fight or flight response, hunting, physical and psychological traumata) not entirely compatible with the lifestyles of contemporary post-agriculturists.

The introduction of cannabimimetic spices during agriculture

In 1997, Eaton *et al.* revisited their seminal paper on the dietary origin of chronic metabolic disorders as the result of a mismatch between ancient genes and high-calorie diets (Eaton and Konner, 1985; Eaton *et al.*, 1997). The multimillion year evolutionary process during nearly all of which genetic change reflected the life circumstances of our ancestors was suddenly disturbed by the introduction of agriculture about 12 000 years ago. Dietary carbohydrates once essential for the cognitive and social development of Paleolithic humans gradually turned into a metabolic stress factor as a function of their glycaemic indices. Epidemiological evidence points towards a pandemic diet-induced glucotoxicity due to excess sugar intake (Hite *et al.*, 2011). Likewise, excessive intake of fat can lead to lipotoxic pathophysiological effects, yet there is a more direct strong link between glucotoxicity and the metabolic syndrome and T2DM in humans (Guldbrand *et al.*, 2014). The independent Swedish Council on Health Technology Assessment has concluded that dietary fat is not associated with obesity (Hansen, 2013) and, consequently, T2DM and cardiometabolic risk. The committee reviewed 16 000 studies published through until 2013 and recommended that a low-carbohydrate, high-fat diet should be the most effective measure against obesity. Yet the reality of post-agriculturist societies is a concomitant high-carbohydrate and high-fat intake. Most of the rodent studies on the pathophysiological role of the ECS in energy homeostasis stem from high-fat diets and not from high-carbohydrate diets, with few exceptions. Interestingly, CB_1 receptor inverse agonist/antagonist-treated rats fed with either high fat or high-carbohydrate diet showed differential responses (Rivera *et al.*, 2013), indicating that the dietary context for the role of the ECS is important.

With the onset of agriculture, the cultivation and consumption of green leafy vegetables and spices was also initiated. The regular use of green leafy vegetables and spices can be seen as an innovation of agriculturists as both an adaptive process to environment and taste (Heinrich *et al.*, 2006; Krebs, 2009; Leonti, 2012). Spices are typically rich in essential oils and terpenes, thus providing a source of potential lipid modulators of the endogenous lipid systems, including the ECS, TRP channels (TRPV1 and TRPA1), the PPARs and the overall eicosanoid system (see also Russo, 2016). Just like salt increases the palatability of food, certain hot or flavoured spices can do the same. However, there are many spices in agriculturist diets that exert pharmacological effects. For instance, phenylpropanoids from ginger (*Zingiber officinale* L.) have been shown to pleiotropically interfere with the arachidonate signalling system by targeting COX-2 (van Breemen *et al.*, 2011) and PLA_2 (Nievergelt *et al.*, 2011),

leading to potent anti-inflammatory effects by disrupting IL-1β expression (Nievergelt *et al.*, 2011). Numerous plant volatiles among spices modulate ion channels (Maffei *et al.*, 2011), such as TRPV1 that signals to the ECS. NAEs like palmitoylethanolamide (PEA) are very abundant in flowering plants (Gachet *et al.*, 2017), which constitute a major source of food. Given the emerging pharmacology of PEA (Petrosino and Di Marzo, 2017), it will be interesting to assess the biological contribution and significance of NAEs from diet. Overall, this dietary adaptation to eating green leafy vegetables and spices rich in essential oils and NAEs may not be a coincidence but a biological function to counteract metabolic stress induced by the excessive carbohydrate intake. However, the epidemiological evidence does not portray a clear picture. As shown by a recent big epidemiological study from China, 'spicy food' was, quite unexpectedly, positively associated with body weight (Sun *et al.*, 2014). In Chinese cuisine, spicy food is more meat-based rather than vegetable-based with heavy salt and/or oil use for flavour and palatability, the primary spice being hot pepper (*Capsicum* spp.). This contrasts with the findings of other herbal spices that have been shown to reduce body weight and improve glucose tolerance (Grant *et al.*, 2009; Bower *et al.*, 2016; Sikand *et al.*, 2015). While the roles of vitamins, minerals and Ω3 PUFAs for human health have been studied in detail, the role of secondary plant metabolites that directly or indirectly interact with our physiology beyond flavonoids remains largely unknown. One reason for this is the enormous difficulties in studying mixtures of poorly bioavailable natural products *in vivo* (Gertsch, 2011). Nevertheless, the introduction of numerous spices during agriculture is intriguing and might reflect an adaptive process to high-calorie diets.

Diet-induced shifting of the CB_1/CB_2 receptor activation ratio?

Research from animal models but also humans (i.e. RIO studies with rimonabant) impressively shows that in high-calorie diets, CB_1 receptor activation is causally associated with obesity and the metabolic syndrome and thus directly modulates energy balance (Mazier *et al.*, 2015; Gatta-Cherifi and Cota, 2016). In metabolically healthy obese individuals, overactive CB_1 receptors in adipocytes, pancreas and liver may foster the onset of a metabolic syndrome, but probably not in non-obese individuals (Cable *et al.*, 2014). Therefore, a dietary CB_1 receptor antagonist in combination with high-calorie diets could potentially reduce the risk of CB_1 receptor-mediated metabolic pathologies in the context of high-calorie diets. The only dietary antagonist/inverse agonist of CB_1 receptors reported so far is the acetylenic oxylipin falcarinol, which predominantly occurs in carrots (*Daucus carota* L.), but also in many other Apiaceae vegetables such as parsley (*Petroselinum crispum* L.), celery (*Apium graveolens* L.), parsnips (*Pastinaca sativa* L.), fennel (*Foeniculum vulgare* Mill.) and in ginseng (*Panax ginseng* C.A. Meyer). This natural product was introduced into the human diet upon the transition from hunter-gatherers to agriculturists. In addition to apparently irreversibly inhibiting CB_1 receptors *in vitro* (Leonti *et al.*, 2010), falcarinol also covalently blocks the aldehyde dehydrogenase 2 family by alkylation of the active site (ALDH2; Heydenreuter *et al.*, 2015), activates nuclear factor erythroid-2 related factor 2 (Nrf2; Qu *et al.*, 2015) and weakly interacts with PPARγ (El-Houri *et al.*, 2015) and $GABA_A$ receptor subtypes (Czyzewska *et al.*, 2014). It was recently shown that falcarinol inhibits adipocyte differentiation and andipogenesis and improves glucose uptake (El-Houri *et al.*, 2015), but shows opposite effects on lipolysis to the CB_1 inverse agonist/antagonist rimonabant. Overall, the effect of falcarinol on adipogenesis would be in agreement with its inhibitory effects on CB_1 receptors. Purple carrot juice and β-carotene have been compared for their effects in a rat model of metabolic syndrome based on a high-carbohydrate, high-fat diet in which carrot juice improved glucose tolerance, as well as cardiovascular and hepatic structure and function independent of β-carotene (Poudyal *et al.*, 2010). Interestingly, significantly lower glucose, insulin and C-peptide responses and higher satiety scores were elicited with raw carrots than with microwaved ones in humans (Gustafsson *et al.*, 1995), which is in agreement with the loss of falcarinol content upon cooking. In a study addressing the effect of dosage on the metabolic response to vegetables added to a mixed lunch meal, it was found that the larger the carrot portion, the lower the glucose and insulin/C-peptide responses and the higher the satiety scores (Gustafsson *et al.*, 1994), which may suggest that the large carrot meals could provide sufficient falcarinol to exert this effect. A benefit of ginseng supplementation in improving glucose control and insulin sensitivity in patients with T2DM or impaired glucose intolerance has been concluded from a recent meta-analysis (Gui *et al.*, 2016). Although these data are promising, there is not yet any mechanistic *in vivo* evidence that this negative dietary mechanism on CB_1 receptor signalling exists.

More recent evidence points towards a protective action of CB_2 receptors in energy metabolism and diabetes (*vide infra*). Since many of the beneficial (i.e. therapeutic) effects mediated via CB_1 receptors can also be obtained with CB_2 receptor-selective agonists, which do not show any central side effects (Buckley, 2008; Pacher and Mechoulam, 2011), the emerging role of this cannabinoid receptor in the context of diet is remarkable. Although CB_2 receptors can enhance obesity and insulin resistance in high-fat diets in certain mouse strains (Deveaux *et al.*, 2009; Agudo *et al.*, 2010), CB_2 receptor activation seems, generally, to cause the opposite effects to those of CB_1 receptors in rodents (Rossi *et al.*, 2016; Verty *et al.*, 2015; Onaivi *et al.*, 2008). Unlike with the studies using CB_1 knockout mice, global CB_2 knockout mice, due to developmental adaptive processes, may not be suitable models to study the role of this receptor in energy balance and metabolism. Another problem could be the pronounced species differences in CB_2 receptors and the lack of knowledge of CB_2 receptors in humans, in particular in the context of high-fat diet. In light of the evolutionary discussion related to hunter-gatherer and pastoralist diet (*vide supra*), the possibility that in humans, high-fat diet more strongly activates CB_2 receptors than in mice cannot be excluded, thus compensating for CB_1 receptor activation. Therefore, data from rodents could be misleading. It would certainly be interesting to assess CB_2 receptor density and signalling in pastoralists. Nevertheless, CB_2 receptors play a role in inhibiting food intake in the satiated state in rats, whereas the CB_1 receptor promoted food intake in the fasted condition (Ting *et al.*, 2015).

A possible role for central cannabinoid CB_2 receptors in body weight control and glucose homeostasis was deduced from a study artificially triggering CB_2 expression in mouse brain (Romero-Zerbo *et al.*, 2012). In humans, the minor allele of rs3123554 in the CB_2 receptor was associated cross-sectionally with lower body weight, whereas during intervention, the same allele led to a smaller reduction in body weight (Ketterer *et al.*, 2014). In this study, it was proposed that reduced cerebral insulin sensitivity in carriers of this allele might contribute to these disadvantageous effects during lifestyle intervention. Moreover, an association between the CB_2 receptor Q63R functional variant and the age at menarche in a cohort of Italian obese girls was reported (Bellini *et al.*, 2015). These studies clearly provide a rationale to consider a possible protective role for CB_2 receptors in diet-induced metabolic malignancies (Figure 1). CB_2 receptor activation could for example be protective in high-carbohydrate diets (Bermudez-Silva *et al.*, 2007) in obese individuals. Obesity is associated with a low-grade inflammatory state and adipocyte hyperplasia/hypertrophy. This suggests that CB_2 receptor activity, possibly via modulation of immune cells like macrophages, could potentially modulate food intake and could have significant effects on energy metabolism and pro-inflammatory obesity (Schmitz *et al.*, 2016). Moreover, CB_2 receptors could be protective in atherosclerosis, restenosis, stroke, myocardial infarction and heart failure (Steffens and Pacher, 2012). At present, few dietary phytochemicals have been shown to activate CB_2 receptors *in vivo*. The best studied phytochemical is β-caryophyllene (BCP), which has been independently shown to exert numerous CB_2 receptor-mediated cannabimimetic effects in rodents (e.g. Gertsch *et al.*, 2008; Horváth *et al.*, 2012; Bahi *et al.*, 2014; Klauke *et al.*, 2014). As outlined in a previous commentary, BCP is a common phytochemical widely present in vegetables and spices (Gertsch, 2008). It is one of the most widespread plant volatiles and can be synthesized by virtually all plants. Although the exact molecular mechanism of action of this virtually water insoluble sesquiterpene remains unclear and CB_2 receptor interaction/activation data *in vitro* can vary (unpublished observations), *in vivo* data from rodent experiments are convincing and point towards broad CB_2 receptor-mediated protective effects in various animal models (Gertsch *et al.*, 2008; Bento *et al.*, 2011a; Horváth *et al.*, 2012; Cheng *et al.*, 2014; Klauke *et al.*, 2014). Oral administration of high doses of BCP has beneficial effects on glucose homeostasis in diabetic rats similar to glibenclamide, a standard antidiabetic drug (Basha and Sankaranarayanan, 2014 and 2016). Glucose-stimulated insulin secretion is essential for the control of metabolic fuel homeostasis, and its impairment is a key element in the failure of beta cells in T2DM. BCP has been shown to dose-dependently stimulate insulin secretion in MIN6 cells in a CB_2 receptor-dependent manner (Suijun *et al.*, 2014). BCP potently inhibits solid tumour growth and lymph node metastasis of B16F10 melanoma cells in high-fat diet-induced obese C57BL/6N mice (Jung *et al.*, 2015). BCP can be found in cows milk where it

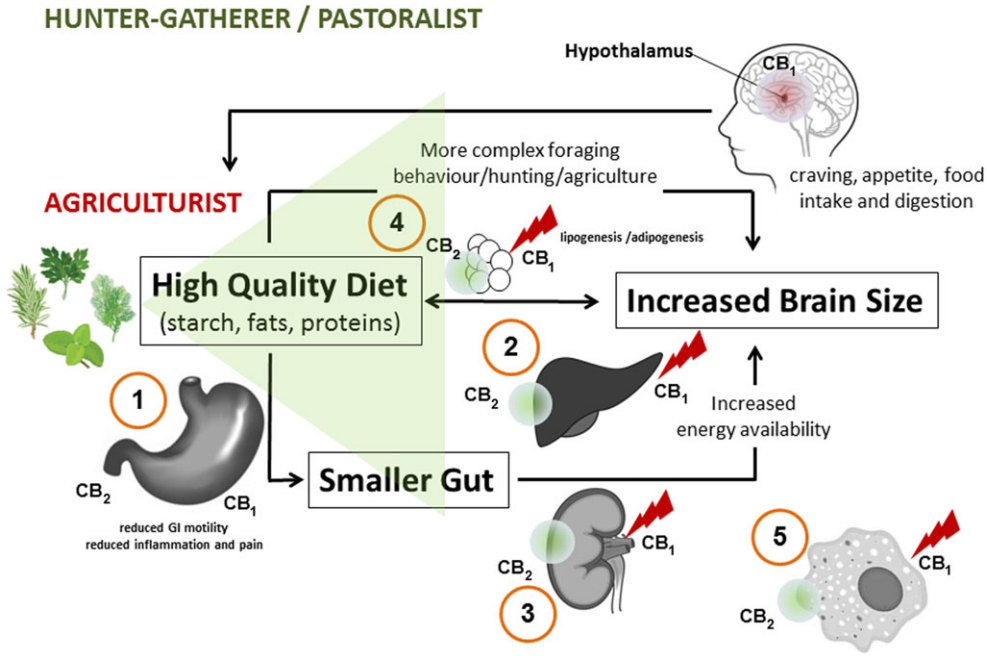


Figure 1

Hypothetical evolutionary model of the differential roles of CB_1 and CB_2 receptors in human (patho)physiology. The ECS integrates dietary stimuli from different lifestyles leading to a potential mismatch in agriculturist societies where high-calorie food (sugars and fats) predominates. To compensate for the detrimental effects of chronic CB_1 receptor activation in peripheral organs, CB_2 receptors may have evolved as a protective mechanism. While both CB_1 and CB_2 receptors are protective in the GI tract (1), in the liver (2), kidney (3) and adipocytes (4), CB_2 receptor activation could counteract the pro-obesity and pro-fibrotic action of CB_1 receptor activation. In addition, CB_2 receptor activation may ameliorate chronic inflammation [e.g. via macrophage polarization (5)] and metabolic disease. Some phytochemicals introduced during agriculture (spices, leafy vegetables, etc.) may modulate the CB_1/CB_2 receptor activation ratio, thus linking diet with physiology.

accumulates with a BCP rich diet (Borge *et al.*, 2016). Attempts to establish structure–activity relationships with BCP at the CB_2 receptor have failed (Chicca *et al.*, 2014) as this simple bicyclic hydrocarbon scaffold offers limited possibilities. Another interesting natural CB_2 receptor agonist is 3,3′-diindolylmethane (DIM), which is an anticarcinogenic metabolite generated upon ingestion and hydrolysis of glucobrassicin commonly found in vegetables of the Brassicaceae family. It has been shown to be a partial CB_2 agonist (Yin *et al.*, 2009). The intake of BCP and potentially DIM could, at least in theory, directly shift the CB_1/CB_2 receptor activation ratio away from CB_1 receptor activation.

Hunting, pastoralism and agriculture – possible crossroads for the endocannabinoid system

Many metabolic human genes that evolved in the context of carnivory and a hunter-gatherer lifestyle may not have necessarily been associated with famine (Pijl, 2011; Berbesque *et al.*, 2014). However, carnivory demands efficient lipid metabolism. Dietary fat stimulates the intestinal release of the incretin hormones glucagon-like peptide 1 (GLP-1; Edfalk *et al.*, 2008; Mandøe *et al.*, 2015) and glucose-dependent insulinotropic polypeptide (GIP) (Thomsen *et al.*, 1999), metabolically connecting animal and plant foods. A hunter-gatherer diet rich in animal food (about 65% of total energy intake) does not lead to metabolic problems or cardiometabolic risk (Cordain *et al.*, 2002). Indeed, as already pointed out, pastoralist societies of the sub-Saharan region, which have a history more ancient than agriculture, provide strong evidence that the consumption of milk and meat (proteins and fat) in a high physical activity context do not correlate with increased cardiovascular disease. For instance, despite a diet high in saturated fat, Fulani adults in Nigeria have a lipid profile indicative of a low risk of cardiovascular disease (Glew *et al.*, 2001). This is in agreement with findings that high-fat diets may not cause obesity and cardiometabolic pathologies in the context of sufficient physical activity (Hansen, 2013). While hunter–hunter gatherers have limited carbohydrate intake (Ströhle and Hahn, 2011), their energy demands are covered through fat-based diets. This would fit the hypothesis that the ECS evolved in the context of sympathetic stimuli (Szabo *et al.*, 2001), linking the CNS to metabolism and potentially also the control of brown adipose tissue (BAT) thermogenesis (Labbé *et al.*, 2015). Interestingly, endogenous CB_1 receptor negative allosteric modulatory peptides (pepcans; RVD-hemopressin) have been discovered in noradrenergic neurons and chromaffin cells of adrenal glands in mice (Bauer *et al.*, 2012, Hofer *et al.*, 2015), thus potentially revealing an endogenous modulatory mechanism that has negative effects on CB_1 receptors. Further research is needed to understand the physiological role of these peptides in the context of diet. Hypothalamic CB_1 receptor signalling is a key determinant of energy expenditure under basal conditions and plays a role in conveying the effects of leptin on food intake (Cardinal *et al.*, 2012). Since CB_1 receptors are strongly expressed in adipocytes, in addition to the hypothalamic regulation of thermogenesis, these receptors may have additional roles, for example, in the differentiation of white adipose tissue (WAT) and BAT. Apart from diet, weight control, exercise and the use of recreational substances like alcohol, tobacco and coffee also modulate the ECS (McPartland *et al.*, 2014). In contemporary post-agricultural societies, sugars and fats constitute a major source of energy that can be obtained at basically no physical cost. It would be interesting to compare the functioning of the ECS between hunter-gatherers, pastoralists and agriculturists in different energetic circumstances, taking into account possible genetic adaptations. Experimentally more accessible, the role of the ECS in fast-growing meat-producing animal strains versus normal growing animals of the same species should be studied to better link genetics with food intake. Along this line, cursorial animals produce AEA upon exercise, whereas non-cursorial animals do not (Raichlen *et al.*, 2012), suggesting a physical activity reward (runners high) potentially interlinked to energy metabolism (Fuss *et al.*, 2015). Upon moving to urban centres or as income rises, developing nations typically replace plant-based diets with more refined carbohydrates, isolated animal fats, vegetable oils and caloric sweeteners, a phenomenon known as the 'nutrition transition' (Popkin *et al.*, 2012), which goes along with less physical activity.

Prospects for nutraceutical research?

With the nutrition transition ongoing in industrialized societies and the interrelated phenomena of glucotoxicity and lipotoxicity, CB_2 receptor-selective cannabimimetic dietary lipids should be considered as potential novel food supplements. They are generally anti-inflammatory and anti-fibrogenic and may potentially counteract CB_1 receptor signalling. An interesting candidate is the FDA-approved nontoxic food additive CB_2 receptor agonist BCP (CAS 87–44-5) (Schmitt *et al.*, 2016), which also targets PPARs (Sharma *et al.*, 2016) and is already an active ingredient of certain nutraceuticals. However, a clinical assessment of the controlled intake of higher doses of this phytochemical in diseases related to the metabolic syndrome and T2DM, such as, for example, hepatorenal inflammation, would be necessary. It was recently suggested that BCP could have potential in preventing or ameliorating non-alcoholic fatty liver disease via stimulation of the CB_2 receptor-mediated calcium-triggered activation of AMP-activated protein kinase (AMPK; Kamikubo *et al.*, 2016). BCP is orally bioavailable and accumulates in adipose tissue (unpublished data) with yet unclear clearance mechanisms. It is estimated that the daily intake of BCP from spices and vegetables is less than 10 mg but may vary with diet. The spices and vegetables of the Mediterranean and Indian cuisines may already contain sufficient amounts of cannabimimetics like BCP, DIM and EC modulating PUFAs. Dietary black pepper, which is a major source of BCP, also contains the potent AEA reuptake inhibitor guineensine (Nicolussi *et al.*, 2014), an interesting dietary natural product, which could exert weak indirect agonistic effects on CB receptors if orally bioavailable. Clearly, phytochemicals able to inhibit peripheral CB_1 receptors could represent novel therapeutic agents in diet. Since the intake of falcarinol is limited to few vegetables and spices, such as carrots and parsley, and the pharmacokinetics of this plant lipid remains unknown; further research is necessary. There is compelling evidence that numerous vegetables and spices

exert beneficial effects in the context of obesity, the metabolic syndrome and diabetes (Leiherer *et al.*, 2013). There could even be a diet-mediated metabolic plant feedback beyond nutrients and vitamins (Gertsch, 2016). Diet is important for the development of the immune system, stress axis and neurobiological fitness in infants, and the ECS appears to play a critical role in this process (Harrison and Baune, 2014; Moretti *et al.*, 2014). It will thus be interesting to assess the possibility of 'reprogramming' energy metabolism in infants of obese parents, for example, by tuning the Ω3/6 PUFAs in early development. Intervention studies have demonstrated an improvement in immune function in infants fed diets supplemented with AA and DHA compared with normal diets (Richard *et al.*, 2016). Thus, increased EC levels in infants may be beneficial and result in positive health outcomes, including a reduction in the risk of developing allergic and atopic disease early in life. However, in adults, in addition to absolute amounts of Ω6 and Ω3 fatty acid intake, the Ω6/3 ratio plays an important role in increasing the development of obesity via AA-derived eicosanoid metabolites, including ECs. This can be reversed by increasing the intake of EPA and DHA (Simopoulos, 2016). In dietary obese mice, DHA/EPA administered as phospholipids prevented glucose intolerance and obesity more effectively than the corresponding tracylgylcerols, and only the phospholipid form reduced plasma insulin and adipocyte hypertrophy, being also more effective in modulating 2-AG levels and reducing hepatic steatosis and low-grade inflammation of WAT (Rossmeisl *et al.*, 2012). Overall, an age- and food-dependent balanced Ω6/3 ratio seems to be important for health and in the prevention and management of obesity in adults; the link between Ω3 fatty acid intake and ECS function is of great interest in nutrition. Noteworthy, ethanolamide metabolites of EPA and DHA (i.e. EPEA and DHEA) have been shown to exist, and interact and activate CB_1 and CB_2 receptors, although less potently than classical ECs (Brown *et al.*, 2010). *In vivo*, EPA and DHA-derived ECs could nonetheless act as CB receptor ligands or *bona fide* ECs, although further research is necessary to determine their physiological role and signalling effects via CB receptors. Intriguingly, EPEA and DHEA become detectable *in vivo* after consumption of diets rich in EPA and DHA (Wood *et al.*, 2010). Quite surprisingly, the fact that low levels of Ω3 PUFAs in humans are linked to neuropsychiatric diseases (Hashimoto *et al.*, 2014) might also be due to their fundamental, yet poorly understood interaction, with CB_1 receptors and modulation of synaptic plasticity (Lafourcade *et al.*, 2011). Inhibitory long-term depression of inhibitory inputs and long-term potentiation via NMDA glutamate receptors have both been shown to be impaired in Ω3 PUFA-deficient mice (Thomazeu *et al.*, 2016). A translation of the current state of knowledge into a potential nutraceutical strategy may involve the formulation of CB_2 receptor active dietary cannabimimetics together with Ω3 PUFAs.

Discussion

'Little strokes fell the big oaks'

The pro-homeostatic (allostatic) role of the ECS needs to be seen in the light of the evolutionary pressures, including dietary habits, but also development and ageing. Recent human genetic studies show that the ECS system is under purification pressure, most likely also driven by diet. Without an evolutionary perspective, it is difficult to draw general conclusions on the functioning of the ECS in energy metabolism. It is even likely that there is opposite roles of ECs and CB receptors, depending on diet and age. Thus, we need to also better understand the role of CB receptors in energy metabolism in elderly people. Furthermore, species differences, in particular for CB_2 receptors, are likely to limit the conclusions from animal studies. The potential hormetic effects of ECs on their receptors (CB, GPR55, PPARs, ion channels, etc.) should be studied in more detail as frequently inverse dose–response effects are observed *in vitro* and in animal experiments (mostly inbred strains). Independent of fatty acid intake, in high-calorie diets and conditions of obesity, CB_2 receptors may mediate protective effects, thus enabling metabolic stress adaptation to high-carbohydrate diets in agriculturist societies. Noteworthy, CB_2 receptor activation can potentially prevent or ameliorate diabetes-associated nephropathy (Barutta *et al.*, 2011; Barutta *et al.*, 2014), suggesting that CB_2 receptor-selective cannabimimetics in the diet may have a broad anti-inflammatory and protective role (Figure 1). However, the differential activation, by ECs, of CB_1 versus CB_2 receptors that are found to be co-expressed in peripheral cells is far from being understood. By elucidating beneficial cannabimimetics in the diet (e.g. those that shift the CB_1/CB_2 receptor activation ratio), we will be able to change dietary patterns and take into account the ECS in nutrition. Never in the history of human diets have we consumed more carbohydrates and less phytochemicals than today. It is highly likely that numerous small modulatory effects of phytochemicals (the little strokes), such as PUFAs, BCP, DIM, guineensine, falcarinol, β-amyrin, oleanolic acid and flavonoids. on the different proteins of the ECS may have significant physiological effects. The dietary input into the ECS drives the complex physiological path of appetite stimulation, energy intake and metabolism to craving, modulation of obesity, metabolic stress and cardiometabolic problems. As with Ω3 fatty acids, nutrition that favours CB_2 receptor activation should be beneficial and could open up new prospects for nutraceuticals. Ultimately, unsatisfactory diets augment drift and diminish gene flow, which reduces genetic variation in local populations and prevents the spread of genes involved in homeostasis, thereby disrupting adaptive processes and contributing to the onset of lifestyle diseases. Clearly, nutrition is fundamental in the context of population dynamics and healthy ageing. In the end, we are what we eat and eat what we are (our biochemical blueprint).

Acknowledgements

The EU MedPlant, a Marie Curie Initial Training Network (ITN), is acknowledged for financial support.

Conflict of interest

The authors declare no conflicts of interest.

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