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Complete List of Authors:	Tarragon Cros, Ernesto; Universitat Jaume I, Psychobiology Moreno, Juan José; University of Barcelona, Dept. of Nutrition, Nutritional Sciences and Gastronomy
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Cannabinoids, chemical senses and regulation of feeding behavior

Ernesto Tarragon[1] and Juan José Moreno[2]

[1] Department of Psychobiology, Faculty of Health Sciences, University Jaume I of Castellon, Castellon, Spain

[2] Department of Nutrition, Food Sciences and Gastronomy, Institute of Nutrition and Food Safety, University of Barcelona, Barcelona Spain. CIBEROBN Fisiopatologia de la Obesidad y Nutrición, Instituto de Salud Carlos III, Madrid, Spain

Correspondence to be sent to: Ernesto Tarragon, Department of Psychobiology, Faculty of Health Sciences, University Jaume I of Castellon, Av Sos Baynat s/n, 12071, Castellon de la Plana, Spain

Abstract

The herb *Cannabis sativa* has been traditional used in many cultures and all over the world for thousands of years as medicine and recreation. However, since it was brought to the Western world in the late 19th century, its use has been a source of controversy respect to its physiological effects as well as the generation of specific behaviors. In this regard, the CB_1 receptor represents the most relevant target molecule of cannabinoid components on nervous system and whole-body energy homeostasis. Thus, the promotion of CB_1 signaling can increase appetite and stimulate feeding, while blockade of CB_1 suppresses hunger and induces hypophagia. Taste and flavor are sensory experiences involving the oral perception of food-derived chemicals and drive a primal sense of acceptable or unacceptable for what is sampled. Therefore, research within the last decades focused on deciphering the effect of cannabinoids on the chemical senses involved in food perception and consequently in the pattern of feeding. In this review, we summarize the data on the effect of cannabinoids on chemical senses and their influences on food intake control and feeding behavior.

Keywords: endocannabinoids , obesity , sensory perception , flavor , synthetic cannabinoids

1. Introduction

For more of 10,000 years, *Cannabis sativa* (*C. sativa)* has been used medically and recreationally for its diverse pharmacological actions and psychotropic properties in many cultures and all over the world. However, its use has been a source of controversy since it was brought to the Western world in the late 19th century due to its specific effects on physiology and behaviors. The study of *C. sativa* components has nonetheless contributed to discover various key elements of the endocannabinoid system (ECS). At the same time, the insight gathered about the ECS has helped to understand the mechanisms involved in the physiological/pharmacological effects of the bioactive components of *C. sativa*.

Central regulation of feeding behavior is indispensable to energy homeostasis and to maintain essential daily functions (Gao and Horvath 2016). The ECS is one of the most prominent actors in the complex neural circuitry involved in this central regulation of energy homeostasis. Several studies revealed that endocannabinoids (eCBs), a highly conversed group of autacoids, play a role in central and peripheral regulation of energy balance (Nogueiras et al. 2010; O'Keefe et al. 2014). Specifically, it has been shown that stimulating CB_1 signalling can induce adipogenesis (Vettor and Pagano 2009) and increase pancreatic insulin secretion (Juan-Pico et al. 2006), indicating that circulating eCBs may act as modulators of endocrine signals in peripheral organs (Hillard 2018). At the same time, energy status modulates eCB levels. For instance, it was shown that 2-arachidonoylglycerol (2-AG), a representative eCB, increases specifically after acute food deprivation and decreases during feeding (Kirkham et al. 2002). There is as well a compelling amount of evidence suggesting that the dysregulation of the ECS contributes to obesity (Bluher et al. 2006).

However, energy balance is not the only way through which the ECS influences feeding. An increasing number of studies in the last decade have shown that eCBs and

cannabinoid (CB) receptors participate in relevant processes of eating behavior, including reinforcement and reward processes (D'Addario et al. 2014; Gatta-Cherifi and Cota 2016), and food preference (Di Patrizio et al. 2013). In a recent review, we summarized much of the evidence on the role of the ECS on sweet taste perception, food preference and obesity (Tarragon and Moreno 2018). In this review, we will try to expand the coverage to how the ECS and especially exogenous cannabinoids (CBs) are involved in chemosensory perception (olfaction, gustation) and its influence on eating behavior and food intake control.

2. The endocannabinoid system.

The ECS comprises the eCBs, the enzymes/proteins that regulate their synthesis and degradation, and the receptors through which they signal. The identification of the tetrahydrol structure of cannabidiol (tetrahydrocannabinol, THC) was discovered in *Cannabis sativa* (*C. sativa*) in the 1940s (Adams et al. 1941). Years later, Gaoni and Mechoulam (1964) were able to identify the positioning of the Δ^9, which confers THC (Δ^9-THC) its main psychoactive properties . However, it was not until 1988 that the CB_1 receptor was characterized (Devane et al. 1988; Gerard et al. 1991). The discovery of specific CB receptors implied the existence of endogenous ligands capable of activating these receptors, leading to propose the concept of an ECS (Howlett et al. 1990). This was rapidly confirmed by the isolation of the first endogenous CB ligand, anandamide (AEA) (Devane et al. 1992), the identification and characterization of the CB_2 receptor (Munro et al. 1993), and the identification of a second endogenous ligand, 2-arachidonoylglycerol (2-AG) a few years later (Mechoulam et al. 1995; Stella et al. 1997; Sugiura and Waku 2000). These and other lipid mediators capable of activating the CB receptors were named eCBs. Interestingly, these compounds were shown to activate several other receptors in addition to CB receptors, including the

transient receptor potential cation channel, subfamily V, member 1 (TPRV1) (Sartim et al. 2017), and a novel orphan CB receptor GPR55 (Ryberg et al. 2007).

Today we know that eCBs serve as retrograde synaptic messengers within the central nervous system (CNS) (Pertwee and Ross 2002). This suggests that eCBs act as both neuromodulators and immunomodulators. The ECS functions have been characterized as "relax, eat, sleep, forget and protect" (Di Marzo 1998), but the number of processes in which the ECS participates increases each year with additional research discoveries.

2.1. Cannabinoid receptors

CB_1 and CB_2 receptors were first cloned by Matsuda et al. (1990) and Munro et al. (1993), respectively. Both receptors are members of the G-protein-coupled receptors (GPCR) superfamily and are widely expressed in the brain (Moldrich and Wenger 2000; Gong et al. 2006). CB_1 is one of the most abundant GPCR in the brain. Autoradiographic studies demonstrated that high levels of CB_1 are expressed in the cortex, hippocampus, cerebellum, basal ganglia, and the spinal cord (Herkenham et al. 1990; Tsou et al. 1998; Freund et al. 2003), correlating with the well-known effects of CBs on cognition, memory, motor control, and spinal signaling, respectively. The functional effects of the CB_1 expression in the hypothalamus with respect feeding-related patterns was described few years later (Breivogel et al. 1997; Elmquist et al. 1999). This was further supported by *in situ* hybridation studies that confirmed that CB receptors are found on axon terminals (Matsuda et al. 1993), and by electron microscope studies which also confirmed that cell-surface CB_1 receptors are found almost exclusively on pre-synaptic terminals (Tsou et al. 1998; Katona et al. 2000). CB_1 is also expressed in numerous peripheral tissues including heart, lung, prostate,

liver, ovaries and testis (Galiegue et al. 1995), whereas CB_2 is abundantly expressed in peripheral organs with immune function (Galeigue et al. 1995) and up-regulated in response to immune cell activation and inflammation (Stella 2010). Although it is considered that the majority of the effects on the CNS are related with CB_1 (Freund et al. 2003), recent work has reported some functional expression of CB_2 receptor in the brain (Onaivi et al. 2006) and that these may also be involved in eating behavior (Onaivi et al. 2008).

Although CB_1 and CB_2 receptors are the most relevant CB receptors, it is likely that CBs can also act upon other GPCR, such as GPR18, GPR55 and GPR119. GPR55 was identified in the human brain by Sawzdargo et al. (1999) and it can be considered a third CB receptor. Δ^9-THC (Lauckner et al. 2005) as well as synthetic CB_1 ligands such as AM251 or SR141716A (Kapur et al. 2009) activate GPR55, an "enigmatic" receptor that recent studies have linked to anorexia nervosa (Ishiguro et al. 2010). In addition, although GPR119 was not initially linked to ECS, Overton et al. (2006) showed that N-oleoylethanolamide (OEA), an analogue of AEA, also binds to this receptor. Interestingly, stimulating GPR119 with OEA suppresses feeding in rats (Rodríguez De Fonseca et al. 2001), despite this receptor not being directly involvedin central eCB-mediated feeding (Overton et al. 2006, 2008).

There is still much to clarify about how CBs produce their endogenous effects, and how these effects and other systems might interact with each other (Ben Amar 2006). For instance, the cross talk between the ECS and others such as the opioid system seems to modulate energy balance and food intake to a greater extent than either system alone (Morley and Levine 1982; Solinas and Goldberg 2005).

2.2. Endogenous cannabinoids

eCBs are derivatives of arachidonic acid (AA), resembling other lipid mediators such as eicosanoids. AA is conjugated with ethanolamine to form fatty acid amides such as AEA, or with glycerol to form monoacylglycerols, like 2-AG. AEA biosynthesis occurs in two steps. First, a calcium-dependent transacylase transfers an acyl group to membrane phospholipids in the N-position of phosphatidyletanolamine. This transference generates the N-acylphosphatidylethanolamines that selective phospholipases D hydrolyze to release AEA and phosphatidic acid (Okamoto et al. 2004). 2-AG is mainly synthetized from AA-containing membrane phospholipids through the action of phospholipase C, leading to the formation of diacylglycerol hydrolyzed by diacylglycerol lipase (DAGL) (Bisogno et al. 2005)▪. Finally, AEA is degraded by fatty acid amide hydrolase (FAAH), whereas 2-AG is degraded by monoacylglycerol lipase (MGL) or the α β serine hydrolase domain (ABHD) (Fig. 1).

AEA resembles Δ^9-THC in acting as a partial agonist at CB_1 receptor. 2-AG is an agonist at both CB_1 and CB_2 receptors. However, other eCBs have been identified more recently, such as noladin (2-arachidonyl-glyceryl ether, 2-AGE) (Hanus et al. 2001)▪, virhodamine (*O*-arachidonoyl-ethanolimine) (Porter 2002)▪, *N*-arachidonyl-dopamine (Bisogno et al. 2000)▪, and oleamide (*Cis*-9,10-octadecanoamide) (Leggett et al. 2004)▪ to name some.

2.3. Exogenous cannabinoids

Exogenous CBs are natural molecules, mainly derived from plants (phytocannabinoids), and synthetic compounds that are able to bind to CB receptors and consequently interfere with the ECS functions, offering insights into the mechanisms of eCBs as well as bearing potential for future treatments. Depending on the source, they are defined as phytocannabinoids or synthetic CBs.

155

156 2.3.1. Phytocannabinoids

157 The cannabis plant contains more than 200 chemical compounds, including 120
158 different phytocannabinoids, in addition to other constituents such as terpenoids and
159 flavonoids (Radhakrishnan et al. 2014). Together with cannabidiol (Russo 2013),
160 Δ^9-THC is the best-studied CB, responsible for most of the pharmacological and
161 psychoactive effects of *C. sativa* preparations. However, components of other plants
162 besides cannabis have been reported to interact with CB receptors, binding to these and
163 other CB-affine receptors, promoting diverse physiological effects as well. These
164 components are named phytocannabinoids, a chemical class substance of C_{21}
165 terpenophenolic compounds (Mechoulam and Gaoni 1967) that were considered "a
166 medicinal treasure trove which waits to be discovered" (Mechoulam 2007).

167 Examples of phytocannabinoids are also found in bark extract of *Magnolia officinalis*
168 (Lee et al. 2011) as well as in *Echinacea spp.* (Gertsch et al. 2008). On the other
169 hand, sesquiterpene and caryophyllene, present in essential oils of *Origarum vulgare*,
170 *Cinnamomum spp.*, *Piper nigrum*, and *C. sativa,* are CB_2 receptor agonists; some of
171 them showing promising anti-inflammatory properties in recent, preliminary studies
172 (Gertsch et al. 2008). Another phytocannbinoid newly discovered is cannabidivarin,
173 which has shown effective anticonvulsant properties (Hill et al. 2012) and efficacy as
174 an anti-epileptic agent through activation of CB receptors (Whalley et al. 2015). Other
175 non-lipid derivatives, such as β-caryophyllene also present binding affinity for CB_2
176 (Gertsch et al. 2008).

177 Nonetheless, binding to CB receptors is not the only characteristic to define a
178 phytocannabinoid. For instance, N-acylethanolamines present no affinity for such
179 receptors, although they are able to inhibit AEA degradation enzymes, thus promoting

eCB signaling (McPartland et al. 2014). In addition, pristimerin and euphol, two triterpenoids naturally occurring in several plants, have shown to inhibit MAGL and consequently the enzymatic degradation of 2-AG (Sawai and Saito 2011). This evidence indicates that exogenous CBs may not only act through direct binding to CB receptors, but also throughout different mechanisms that can modulate the ECS.

2.3.2. Synthetic cannabinoids

Synthetic CBs are a class of chemicals with the property of binding to CB receptors. Given the diverse actions and functions of the ECS within the organism, the development of synthetic CBs was an attempt to mimic the various physiological effects of eCBs avoiding their psychotropic consequences.

Based in their chemical structures, CB agonists can be classified into at least four groups; classic CBs of *C. sativa* and its analogues, bicyclic and tricyclic analogues of Δ^9-THC, and non-classical CBs with structure of fatty amides or esters and aminoalkylindoles. Since the review of the hundreds of synthetic CBs is beyond the purpose of this work, we will name only a few of the most representative families (Fig. 2).

An example of synthetic Δ^9-THC is 11-hydroxy- Δ^8-THC dimethylheptyl (HU-210), a particularly potent CB that has efficacy at activating both CB_1 and CB_2 receptors (Mechoulam et al. 1988). Specifically, HU-210 resembles the affinity for CB_1 and CB_2 receptors of other synthetic compounds like CP55,940 and WIN 55,212-2. The replacement of the pentyl side chain of Δ^8-THC with a dimethylheptyl enhanced its affinity and efficacy at CB receptors (Pertwee 2006). Non-classical CBs consisting of bicyclic and tricyclic analogues of Δ^9-THC typically lack a pyran ring. The most commonly used ligand of this class is CP55,940, which has demonstrated relatively

high efficacy through both CB_1 and CB_2 receptors in the low nanomolar range (Pertwee, 2005). The first cannabinergic indoles to be developed were amino-alkylindoles, among which WIN 55,212-2 showed a potent agonism to CB_1 and CB_2 receptors, binding differently to the CB_1 receptor than classical and non-classical CBs (Compton et al. 1992).

3. Effect of cannabinoids on food intake control

The mechanism behind the orexigenic effects of eCBs is still today a matter of active research. Although the observations that marijuana stimulates appetite and food consumption are known for many years (Abel 1971; Foltin et al. 1986), the experimental evidence for CB-induced hyperphagia has beenwas not demonstrated until more recently. In the late 1990s and early 2000s, Williams and co-workers demonstrated showed that Δ9-THC exerts hyperphagic action in pre-fed rats (Williams et al. 1998) as well as free-feeding rats (Koch 2001), a similar effect to that reported using Δ8-THC (Avraham et al. 2004). Additionally, numerous studies demonstrated Kirkham et al (2002) reported that AEA and 2-AG levels are elevated by after food deprivation in the limbic forebrain, while 2-AG is reduced in the hypothalamus during the feeding state but increased during the deprived state, which suggests a role of eCBs in motivation towards food. Further, the reduction of 2-AG in the hypothalamus during feeding indicates that 2-AG can facilitate satiation (Kirkham et al. 2002), suggesting a role of eCBs in motivation towards food.

Consistent with this idea, Di Patrizio and Simansky (2008) demonstrated that direct administration of 2-AG into the pontine parabrachial nucleus promoted high-fat, high-sucrose, and high-fat and high-sucrose food intake while intake of standard pellets remained unaffected. Additionally, many studies show that acute infusion of CB1

agonists into distinct hypothalamic nuclei induce feeding, which provides evidence that the hypothalamic neurons are directly affected by CBs (Jamshidi and Taylor 2001; Koch et al. 2015). Concretely, it has been shown that CB1 agonism in the PVN increased hyperphagia in hungry mice and enhanced the hyperphagic effects of ghrelin in fed animals (Soria-Gómez et al. 2014a). In the lateral hypothalamus, CB1 is involved in physiological control of melanin-concentrating hormones and orexin-A neurons (Silvestri and Di Marzo 2013). In the ARC, Agouti-related protein/neuropeptide Y (AgRP/NPY) neurons acutely promote food intake, and POMC neurons drive gradual onset of satiety (Varela and Horvath 2012). It was also demonstrated that CB1 blockade in the hypothalamus reduced NPY levels, indicating local eCB control over AgRP/NPY neurons (Verty et al. 2009). AgRP/NPY neurons do not express CB1 (Cota et al. 2003), but CB1 is expressed at GABAergic terminals innervating AgRP/NPY neurons (Morozov et al. 2017). This finding led to suggest that eCBs might also promote feeding by retrograde inhibition of AgRP/NPY neurons.

Coherent with the above mentioned, it has been shown that both AEA and 2-AG decrease the latency of feeding onset, increase the duration of intake and the number of meals, but only AEA increased total intake (Farrimond et al. 2011). These effects were reverted by SR 141716A, a CB1 inverse agonist (Landsman et al. 1997), but not by SR 144528, a CB2 antagonist (Williams and Kirkham 2002b). Furthermore, WIN 55,212 similarly increased food intake, whereas SR 141716A reverted this effect (Gomez et al. 2002). It was also demonstrated that daily administration of SR 141716A reduced food intake and body weight in Wistar rats (Colombo et al. 1998). More recently, Vickers et al. (2003) demonstrated that oral, chronic SR 141716A administration decreased food intake and body weight gain in both lean and obese Zucker rats and in diet-induced obese mice (Ravinet Trillou et al. 2003). Similarly, to SR 141716A, AM251 has shown to reduce food consumption in obese animals

(McLaughlin et al. 2003) and in overnight-fasted animals (Shearman et al. 2003). Moreover, AM251 also produces dose-dependent reductions in reinforced response paradigms under fixed-ratio schedules (McLaughlin et al. 2003). Taken together, these data indicate that pharmacological manipulation of the CB receptors not only influences food consumption in total volume, but also appetitive response for food, and appears effective in controlling body weight and preventing weight-gain in experimental models of obesity. A series of relevant studies on this matter are gathered on Table 1.

4. Cannabinoids and energy metabolism.

It is well established that ECS is physiologically involved in the regulation of appetite, pain and inflammation, thermoregulation, intra-ocular pressure, sensation, muscle control, motivation and /reward, mood, memory, and appetite (Silvestri and Di Marzo 2013). Furthermore, it has been suggested a link between eCBs and high prevalence pathophysiological states, including obesity, metabolic syndrome, diabetes (Perkins and Davis 2008; Pacher and Kunos 2013) and cardiovascular disease (Chanda et al. 2017). Indeed, upon stimulation, the ECS through eCBs increases food intake and weight gain, promotes lipogenesis and impairs glucose tolerance (Cota et al. 2003), and modulates growth (Li et al. 2013).

Recently, Simon and Cota (2017) reviewed the effect of CBs on metabolism. They reported that CB_1 receptor activation increases lipogenesis and adipogenesis, impairs mitochondrial biogenesis, favors the white adipocyte phenotype, and that, in the liver, CB_1 receptor exerts a critical role in the regulation of lipid metabolism and insulin sensitivity. In this way, Miederer et al. (2017) reported that THC was able to affect the glucose uptake in the rat brain, which may be of relevance in behavioral studies. Interestingly, CB_1 is involved in the regulation of food intake by digestive system and

insulin release by pancreatic islets. Furthermore, we must consider that some of these metabolic effects of CB ligands could be related, at least in part, with alternative receptors such as GPR55 (Tudurí et al. 2017).

Hypothalamic CB_1 signaling also interfaces with signal transmission of metabolic hormones. For instance, while leptin-suppressed feeding correlates with decreased hypothalamic eCBs levels (Di Marzo et al. 2001), ghrelin-triggered feeding depends on paraventricular nucleus (PVN) CB_1 signaling and accompanies increased hypothalamic eCB levels (Kola et al. 2008). The activation of AMP-activated protein kinase (AMPK) has been proposed as a molecular mechanism by which the CBs might exert its effects on eating behavior (Kola et al. 2005). AMPK plays a central role in the control of energy homeostasis at both individual cellular level and globally in the organism (Hardie 2008). Furthermore, various studies demonstrate that eCBs activate AMPK in the hypothalamus, enhancing orexigenic signals, while decreasing fat oxidation in fat tissue and liver (Tedesco et al. 2010). Interestingly, several feeding-related hormones such as leptin, ghrelin and adiponectin can also influence AMPK activity (Kola et al. 2008). The highly active interaction between ECS and many of such endocrine and paracrine elements suggests a mediating role of eCBs on hormone functioning. This idea is supported by various studies showing data for heterodimerisation of CB receptors with the orexin (Ellis et al. 2006), opioid (Hojo et al. 2008), type 2 dopamine (Kearn 2005) and ghrelin (Edwards and Abizaid 2016) receptors.

Additionally, we must consider that, although to a lesser extent, the CB_2 in the CNS has also shown to be involved in glucose homeostasis and led to a lean phenotype (Romero-Zerbo et al. 2012). Recent localization of CB_2 receptors in metabolically active tissues suggests that this receptor might also have a significant role in energy homeostasis and body weight regulation. Accordingly, Verty et al. (2015) observed that JWH-015, a

CB_2 agonist, reduced food intake, fat mass and adipocyte cell size in lean and obese mice without any adverse impact on mood. Thus, in the interest of pursuing improved pharmacotherapy treatment involving the eCB, it would be negligent to exclude a role of CB_2 agonist/antagonists as putative target in the future of obesity-related treatments.

Surprisingly, it was recently described that CB_1 receptor activation in the POMC neurons is also relevant for the hyperphagic properties of CBs, acting at pre- and post-synaptic levels (Koch et al. 2015). The stimulation of CB_1 receptors in these POMC neurons inhibits the synthesis of the α–melanocyte-stimulating hormone (α-MSH) but not β-endorphin peptides, a process mediated via mitochondrial activation (Koch et al. 2015). Further, CB_1 receptors co-exist in POMC neurons with orexin-A receptors, whose stimulation initiate the synthesis of 2-AG thus promoting hyperphagia even in sated rats (Morello et al. 2016). Finally, it was also reported that CB_1 signaling modulates dopaminergic signaling in the nucleus accumbens and ventral tegmental area (Di Marzo et al. 2009a), a phenomenon that has been directly related to the attribution of salience to stimuli in general and food in particular (Salamone and Correa 2012, 2013).

Importantly, hypothalamic AgRP/NPY and POMC neurons are not only directly affected by food intake itself, but also rapidly respond to sensory detection of available food (Chen et al. 2015). Thus, hypothalamus not only regulates hunger and satiety in response to eating and internal signals of energy resources, but also receives external information on the incentive value of food, such as sight, smell, and taste (Seeley and Berridge 2015).

5. Cannabinoid-based pharmacotherapy in obesity

Interestingly, in addition to its orexigenic effects, THC has been reported to be anorexigenic as well. While low, oral doses of THC increase acute food intake, higher doses decrease feeding when administered systemically (Sofia and Knobloch 1976). Other studies also indicate that the hyperphagic effect produced by is not long-lasting (Järbe and Di Patrizio, 2005). Hence, CBs and eCBs seem to have a biphasic effect on feeding, which is to say that different levels of stimulation lead to opposite outcome. Further, many studies report elevated levels of circulating eCB in obese individuals (Engeli et al. 2005; Di Marzo et al. 2009b; Matias et al. 2012. Little et al. 2018). Since eCBs levels are increased in both the food deprived and in obesity, the theory that eCB dysfunction plays an important role in this condition seems especially relevant.

A recent examination of two US national surveys identified a lower prevalence of obesity in cannabis users (Le Foll et al. 2013). These observations are paradoxical considering previous reports of acute cannabis stimulating appetite and food intake. However, preclinical studies also support this observation, showing that both lean and obese animals decreased body weight after chronic combined administration of CBD and THC (Klein et al. 2011). Interestingly, this reduction in energy intake was also observed after the chronic administration of THC alone, an effect which has been attributed to interactions with the gut microbiota (Cluny et al. 2015). Thus, chronic agonism of the ECS may be an under-explored therapeutic strategy in treating obesity. The mechanism underlying the relationship between chronic cannabis use and absence of obesity is unclear. However, provided that THC is a partial agonist and may functionally act as an antagonist under conditions of high eCB tone such as in obesity (Le Foll et al. 2013), chronic cannabis use may share a similar mechanism of action to Rimonabant (Acomplia®) and other CB_1 antagonist in preventing weight gain. In this regard, Rimonabant was approved as an anti-obesity drug by European Union, UK and USA after clinical trials conducted by Sanofi-Aventis successfully showed weight loss,

a decrease in plasma triglycerides, a reduction of waist circumference, and an increase in high density lipoprotein cholesterol (HDL) (Van Gaal et al. 2005; Despreś et al. 2006; Pi-Sunyer et al. 2006).

Unfortunately, Rimonobant was discontinued due to an increased risk of depression and suicide after continuous use. Since this withdrawal, other CB_1 antagonist drugs have been halted in the process of development. Taranabant (Merch & Co.) also induced weight loss (Addy et al. 2008), although phase III trials were stopped in October 2008 due to a high level of central side effects, including anxiety and depression. Interestingly, Willimas and Kirkham (2002a) observed that Δ^9-THC-induced hyperphagia could be attenuated by the opioid antagonist naloxone, which provides further evidence of the aforementioned link between opioid food reward processing and the ECS (Koch et al. 2015). Promisingly, Dronabinol (Marinol®), an oral preparation of Δ^9-THC, and nabilone (Cesamet®), a synthetic analogue of Δ^9-THC are already licensed for clinical use in some countries as appetite stimulants and attenuating weight loss associated to anorexia (Verty et al. 2011) or AIDS (Badowski and Perez 2016) .

A key aspect of the history of pharmacological strategies targeting the ECS in managing obesity and metabolic disorders is the severe affective symptomatology and/or the focus on neurobiological systems involved in the affective response. This is interesting in the context of this review, since depression and anxiety disorders often co-exist with alterations in chemosensory perception (Parker et al. 2014; Takahashi et al. 2015; Taalman et al. 2017; Hur et al. 2018). Traditionally, it is assumed that the alterations in chemosensory response are consequence of the neurobiochemical changes induced by depression-like states. However, the opposite direction of this relationship has never been tested. How is it to know that disturbances in perception do not act as a trigger for altered, negative mood? Indeed, there is evidence showing that changes in taste can affect mood (Karita et al. 2012; Platte et al. 2013; Sugawara et al. 2013).

6. Effect of cannabinoid on chemo perception

Taste and flavor are sensory experiences involving the oral perception of food-derived chemicals and drive a primal sense of acceptable or unacceptable for what is sampled. Therefore, deciphering the effect of CB on the perception of chemical senses and consequently in the pattern of feeding has been a focus of interest within the CB research in the last decades. There is considerable amount of evidence describing the participation of the ECS on the chemosensory response to food (Ward and Dykstra 2005; Yoshida et al. 2010). Specifically, circulating eCBs influence olfactory perception, with differences between lean and obese individuals (Pastor et al. 2016). Additionally, the activation of CB_1 has been shown to enhance gustatory properties of food in both animals and humans (Limebeer et al. 2012; Niki et al. 2015). Other studies show that the processing of olfactory or gustatory sensations involves CB_1 signaling (Table 2). For instance, fasted mice displayed CB_1 dependent increased odor detection in the olfactory bulb (Soria-Gómez et al. 2014b). As described above, CB receptors and other CB-binding receptors (i.e. TPRV1) are not only modulated by eCBs and Δ^9-THC, but also by other phytocannabinoids like cannabidiol (Campos et al. 2013) and other synthetic CBs (Castaneto et al. 2014). In this section, we summarize relevant research covering the effect of the ECS and CBs on smell and taste, as primary chemosensory processes relevant to food choice and food intake.

6.1. Cannabinoids and smell

Smell is one of the primary senses among mammals. In humans, contributes drastically to experience flavor not only as a chemosensory response, but also as an important component of the affective response to food (Stevenson 2009). The olfactory

information is processed within brain regions also associated with the processing of cognitive and affective information (i.e. amygdala, hippocampus, PFC). Many studies show that olfactory perception is affected in metabolic disturbed states, including obesity but also anorexia and bulimia nervosa (Richardson et al. 2004; Palouzier-Paulignan et al. 2012; Karine et al. 2014; Soria-Gómez et al. 2014c). Furthermore, it was recently demonstrated that smell is associated with central and peripheral systems that regulate food intake. Interestingly, people with obesity show significant differences regarding olfactory capacity in comparison with healthy subjects (Richardson et al. 2004; Pastor et al. 2016). And this has been shown even in children (Jansen et al. 2003). Thus, the olfactory system can influence eating behavior by acting on hunger and satiety signals as a sort of metabolic regulator, hence affecting energy homeostasis (Yeomans 2006; Palouzier-Paulignan et al. 2012).

One of the systems with which olfaction interacts closely is the ECS (Palouzier-Paulignan et al. 2012). From basic organisms to humans, experimental evidence demonstrates the close participation of the ECS on olfactory function. For instance, Breuning and colleagues showed that hunger-induced 2-AG synthesis in the olfactory epithelium increases neuron activity and controls odor sensory threshold via CB_1 activity in *larvae X. laevis* (Breunig et al. 2010). Interestingly, despite these properties, it seems that eCBs do not modulate olfaction *per se* (Hutch et al. 2015).

Further evidence shows that one of the mechanisms through which the ECS stimulates eating behavior is smell. This is coherent with findings of numerous CB_1 receptors in terminal axons project towards the olfactory bulb (Busquets-Garcia et al. 2015). In a series of experiments, Soria-Gomez and colleagues demonstrated that AEA, 2-AG and THC increased odor detection and food intake in fasted mice by decreasing signal input from the olfactory cortex to the olfactory bulb (Soria-Gómez et al. 2014b). Also, it is known that ECS-interacting endocrine and paracrine hormones involved in the hunger-

satiety processes can influence smell thresholds (Ketterer et al. 2011; Thanos et al. 2013). And evidence from clinical studies indicates that the activation of the CB receptors enhances smell, taste, and has an orexigenic effect (Støving et al. 2009; Brisbois et al. 2011).

Recently, some research investigated the participation of phytocannabinoids and synthetic CBs on smell. It was recently demonstrated that WIN-55212-2 and WIN-55212-3, are capable of binding to CB_1 and CB_2 receptors in neurons of the olfactory bulb, not affecting olfactory function (Hutch et al. 2015). Considering the resurgence of THC in medical use, including neuropathic pain or analgesia treatment in cancer, it is important to assess the olfactory effects of phytocannabinoids and synthetic CBs. Walter et al. (2014) reported that Δ^9-THC impaired the performance of healthy volunteers in olfactory tests. Furthermore, these authors demonstrated that THC-induced reduction in the pleasantness of a pleasurable odor was accompanied by reduced activation in the limbic system. These findings suggest that THC-based medications will be among the drugs displaying side effects on chemoperception. Interestingly, when THC was administered to cancer patients with chemosensory alterations, THC was effective in palliating chemosensory alterations and improving food enjoyment (Brisbois et al. 2011).

6.2. Cannabinoids and taste

Smell is not the only chemosensory system interacting with the ECS to modulate feeding. Gustatory perception is also closely related to the ECS, and genetic variations of various elements within the ECS has shown to also influence taste and food preference (De Luis et al. 2010, 2013b, 2013a, 2016a, 2016b), together with other processes related to eating behavior, such as reward sensitivity (Hariri et al. 2009),

binging (Monteleone et al. 2009) and cravings (Haughey et al. 2008). Thus, the perception of taste is also essential for the assessment of edibility of food and for the evaluation of its nutritional values. For instance, a polymorphism in the CB_1 receptor gene (CNR1), the (AAT)n, is associated with changes in the sensitivity to sweetness. Concretely, the sweetness threshold in women with obesity that carried was significantly lower compared to those without the (AAT)n repeat (Umabiki et al. 2011).

Yoshida and colleagues (2010) observed that the administration of AEA and 2-AG increased taste responses to sweet rather than salty, sour, bitter or umami flavors in wild-type but not in CB_1 knock-out animals. This effect has been further explored as an opposite action of the anorexigenic hormone leptin (Yoshida et al. 2010; Niki et al. 2015). These opposite effects of eCBs and leptin on sweet taste were also confirmed by Jyotaki et al. (2010). However, Wierucka et al. (2014) reported that CB_1 antagonist, AM251, attenuated body weight gain in rats maintained on high-calorie rich in fat and carbohydrates but did not affect preferences for sweet food. Thus, the effects of ECS and CBs on sweet taste seem to be still controversial.

Interestingly, some evidence indicates that circulating levels of eCB can also modulate bitterness sensitivity in non-overweight individuals (Tomassini Barbarossa et al. 2013; Tepper et al. 2014). Furthermore, the ECS seems to participate in the gustatory perception of fats (Di Patrizio 2014). According to various studies, the ECS is specifically related to the perception of one kind of unsaturated fatty acids (FA), as the presence of saturated FA failed to stimulate the synthesis of eCB in the small intestine (Mindell et al. 1990; Di Patrizio et al. 2011, 2013). However, these findings should be considered carefully, since physiological differences between humans and rodents may affect FA taste sensitivity thresholds (Kawai and Fushiki 2003; Stewart et al. 2010). All

together suggest that eCBs and CBs seem to constitute a selective reinforcement signal for palatable food.

Finally, given the relevance on taste in regards hedonic salience to food, there is an increasing interest in elucidating the mechanisms behind the affective response to different foods. It seems clear that the ECS plays an important part on this process. Pharmacological studies provide strong evidence to support this. For instance, CP55,940 increases beer and sucrose consumption whereas both SR 141716A, a CB_1 antagonist, and naloxone block these effects on spontaneous sucrose drinking (Higgs et al. 2003)· and operant responding for sucrose (McLaughlin et al. 2003), suggesting a role of CB_1 and opioid receptors (Gallate et al. 1999)· in these behaviors. In this way, Simiand et al. (1998)· reported that SR 141716A reduced consumption of a highly palatable sweetened food and suggested that eCBs may modulate "the appetitive value of food". However, other authors have challenged this idea. Particularly, the results obtained by Freedland et al. (2000)· suggested that appetitive value or enhanced palatability was not necessary to the anorectic effects of this CB_1 antagonist. Recently, Wakeford et al. (2016)· observed that THC exposure had no effect on taste conditioning in adolescent animals. However, de Brujin and colleagues investigated whether low doses of inhaled Δ^9-THC and cannabidiol affected sweet taste sensitivity, reported no change in sweet sensitivity either perception or subjective response (i.e. liking) after inhalation of the various cannabis preparations (de Bruijn et al. 2017)· . It is also worth mentioning that Jarret et al. (2005)· observed that THC increases intake of palatable (sweet) food 2 hours, but not earlier, following a low dose of THC, an effect that involved CB_1 receptor and can partially explain the above apparent incongruities. On the other hand, SR 141716A is sufficient to attenuate the reinforcing effect of fat, while activation of the central CB_1 system is enough to enhance its reinforcement properties (Ward and Dykstra 2005)· .

Apparently, the debate on the role of the ECS and CBs on food-related affective response is not over, and it will be necessary more studies on this topic. Unfortunately, the research on the role of the ECS and CBs on chemosensory response is not as abundant as in other fields. With the increasing rate of dysfunctional dietary habits, we believe this should be neglected no longer.

CB_2 is a recent guest to this history. β-caryophyllene, a CB_2 agonist, was used to investigate the role of this receptor in mediating alcohol intake and ethanol-induced conditioned place preference and sensitivity in rodents. Specifically, β-caryophyllene decreased alcohol consumption and ethanol-induced place preference in a dose-dependent manner but did not alter taste function. Interestingly, this effect was abrogated by a selective CB_2 receptor antagonist (AM630) (Al Mansouri et al. 2014)▪ , thus suggesting a connection between the CB_2 receptor and ethanol consumption and representing a potential novel pharmacological target for the treatment of alcoholism. In this way, Marcus et al. (2017)▪ reported that mutant mice expressing a "hyper-sensitive" form of CB_1 show similar taste preference for sucrose, quinine and alcohol and did not change ethanol consumption.

7. Effects of cannabinoids on food flavor and on peripheral mechanisms to the control of feeding pattern

Flavor corresponds to the combination of sensations that includes taste, odor and trigeminal inputs. Innate and learned flavor preferences influence food and drink choices (see Tarragon and Moreno 2017 for a more in-depth description of the role of the ECS on food preference). It has a major role in the final (*gestalt*) perception and enjoyment of food, thus being considered the main endogenous factor for food preferences and intake (Bodnar 2016)▪ .

The two primary forms of learned preferences involve flavor-flavor and flavor-nutrient associations. In these, a specific flavor element (e.g., odor) is paired with an innately preferred flavor element (e.g., sweet taste) and/or with a positive post-oral nutrient consequence (i.e. higher energy available) (Touzani et al. 2010). It has been proposed that these two dimensions of learned preferences are driven by related albeit different neural mechanisms, among which the dopaminergic, the opioid and the eCBs are of remarked relevance. Given the scope of this review, we will focus primarily on the latter.

Pharmacological manipulations of CB_1 receptors with eCBs, synthetic CBs, Δ^9-THC and other phytocannabinoids are widely reported among the literature on eating behavior (Gamage and Lichtman 2012). For instance, the exogenous administration of AEA has proved to affect eating pattern by reducing the latency to food consumption, and by increasing the size of the meal and consumption duration (Hao et al. 2000; Jamshidi and Taylor 2001; Williams and Kirkham 2002a). Also, the administration of dronabiol (a synthetic CB), Δ^9-THC, THC-derived phytocanabinnoids, and non-THC-derived phytocannabinoids are capable of stimulating feeding behavior in rats (Williams and Kirkham 2002b; Farrimond et al. 2010, 2012a, 2012b). According to these studies, the enhanced feeding response is mediated by the activation of the CB_1 receptor. Further, CB_1 agonist did not only increased total volume of food, but also affected other parameters of feeding pattern including the aforementioned delay to food and meal size, two features that mostly fall within the flavor-flavor category mentioned above.

In the 1970s some of the first experimental studies investigating the effects of THC on food intake in humans reported significant increases in consumption of chocolate milk shakes and marshmallows (Abel 1971), a finding which now underlines the two main aspects of the ECS in modulating both appetite and the hedonic of highly palatable

foods such as sweets and fats (Harrold and Williams 2003). The implication of CB_1 receptor in human weight homeostasis has also been confirmed measuring CB_1 availability by positron emission tomography in volunteers and patients with food eating disorders (FED) such as anorexia nervosa, bulimia nervosa, and also in obesity (Ceccarini et al. 2016). More specifically, data shows an inverse association between CB_1 receptor availability and body mass index (BMI) in the hypothalamus and the brainsteam in healthy subjects and patients with food eating disorders both. However, other brain regions involved in the processing of reward and hedonic value of food (i.e. striatum, insula, amygdala, and OFC) only correlated with BMI in FED patients. Coherent with this, a recent study showed that cannabivarin, a CB_1 antagonist, increased responses to chocolate stimuli and to aversive stimuli in the amygdala, the insula and the OFC (Tudge et al. 2015).

A recent study shows that the hyperphagia observed in obese mice that followed a typical western style diet for 60 days is dependent on CB_1 receptors. Specifically, the inhibition of peripheral CB_1 receptors reduced food consumption in the western diet but not in the standard diet group (Argueta and Di Patrizio 2017). This information is coherent with other studies showing that smell can enhance response to food via CB_1 receptors in terminal axons project towards the olfactory bulb (Soria-Gómez et al. 2014b; Busquets-Garcia et al. 2015). In addition, Mathes and colleagues demonstrated that the blockade of CB_1 receptors is able to prevent body weight by selectively decreasing the selection of fattening foods in an obesity-induced protocol in rats (Mathes et al. 2008).

Interestingly, another recent study showed that there is no difference when comparing the administration of phytocannabinoids, synthetic CBs, and eCBs with respect body weight regulation, food intake, and glucose homeostasis (Marcus et al. 2016). Also, it has been shown that cannabidiol does not affect negatively the affective response to

emotional stimuli in humans (Arndt and de Wit 2017). Despite that this study was carried out with facial stimuli, the results from Arndt and de Wit could provide a starting point to explore the effect of phytocannabinoids and synthetic CBs on other levels of the emotional continuum, like the affective response to food.

It has also been observed that the presence of fat in the oral cavity induces a cephalic-phase response resulting in jejunal production of eCBs, further linked with increased fat intake (Di Patrizio et al. 2011). It was hypothesized that this effect might be triggered by ghrelin, since gastric CB_1 activation leads to ghrelin secretion, which increases fat-taste perception and promotes fat intake (Perello et al. 2010). Interestingly, salivary eCBs are found in higher concentration in obese patients in comparison with healthy subjects (Matias et al. 2012) and might be associated with ω-6/ω-3 ratio intake (Zimmer et al. 2018, unpublished data). Further, eCBs can increase neural response specifically to sweet taste through a CB_1-dependent mechanism (Yoshida et al. 2010).

Considering that ECS can also modulate olfactory responses, it is worth noting the role of this system in the regulation of sensory information (flavor) associated with food intake and feeding pattern. Both exogenous and endogenous CBs strongly stimulate intake of sugars and fats in particular (Koch 2001; Kirkham 2005). Moreover, it has been observed that CB_1 antagonism reduced the expression of fructose-conditioned flavor preference while failing to affect the acquisition of such preference (Miner et al. 2008).

The evidence presented indicates that modifications in the strength of learned flavor associations could influence behavior towards food. Moreover, given the motivational properties of palatability, manipulating these flavor-flavor and flavor-nutrient associations could serve as a therapeutic tool in illnesses where taste perception is altered, thus potentiating adherence to the treatment. Unfortunately, despite all the

information collected around the CB system and the flavor-flavor dimension, the role of CB_1 in flavor-nutrient learning has yet to be investigated.

There is no literature, to the best of our knowledge, covering the affective response to food after the administration of CB derivatives nor synthetic CBs. It is reasonable to hypothesize that the same operating mechanisms for eCBs and Δ^9-THC are operating in the brain, thus exerting similar effects regarding energy homeostasis and the regulation of eating behavior (Fig. 3). However, as mentioned, the experimental evidence to claim this is circumstantial.

The evidence on human subjects with respect the effect of ECS on feeding pattern is not as numerous as in rodent models. Ethical concerns with respect the use of THC-derivatives with potential psychotropic effects on the volunteers maybe a reason for the limited number of studies. Hence, synthetic and non-psychotropic THC derivatives may represent a promising alternative to study how the ECS participates in eating behavior in general, and in chemosensory response to food, particularly. Thus, THC and ghrelin have been proposed in the palliation of chemosensory alterations (dysgeusia) to improve food enjoyment (Vancleef et al. 2015; Sun et al. 2016)▪ . A growing number of studies currently focus on this promising area, although more research is needed to fully grasp the potential implication of these CB-related compounds on smell, taste, and other properties of the eating experience.

8. Conclusion

Since the isolation of the psychoactive component of the *C. sativa* in the early 1960s, hundreds of CB derivatives have been discovered in plants and developed in laboratories. All these compounds bind to a certain degree to specific CB receptors located both in the brain and peripherally, from where regulate and modulate a great

deal of physiological and psychological processes. Some of these compounds present promising properties as therapeutic drugs for several conditions, particularly in those related to obesity. Unfortunately, the amount of research covering the putative effects of phytocannabinoids and synthetic CBs on metabolic-related disorders is remarkably scarce, particularly in regard to relevant aspects of eating behavior, such as smell, and sweet and fat taste sensitivity. In this review, we summarized the role of the ECS in chemosensory perception, given it is pivotal function in eating behavior. Understanding that the ECS also affects energy homeostasis through its influence on how taste and smell are perceived is relevant for developing better strategies targeting body weight homeostasis disruption-related conditions. Further, we believe that both phytocannabinoids and synthetic CB compounds would be promising pharmacological alternatives in the treatment of high prevalence diseases such as obesity, type 2 diabetes and metabolic syndrome.

9. References

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1263 Table 1. Brief overview of the main CB receptor ligands, giving basic information and effects on food intake and body weight

Ligand	Original report	Company	Commercial name	CB_1	CB_2	Similar molecules	Effect on food intake	Effect on body weight
2-AG	Mechoulam et al., 1995			Ag	Ag		↑(Lambert & Muccioli 2007)	↑(Kirkham 2005)
AEA	Devane et al., 1992			Ag	Ag	oleoylethanolamide	↑(Lambert & Muccioli 2007)	↑(Kirkham 2005)
Δ^9THC	Ben-Zvi et al., 1970		Marinol, Syndro, Sativex	Ag	Ag			↑(Jarbe and Di Patrizio, 2005)
Δ^9THCV	Gill et al., 1970			Ag	Ag		↓(Riedel et al. 2009)	↓(Riedel et al. 2009)
CBD	Adams and Baker, 1940			Ag	Ag			↓(Ignatowska et al. 2011)
HU-210	Mechoulam, 1988	Hebrew Univ.	Dexanabinol	Ag	Ag	HU211, HU239, HU243, HU308, HU320, HU345		↓(Giuliani et al. 2000)
CP 55,940	Little et al., 1988	Pfizer		Ag	Ag	CP 47,497		
CP945,598	Kim et al., 2008	Pzifer	Otenabant	Antag			↓(Hadcock et al. 2010)	↓(Hadcock et al. 2010)

AM251	Gatley et al., 1996	Sanofi Aventis		Antag			↓(Riedel et al. 2009)	↓(Riedel et al. 2009)
AM630	Pertween et al., 1995	Sanofi Aventis	Drinabant	Antag	Antag			
AM4113	Sink et al., 2007	Sanofi Aventis		Antag	Antag		↓(Cluny et al. 2011)	↓(Cluny et al. 2011)
AM6545	Makriyannis et al., 2010	University of Connecticut		Antag	Antag		↓(Cluny et al. 2011)	↓(Tam et al., 2010)
JWH015	Huffman et al., 1994	John W Huffman		Ag	Ag	JWH018, JWH133		
MK0364	Arstrong et al., 2007	Merck	Taranabant	Antag			↓(Fong et al. 2007)	↓(Fong et al. 2007)
PSNCBAM-1	Horswill et al., 2007			Negative allosteric Ag		GAT100, Org27,569, ZCZ-011	↓ (Horswill et al. 2007)	↓(Horswill et al. 2007)
O-2050	Martin et al., 2002	Virginia Commm Univ.		Antag		O2113, O2372, O2545	↓(Gardner and Mallet 2006)	
SR141716A	Rinaldi et al., 1994	Sanofi Aventis	Rimonabant (Acomplia, Zimulti)	Antag		SR147778 (Surinabant)	↓(Jarbe and Di Patrizio, 2005)	
SR144528	Rinaldi et al., 1998	Sanofi Aventis		Antag		UR12, UR144, JWH203, MDA19, WIN55,225,		

					WIN56,098		
SM-11	Fois et al., 2016	University of Sassari		Antag	NESS06SM	↓(Fous et al., 2016)	↓(Fous et al., 2016)
WIN55212-2	Pacheco et al., 1991			Ag	CP55,940	↑(Merroun et al., 2009)	
LY320135	Felder et al., 1998	Elli Lilly		Antag			

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Table 2. Summary of studies exploring the influence of the ECS on chemosensory perception

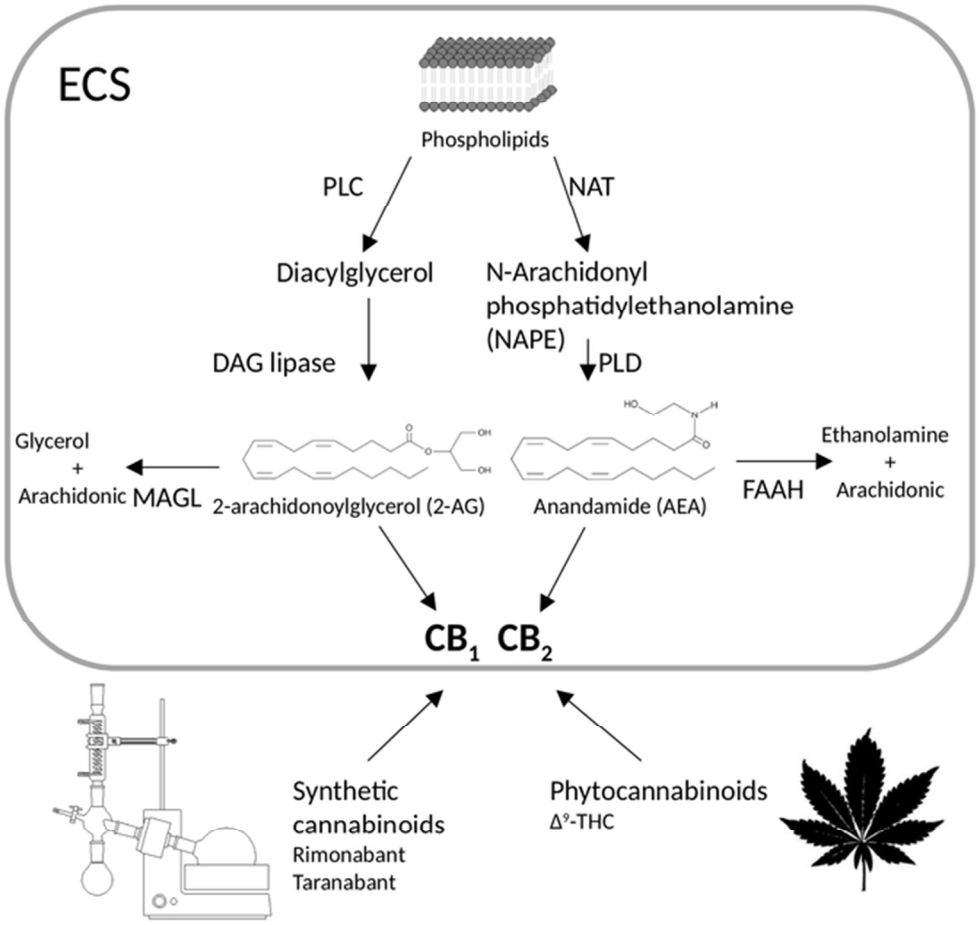
Reference	Ligand	Effect on ECS	Effect on chemosensory perception
Simiand et al., 1998	SR141716A	CB_1 antag	Selectively reduced sweet food intake compared to standard food pellets.
Ward and Dykstra, 2005	CP-55940	CB_1 ag	Facilitates response acquisition for sweetened and fatty solutions following a progressive ratio learning protocol.
	SR141716A	CB_1 antag	Impairs enhanced response for sweetened and fatty solutions following a progressive ratio learning protocol.
Czesnik et al., 2007	AM281, AM251, and LY320135	CB_1 antag	Diminish and delay food odor responses.
Di Patrizio and Simansky, 2008	AM251	CB_1 antag	Impaired pontine parabrachial nucleus response, associated with the gustatory properties of food.
	2-AG	CB_1 and CB_2 ag	Strong increase of fat and sucrose, sucrose, and fat intake.
Breuning et al., 2010	RHC80267, OMDM-187, and OMDM-188	DAG lipase blockers	The delay and amplitude of individual olfactory response neurons were prolonged in the presence of odorants.
	HU210	CB_1 ag	Restored olfactory sensitivity and lowered the olfactory sensitivity threshold.
Yoshida et al., 2010	AEA, 2-AG	CB_1 and CB_2 ag	Increases gustatory response to sweeteners but not to salty, sour, bitter, and umami compounds.
	AM251	CB_1 antag	Diminishes gustatory response to sweeteners.
	AM630	CB_2 antag	Does not affect gustatory response to sweeteners.
Brisbois et al., 2011	THC	CB_1 ag	Improved improved and enhanced chemosensory perception and gustatory response in chemotherapy patients.

Umabiki et al., 2011	(AAT)12 repeat	CB_1 receptor gene	Higher sweet sensitivity threshold in non carriers of the (AAT)12 repeat gene, coding for the CB_1 receptor.
Wang et al., 2012	AEA, WIN55,212-2 AM251	CB_1 ag CB_1 antag	Cannabinoid agonism/antagonism regulates neuron firing patterns in the glomeruli of the main olfactory bulb.
DiPatrizio et al., 2013	AM6546, URB447	CB_1 antag	Diminishes preference for solutions rich in monoenoic and dienoic fatty acids, observed in non-treated rats.
Barbarossa et al., 2013	AEA, 2-AG	CB_1 and CB_2 ag	Highly sensitive individuals to 6-n-propylthiouracil showed greater levels of plasmatic AEA and 2-AG compared to individuals with lower sensitivity.
Soria-Gomez et al., 2014	AM251 THC	CB_1 antag CB_1 and CB_2 ag	Administration into the granular layer of the main olfactory bulb reduced intake in fasted mice with elevated levels of AEA. Administration into the granular layer of the main olfactory bulb enhanced fasting-induced food intake.
Niki et al., 2015	AM251	CB_1 antag	Enhanced response for sweetened solution impaired in lean mice, but not genetically obese or diet-induce obese mice. Genetically obese mice showed increased levels of 2-AG and DAGL in taste cells after the administration of AM251.
Pastor et al., 2016	AEA, 2-AG	CB_1 and CB_2 ag	Threshold-discrimination-identification capacity was associated with lower 2-AG and higher body fat percentage in obese women compared to non-obese women.
de Brujin et al., 2017	THC, CBD	CB_1 and CB_2 ag	When inhaled, neither THC nor CBD affected sweetness sensitivity threshold, liking, or ad libitum consumption of the preferred drink. Food preference was not affected neither.

Figure 1. Synthesis of synthetic, phyto-, and endocannabinoids. Schematic representation of the synthesis process from which synthetic cannabinoids, phytocannabinoids and endocannabinoids are obtained.

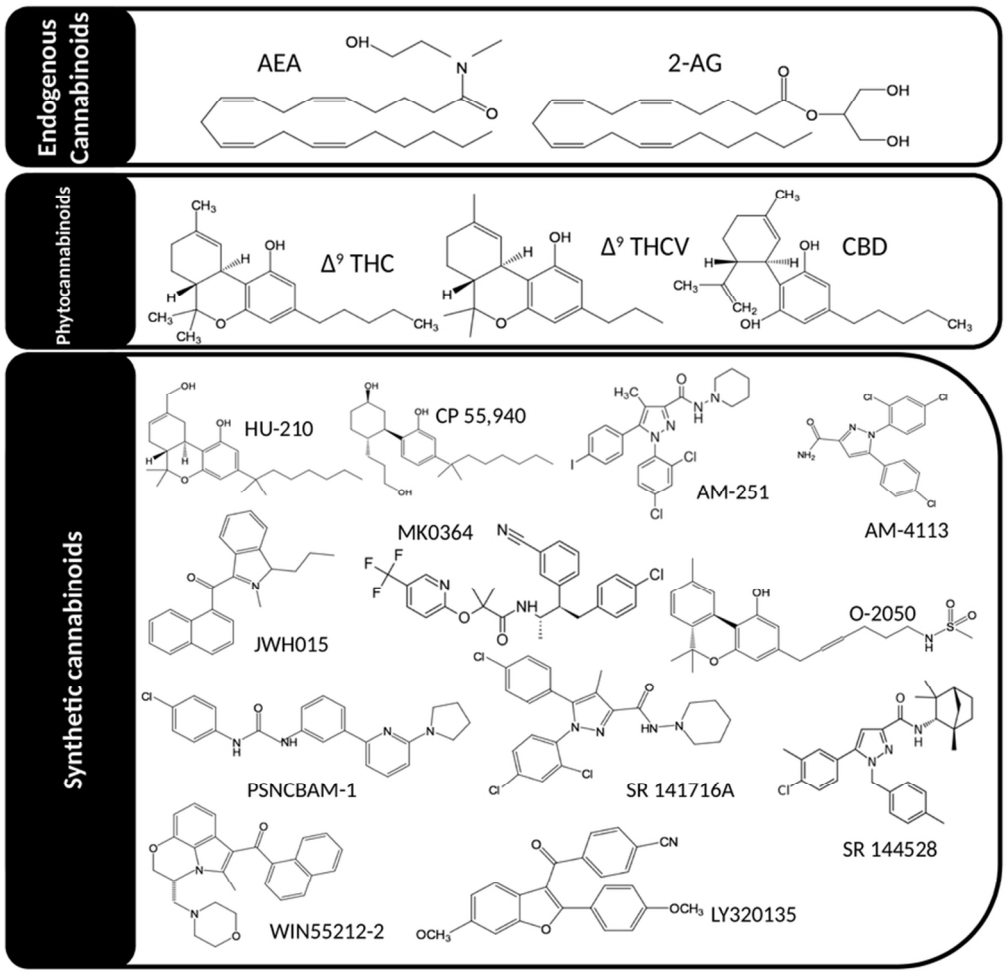
Figure 2. Synthetic, phyto-, and endocannabinoids. Here there are some of the most popular among the hundreds of cannabinoid molecules discovered since the 1970s.

Figure 3. Chemosensory response and the ECS. The molecular reaction initiated by the perception of aromas is entangled with the ECS functioning. As well as by endogenous and exogenous cannabinoids, CB receptors are activated by the chemosensory response in the olfactory bulb and along the brain circuitry involved in the emotional and cognitive effect triggered by taste and smell. This activity is afterwards involved in several physiological and psychological aspects of eating behavior, such as developing preferences for certain tastes and foods, and even modulating food intake.



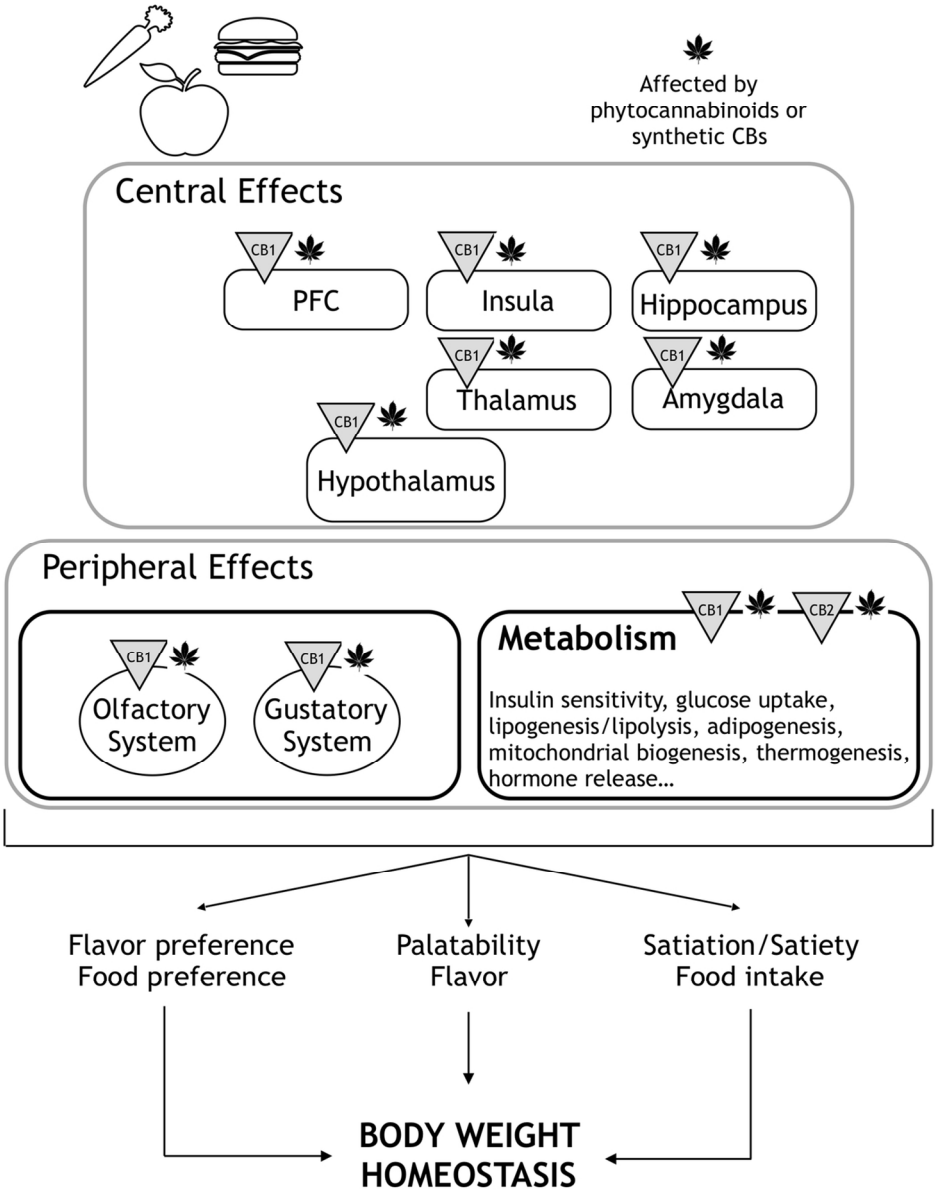
Synthesis of synthetic, phyto-, and endocannabinoids. Schematic representation of the synthesis process from which synthetic cannabinoids, phytocannabinoids and endocannabinoids are obtained.

116x108mm (150 x 150 DPI)



Synthetic, phyto-, and endocannabinoids. Here there are some of the most popular among the hundreds of cannabinoid molecules discovered since the 1970s.

153x149mm (150 x 150 DPI)



Chemosensory response and the ECS. The molecular reaction initiated by the perception of aromas is entangled with the ECS functioning. As well as by endogenous and exogenous cannabinoids, CB receptors are activated by the chemosensory response in the olfactory bulb and along the brain circuitry involved in the emotional and cognitive effect triggered by taste and smell. This activity is afterwards involved in several physiological and psychological aspects of eating behavior, such as developing preferences for certain tastes and foods, and even modulating food intake.

224x286mm (150 x 150 DPI)