CellPress

Neuron
Perspective

The CB1 Receptor as the Cornerstone of Exostasis

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http://dx.doi.org/10.1016/j.neuron.2017.02.002

The type-1 cannabinoid receptor (CB1) is the main effector of the endocannabinoid system (ECS), which is involved in most brain and body functions. In this Perspective, we provide evidence indicating that CB1 receptor functions are key determinants of bodily coordinated exostatic processes. First, we will introduce the concepts of endostasis and exostasis as compensation or accumulation for immediate or future energy needs and discuss how exostasis has been necessary for the survival of species during evolution. Then, we will argue how different specific biological functions of the CB1 receptor in the body converge to provide physiological exostatic processes. Finally, we will introduce the concept of proactive evolution-induced diseases (PEIDs), which helps explain the seeming paradox that an evolutionary-selected physiological function can become the cause of epidemic pathological conditions, such as obesity. We propose here a possible unifying theory of CB1 receptor functions that can be tested by future experimental studies.

CB1 Receptor: Multiple Functions for a Single Purpose?

One of the most fascinating chapters in the physiology of multicellular organisms lies in the discovery and study over the last decades of the functions of the endocannabinoid system (ECS) and its main effector the cannabinoid type-1 receptor (CB1). Despite an intense accumulation of data, the diverse physiological roles of CB1 still constitute the pieces of a jigsaw puzzle that taken one by one give the impression of scattered and seemingly unrelated tissue-specific actions.

CB1 was discovered as the target of the main psychotropic component of the plant *Cannabis sativa* (marijuana) Δ^9-tetrahydrocannabinol (THC) (Howlett et al., 2002; Piomelli, 2003). Since the identification of THC (Adams, 1942; Gaoni and Mechoulam, 1964) and the later characterization of cannabinoid receptors (Matsuda et al., 1990), enormous progress has been made in understanding cannabinoid mechanisms of action and in identifying the physiological roles of cannabinoid receptors. Endogenous ligands for these receptors exist (endocannabinoids), which are mainly lipid compounds derived from arachidonic acid. Endocannabinoids, cannabinoid receptors, and the enzymatic machinery for endocannabinoid synthesis and degradation form the endocannabinoid system (ECS). The functions of the ECS are difficult to enumerate because almost all body processes can involve endocannabinoid signaling in physiological or pathological conditions. Due to this huge diversity, these functions have been addressed separately, suggesting that multiple forms of evolutionary pressure contributed to the development of the ECS to fulfill different and unrelated functions. In this Perspective, we argue that this might not be the case. We propose that the main function of the ECS, and in particular of CB1 receptors, is to promote exostatic processes in the regulation of body energy balance. Energy homeostasis is provided by two evolutionarily conserved processes: endostasis, which is aimed at fulfilling *immediate* energetic needs, and exostasis, aimed at promoting the accumulation of energetic stores for *future* needs. Most of CB1 receptor functions largely fulfill the requirements for a prototypical exostatic system, providing a novel unified perspective for future studies.

Body Energy Homeostasis: A Combination of Endostasis and Exostasis

In this section, we will introduce the concepts of endostasis and exostasis, key physiological processes selected during evolution to guarantee individual and species survival.

Most animals when exposed to ad libitum access to food, especially palatable and attractive foods, will eventually overeat and become overweight and obese (Bernstein et al., 1975). Obesity is a pathological state with the potential to reduce the chance of survival, making this over consumption behavior paradoxically self-damaging. This observation indicates that the motivational and metabolic processes regulating food intake and energy balance can go *beyond* the immediate energetic needs of subjects.

This apparent paradox is difficult to understand without taking into account the evolutionary constraints that contributed to the development of the systems that regulate energy balance. It is well established that energy balance defined here as the balance between the intake and the use of energy by the organism is regulated by two major systems classically called the homeostatic or compensated system (Berthoud, 2003; de Castro and Plunkett, 2002) and the non-homeostatic or uncompensated system (Berthoud, 2003; de Castro and Plunkett, 2002).

The compensated or homeostatic system responds to a decrease in the internal energy status of the organism by eliciting hunger and food intake. This system is motivationally controlled by an internal drive, a decrease in available energy levels, and sub-serves the function of coping with the immediate need of the organism (Berthoud, 2003; de Castro and Plunkett, 2002). The adjectives homeostatic or compensated were used because eating and the related signals of replenished energy (nutrients, hormones) generally induce an inhibition of food intake in order

to avoid overeating and metabolic overload (Berthoud, 2003, 2011; de Castro and Plunkett, 2002).

In contrast, non-homeostatic or uncompensated mechanisms are activated by the presence of food in the environment (Berthoud, 2003, 2011; de Castro and Plunkett, 2002). The presence, detection, and specific organoleptic characteristics of food act as triggers to stimulate food intake. Whereas hunger is generally considered the only motivational drive to ingest food, we often eat simply because food is available. In this case, the incentive properties of food (i.e., its presence, organoleptic features, and palatability) represent the motivational force to eat (Berthoud, 2003, 2011; de Castro and Plunkett, 2002). The presence of food, especially if palatable and rich in calories, exerts a positive, motivational pull that seems independent from the immediate needs of the individual. This results in eating in an apparently unregulated fashion (Berthoud, 2003, 2011; de Castro and Plunkett, 2002). The uncompensated mechanism of food intake is responsible for the reinstatement of food intake in sated animals that are presented with a new and/or more palatable food. This system is responsible for the higher amount of food ingested in circumstances where the diet is composed of several types of food with different organoleptic features (Berthoud, 2003, 2011; de Castro and Plunkett, 2002). The uncompensated system is also responsible for the increase in food intake induced by the presence of congeners (Berthoud, 2003, 2011; de Castro and Plunkett, 2002). These mechanisms can be illustrated in an anecdotic everyday-life example: imagine being at the end of a copious dinner with friends. Of course, you feel satiated. However, suddenly a fantastic dessert is brought to the table, which is the same one that your grandmother used to prepare for you when you were a kid. Sated or not, you will eat and probably have two or three helpings, likely with negative consequences on your metabolic profile (at least for the next few days). However, this behavior is perfectly normal, and it does not indicate psychological unbalance or lack of control. It is just a sign that in those moments you are experiencing the power of the major system controlling food intake. Indeed, not only personal experiences, but also mathematical models have shown that the influence on behavior of the uncompensated system is stronger and can overcome the compensated one (Berthoud, 2003, 2011; de Castro and Plunkett, 2002).

It is worth noting that the distinction between the different motivational forces is schematic in nature: drive and incentive can overlap in terms of both behavioral processes and cellular mechanisms. Incentive properties of food increase with hunger, and hormones associated with low energy status can increase the activity of incentive-related brain circuits such as the mesocorticolimbic circuitry that includes dopamine neurons of the ventral tegmental area (VTA). The stomach-derived hormone ghrelin, whose levels are high in fasting, increases impulsive behavior and drives binge eating by acting through VTA dopamine neurons (Anderberg et al., 2016; Valdivia et al., 2015). Conversely, hormones that signal energy surfeit to the brain, such as leptin and insulin, decrease reactivity to cues associated with palatable foods and reduce food intake by inhibiting VTA dopamine neurons (Hommel et al., 2006; Khanh et al., 2014; Mebel et al., 2012; van der Plasse et al., 2015). Accordingly, hypothalamic circuits that are classically viewed as the target of the action of hormones involved in the regulation of feeding behavior (Berthoud, 2011) can also be rapidly modulated by incentive stimuli (Chen et al., 2015). Fasting-induced hyperphagia might represent an example of the overlap between different forces, where different mechanisms (e.g., endogenous drive to eat, inhibition of satiety signals, increased palatability of food, etc.) converge to increase the intake of energy.

Nevertheless, the discrimination between compensated and uncompensated systems is valid and represents an optimal theoretical frame to understand the motivational mechanisms underlying food intake and energy accumulation.

A question immediately arises from these observations: why do we have an uncompensated, non-homeostatic system whose consequence is to make us overweight and eventually more prone to develop diseases, such as cardiovascular disorders, diabetes, and cancer? How is it possible that such a system has survived evolutionary selection? The adaptive value of this system is quite difficult to understand in the present environmental conditions of developed western countries, where food availability is virtually unlimited. However, humans have been hunters and gatherers for approximately four million years (Harari, 2015). Consequently, during the largest period of the evolution of our species, there was no direct control on food availability and our ability to store gathered or hunted food was extremely limited. In these variable foraging conditions, having a system that was able to overcome immediate needs and increase energy storage to cope with future foraging difficulties was clearly fundamental for survival (Figure 1). Sufficient calorie storage in the form of fat also favored reproduction. Individuals under a stronger control of "non-compensated" motivational forces acquired a clear advantage for the maintenance of the species.

By definition, physiological mechanisms have all evolved to maintain survival of individuals and species. Thus, physiological processes have to be considered "homeostatic," as opposed to pathological ones, which are "non-homeostatic." In this sense, defining a biological and non-pathological process as "non-homeostatic" could appear as an oxymoron. Similarly, the term "uncompensated" recalls unbalanced conditions, which are difficult to conceptualize for physiological states and mechanisms. Conversely, we believe that both systems regulating energy balance are "homeostatic" and "compensated" in nature in the sense that both have been selected during evolution to maximize the chances of survival. We propose to rename the two systems described above to reflect the homeostatic control of energy balance. We prefer to think of the homeostatic or compensated system as *endostatic* and the non-homeostatic or uncompensated system as *exostatic* (Figure 2). The endostatic system ("I eat when hungry") has evolved to counteract a decrease in endogenous levels of energy and to allow individuals to cope with *present* energy needs. It is endostatic because motivational and metabolic processes respond mainly to endogenous signals of the organism. Conversely, the exostatic system ("I eat when food is available") has the role of compensating for potential decreases in the external levels of nutrients and allows individuals to cope with *future* needs. It is exostatic, because the stimuli triggering ingestion and accumulation of energy are external to the individual and involve innate and learned responses to food and associated stimuli (Figure 2).

Figure 1. Evolution of Food Sources over the Time

For approximately four million years, humans have evolved in an environment where foraging supplies were very variable. Therefore, during the largest period of the evolution of our species, we had no control over food availability and were unable to store food and prevent food shortages. At around 10,000 BC, farming began, which stabilized the energy sources. One hundred years ago, the introduction of the fridge and other technological advances finally allowed producing and preserving food in large amounts, provoking a shift from "stable" to "supra-stable" environmental conditions. However, the supra-stable condition of modern time (100 years) is virtually nonexistent in an evolutionary time frame.

Both endostatic and exostatic mechanisms confer clear advantages to the adaptive possibilities of individuals in an environment with variable foraging conditions where food availability can rapidly change due to unforeseen events such as climatic perturbations or epidemics in a principal foraging source. Maintaining both endostatic and exostatic systems within a species confers a clear evolutionary advantage. Individuals with a stronger endostatic phenotype will have a greater chance of surviving periods of abundant food availability by avoiding over-eating and excessive accumulation of fat. These same individuals will be at a disadvantage during periods of paucity. Conversely, predominantly "exostatic" subjects will have a greater chance during periods of scarce energy sources but will be at risk of over-eating, obesity, and associated metabolic problems in conditions of abundance (Figure 2). The large availability of calorie-rich food that can be obtained with very limited energy expenditure (going to the fridge costs less energy than hunting in the forest) sets the physiological exostatic system as a danger for the health and wellbeing of individuals in Western, developed countries.

We propose that CB1 receptor signaling in the body largely contributes to exostatic functions. In the following section, we will expand this idea by first describing the molecular organization of the ECS and then discussing how the large majority of CB1 receptor-dependent functions fit with the theoretical properties of an exostatic system.

Molecular Organization of the Endocannabinoid System

The ECS is comprised of the cannabinoid receptors CB1 and CB2, their endogenous ligands, the classical arachidonic acid-derivate lipid endocannabinoids (De Petrocellis et al., 2004; Piomelli, 2003), and more recently described ligands including the peptide endocannabinoids, the so-called pepcans (Bauer et al., 2012; Hofer et al., 2015), the lipid lipoxin A4 (Pamplona et al., 2012) and the neurosteroid pregnenolone (Vallée et al., 2014). The enzymatic machinery for synthesis and degradation of endocannabinoids is also part of the ECS (De Petrocellis et al., 2004; Piomelli, 2003). Endocannabinoids have been identified in many species (De Petrocellis et al., 1999; McPartland et al., 2006a, 2006b). However, orthologs of CB1 receptors with various degrees of homology have been identified in fishes, amphibians, birds, and mammals (Elphick, 2012). Insects do not have cannabinoid receptors (McPartland et al., 2001), whereas the genome of non-verebrate cordates, such as the sea squirt, contain a gene expressing a combined CB1-CB2 receptor (Elphick, 2012). CB1 receptor orthologs are likely present in reptiles (St John et al., 2012). In this section, we will briefly describe general aspects of the molecular organization of the ECS in

Figure 2. Endostasis and Exostasis: Two Equally Important Homeostatic Functions Increase the Chance of Survival

Eating behavior and energy accumulation is governed by two homeostatic systems. The endostatic system pushes the individual to eat to compensate for a decrease in the level of fuel in the organism to maintain an ideal energy level. The exostatic system (previously described has non-homeostatic or uncompensated) pushes the individual to eat as a function of food availability allowing increased energy storage to overcome future decreases in energy source availability.

(A–C) The "Homo Endostaticus," in which the endostatic system is prevalent, by eating as a function of internal needs, will have a greater chance of surviving during periods of plenty (A and C), but will be disadvantaged during periods of scarce food availability (B). Conversely, The "Homo Exostaticus," in which the exostatic system is prevalent, by eating every time food is available, will have greater chances of survival during future periods of scarce energy sources (B), but will over eat (A) and will be at risk of developing obesity and associated metabolic disorders when food is abundantly available, as it happens presently (C).

mammals, particularly in humans and rodents. Several excellent reviews exist on this subject, and we refer the reader to them for a more exhaustive discussion (Lutz et al., 2015; Mechoulam et al., 2014; Piomelli, 2003; Silvestri and Di Marzo, 2013).

Endogenous Ligands

Typical endocannabinoids have the peculiarity of being lipids derived from arachidonic acid (Piomelli, 2003). This characteristic explains why these endocannabinoids are not stored but mostly produced on demand by cell membranes. Water-soluble endogenous mediators are generally kept in the intracellular compartment in lipid vesicles that would be unable to hold lipid molecules. Classic lipid endocannabinoids are believed to originate from cellular membranes and to be mobilized upon specific stimuli (Piomelli, 2003). Little is known concerning the storage and release of pepcans; however, they likely use vesicle-dependent mechanisms (Bauer et al., 2012; Hofer et al., 2015). The mechanisms of production, storage, and release of the allosteric CB1 receptor enhancer lipoxin A4 in the brain are not known, but they might be similar to the ones described in blood cells, through transcellular generation (McMahon et al., 2001). Like all steroids, the signal specific CB_1 allosteric inhibitor pregnenolone is produced in mitochondria from cholesterol processing (Vallée, 2016).

The most studied lipid endocannabinoids are arachidonoylethanolamide (anandamide) (Devane et al., 1992) and 2-arachidonoylglycerol (2-AG) (Mechoulam et al., 1995; Sugiura et al., 1995). Several pathways are known to regulate the synthesis of these endogenous compounds, but the best characterized are as follows. Anandamide is synthesized in plasma membranes of mammalian cells mainly in two steps (Cadas et al., 1997). The first is the formation of the N-arachidonylphosphatidylethanolamine (n-arachidonyl-PE, NAPE). NAPE is obtained from arachidonic acid and phosphatidylethanolamine by the enzyme N-acyltransferase NAT (Cadas et al., 1997). The NAPE is the precursor of anandamide that is obtained by the action of a specific phospholipase, the NAPE-PLD that transforms NAPE in anandamide and phosphatidic acid (Okamoto et al., 2004).

Two synthetic pathways, both starting from phosphatidylinositol, have been hypothesized for 2-AG (Piomelli, 2003). The first pathway involves the phospholipase C (PLC) that transforms phosphatidylinositol in 1,2 diacylglycerol (1,2 DAG), which is then hydrolyzed into 2-AG by diacylglycerol lipase (DAGL) (Bisogno et al., 2003; Stella et al., 1997). The second pathway (Piomelli, 2003) involves phospholipase A1, which transforms phosphatidylinositol into 2-arachidonoyl-lysophospholipid (lyso-PI), which is then hydrolyzed into 2-AG by lyso-PLC.

In the brain, the synthesis of endocannabinoids is mainly stimulated by an increase in intracellular Ca^{2+} and/or activation of specific pathways and receptors such as the metabotropic glutamate receptors or the muscarinic acetylcholine receptors (Kano et al., 2009; Piomelli, 2003; Stella and Piomelli, 2001). The increase in Ca^{2+} can result from the opening of membrane ionic channels or from the mobilization of the intracellular stores by PLC β (Kano et al., 2009). Although 2-AG and anandamide seem to be regulated by similar intracellular mechanisms, certain stimuli can increase preferentially one or the other ligand. This is the case during the stimulation of the dopamine D2 receptors, which appears to specifically increase the concentration of anandamide but not of 2-AG (Ferrer et al., 2003; Giuffrida et al., 1999).

As lipids, classic endocannabinoids can move within membranes, and thereby bind and activate CB1 and CB2 receptors in the same cells where they are produced via autocrine-like mechanisms (Bacci et al., 2004; Marinelli et al., 2009; Piomelli, 2003). In contrast to reach target cells through the extracellular space, endocannabinoids need to be carried by specific transport proteins. In the blood stream this function is fulfilled by serum albumin, allowing the endocannabinoids to possibly act in an endocrine way (Bojesen and Hansen, 2003), while the specific transport protein for paracrine actions of endocannabinoids has not been identified yet.

Once produced, endocannabinoids are inactivated by two subsequent mechanisms (Piomelli, 2003), including cellular uptake and intracellular enzymatic degradation. The cellular uptake is based on passive diffusion and facilitated transport. The exact nature of the last mechanism, which does not demand energy, remains rather elusive (Beltramo and Piomelli, 2000; Beltramo et al., 1997; Hillard et al., 1997), although certain proteins have been proposed as candidates to fulfill this task (Fowler, 2012, 2013; Nicolussi and Gertsch, 2015). Once inside the cell, endocannabinoids are inactivated by specific enzymes, the fatty acid amide hydrolase (FAAH) for anandamide (Cravatt et al., 1996; Cravatt and Lichtman, 2002, 2003; Piomelli, 2003; Ueda et al., 1995) and the monoglycerol lipase (MAGL) for 2-AG, respectively (Dinh et al., 2002a; Dinh et al., 2002b; Goparaju et al., 1999). Additional degrading enzymes were more recently discovered, including the serine hydrolase ABHD6, which is able to degrade 2-AG (Marrs et al., 2010).

The enzymatic degradation of endocannabinoids plays an important role in the control of their tissue levels. Thus, genetic invalidation of FAAH increases ten times the tissue levels of endocannabinoids (Cravatt et al., 2001) and the deletion of MAGL strongly increases the levels of 2-AG (Schlosburg et al., 2010).

Alternative biochemical pathways have been described for endocannabinoids synthesis and degradation, indicating an important redundancy in these mechanisms (Iannotti et al., 2016).

Cannabinoid Receptors

Cannabinoids and endocannabinoids can target other cell proteins than cannabinoid receptors, making it difficult to establish the specific boundaries of the proper ECS (Begg et al., 2005; De Petrocellis and Di Marzo, 2010; Freund et al., 2003; Gasperi et al., 2013; Lutz et al., 2015; Mo et al., 2004). Based on the fact that they are activated by synthetic, plant-derived, and endogenous cannabinoids, two proteins have been cloned and are considered the bona fide cannabinoid receptors: CB1 (Matsuda et al., 1990) and CB2 (Munro et al., 1993). They belong to the large family of seven transmembrane domains receptors coupled to G proteins (GPCRs) (Howlett, 2002; Howlett et al., 2002). The homology between CB1 and CB2 is rather small (48%), even in regions of the proteins that are well conserved among different members of GPCR family (normally about 78%) (Howlett, 2002; Howlett et al., 2002). The major difference between the two receptors is in the extracellular tail that is 74 amino acids longer in the CB1 than in the CB2. Although recent

data suggest an implication of CB2 receptors in energy balance (Agudo et al., 2010; Verty et al., 2015), most of the published evidence refers to CB1 receptors. For this reason, we will focus the following paragraphs on CB1 receptors.

While the highest levels of expression are observed in the brain, the CB1 receptor is widely distributed in the body and is present in a large number of organs—most of which participate in the regulation of energy homeostasis. CB1 receptors have been observed in the gastrointestinal tract (Izzo et al., 2015), in the liver (Kunos and Osei-Hyiaman, 2008), in the pancreas (Silvestri and Di Marzo, 2013), in the muscle (Arrabal et al., 2015; Mendizabal-Zubiaga et al., 2016; Pagotto et al., 2006) and in adipocytes (Bensaid et al., 2003; Cota et al., 2003b; Pagotto et al., 2006).

Several brain regions contain the CB1 receptor, including the basal ganglia, the hippocampus, the limbic system, the cortex, the olfactory system, the cerebellum, and the hypothalamus (Herkenham et al., 1990; Marsicano and Kuner, 2008; Marsicano and Lutz, 1999; Tsou et al., 1998). In the limbic system, CB1 receptors are expressed in regions controlling motivational aspects of food intake such as the nucleus accumbens. Similarly, CB1 receptors are expressed in hypothalamic nuclei that regulate food intake and peripheral metabolic responses, such as the preoptic, paraventricular, and ventromedial nuclei as well as the lateral hypothalamic area (Marsicano and Kuner, 2008). It is important to note here that the levels of expression of CB1 receptors in specific organs and cell types are very variable with some cells containing extremely high levels of the protein (e.g., cortical GABAergic interneurons) and others having much lower levels (e.g., cortical glutamatergic neurons or astroglial cells) (Han et al., 2012; Marsicano and Kuner, 2008; Metna-Laurent and Marsicano, 2015; Oliveira da Cruz et al., 2016). These different levels of expression do not correlate with the functional importance of the CB1 receptor in specific organs, tissues, or cell types, indicating that, for the ECS, quantity is not quality. The reasons for this lack of correlation between levels of expression and functional relevance of different intercellular pools of CB1 receptors are not presently known, but they likely rely at least in part on cell-type-specific differences in intracellular signaling coupling, as recently shown for hippocampal GABAergic versus glutamatergic neurons (Steindel et al., 2013).

The intracellular signaling machineries activated by the CB1 receptor are very complex. As a GPCR, CB1 receptors modify cellular activities through activation of G proteins, mainly the inhibitory Gi/o (Howlett et al., 2002), although evidence for coupling with other G proteins subunits, such as Gs or Gq in specific cell types has accumulated over the last decades (Díaz-Laviada and Ruiz-Llorente, 2005; McAllister and Glass, 2002; Navarrete and Araque, 2010). CB1 also couples with β-Arrestin 2, which mediates the internalization of the receptor following its activation by agonists (Raehal and Bohn, 2014; Turu and Hunyady, 2010). It is important to note, however, that the internalization of CB1 receptors does not correspond ipso facto to its inactivation. Intracellularly localized CB1 can still activate signaling pathways such as the MAPK (Rozenfeld and Devi, 2008). In addition, recent data suggest that MAPK activation by CB1 receptors can also be G protein independent and be blocked instead by β-Arrestin 1 inactivation (Ahn et al., 2013). Finally, intracellular CB1 receptors located at mitochondrial membranes have been recently shown to regulate bioenergetic processes in the brain and in peripheral organs by directly altering mitochondrial respiration (Arrabal et al., 2015; Bénard et al., 2012; Hebert-Chatelain et al., 2014; Koch et al., 2015; Hebert-Chatelain et al., 2016; Mendizabal-Zubiaga et al., 2016).

Although the respective roles of G proteins, β-Arrestin 2, and β-Arrestin 1 need to be further clarified, the activation of CB1 receptors has two major downstream effects, including the modification of the activity of ion channels and of intracellular kinases (Howlett, 2004; Howlett et al., 2002).

The activation of CB1 receptors by endogenous and exogenous agonists inhibits Ca^{2+} channels of the N and P/Q types (Caulfield and Brown, 1992; Mackie and Hille, 1992; Twitchell et al., 1997), opens ATP-dependent potassium channels (Mu et al., 1999) and G-protein-coupled inwardly rectifying potassium (GIRK) channels (Guo and Ikeda, 2004; Ho et al., 1999). This overall results in a powerful inhibition of neuronal activity and of other Ca^{2+}-dependent cellular activities. Modification of the activity of ionic channels is probably due to a direct interaction with CB1-activated Gi/o proteins (Wilson and Nicoll, 2002) but could also involve, at least for potassium channels, the activation of other second messengers (Azad et al., 2003; Robbe et al., 2001; Ho et al., 1999). Recently, cannabinoids have been shown to increase excitability of retinal ganglion cell (RGC), acting through AMP-activated kinase (AMPK)-dependent inhibition of the Na-K-Cl cotransporter (NKCC1) activity, eventually reducing intracellular levels of Cl^- ions (Miraucourt et al., 2016).

Activation of CB1 receptors also results in modifications of intracellular signaling cascades. The most typical of these effects is the inhibition by Gi/o proteins of the activity of adenylyl cyclase, which leads to a decrease in the levels of cAMP (Howlett et al., 2002) and consequently of the activity of the protein kinase A (PKA). Conversely, activation of CB1 receptors has stimulatory effects on other important families of kinases such as the MAP and FAK kinases (Derkinderen et al., 1996, 2003), which can be G protein- or β-Arrestin 1 dependent (Ahn et al., 2013).

PKA, MAPK, and FAK modulate the expression of several transcription factors such as CREB, EGR1, cFOS, and c-JUN (Glass and Dragunow, 1995; Lazenka et al., 2013; Marsicano et al., 2003), which through modulation of protein transcription regulate a large range of cellular activities spanning from cell proliferation and differentiation to the regulation of intracellular glucose and lipid metabolism. Modulation of CB1 receptor activity leads to changes in the activity of the mechanistic target of rapamycin (mTOR) pathway, a key intracellular signaling regulating protein synthesis, autophagy, lipid metabolism, and, within the CNS, synaptic plasticity (Costa-Mattioli and Monteggia, 2013; Laplante and Sabatini, 2012). Amnesic-like effects of THC have been shown to require increased activity of p70S6K, a downstream target of mTOR, in the hippocampus (Puighermanal et al., 2009). Interestingly, pharmacological blockade of CB1 improves several behavioral abnormalities observed in a mouse model of fragile X syndrome in part by diminishing the overactivation of hippocampal mTOR signaling (Busquets-Garcia et al., 2013). CB1 and mTOR interact also in peripheral organs, such as the stomach and the endocrine pancreas, where the CB1 receptor antagonist rimonabant inhibits ghrelin and insulin

secretion, respectively, through the activation of the mTOR pathway (Bermudez-Silva et al., 2016; Senin et al., 2013).

From this partial and schematic description, the ECS appears to trigger and regulate a very complex network of organ-, tissue-, and cell-specific signaling pathways, explaining the wide impact of CB1 receptor activation on many different functions. The main aim of this Perspective is not to extensively review the detailed mechanisms of action of the ECS. Rather, here we try reconciling this complex picture into a simpler general function for the ECS. We propose its function is to promote exostatic processes in the body that favor the accumulation of energetic reserves.

Physiological Function of CB1-Mediated Effect of the ECS

Based on the literature, our hypothesis is that the different functions of the ECS converge toward an evolutionarily selected purpose of shifting energy balance toward energy storage. At its simplest level, this means increasing body weight through increased lipid production and accumulation.

Toward this purpose, we will first describe the physiological mechanisms that can sub-serve the function of increasing energy storage. In other words, we will describe how metabolism should be modified in order to maximize fat storage. We will then compare the roles of endocannabinoids in different tissues to such hypothetical effects. Finally, we will analyze other functions of the ECS and underline how these might also participate in fulfilling exostatic purposes or in protecting from some of their possible adverse consequences.

Several organs participate in the regulation of energy intake, absorption, and storage, and an exostatic system will have to orient their functions toward the accumulation of reserves under the form of fat. Sensory processes (olfaction, taste, vision, audition, and tactile sensation) provide the detection of food sources. Different brain regions integrate these sensorial inputs with the internal energy state of the individual and promote or prevent food intake. Nutrients are then absorbed and metabolized in the gastrointestinal tract, which informs the brain about food presence and composition, eventually determining satiety. The liver contributes to metabolic processes providing the production of lipids and their transport into the bloodstream. The adipose tissue stores energy under the form of fat and informs the brain and the rest of the body about stored energy levels. Humoral factors, nutrients themselves, and hormones also play an important role in amplifying the efficiency of this mechanism aimed at favoring energy storage. Ideal lipid production from the liver is obtained when insulin, which is produced by the pancreas, and glucose levels are at the highest. Insulin in turn allows glucose uptake in peripheral organs, thereby regulating the circulating levels of this nutrient. Finally, the regulation of energy expenditure through both long-range (e.g., sympathetic and parasympathetic transmission) and local mechanisms (e.g., thermogenesis, mitochondrial activity, muscular activity) also plays a role. Thus, the lower the energy expenditure after consuming a meal, the higher the amount of energy that can be stored.

In order to be called exostatic, a biological system should orient the activity of these organs and integrate processes toward maximizing energy storage. An exostatic system would theoretically exert the following functions: (1) increase the activity of the neural circuits that initiate feeding behavior overriding satiety signals and increasing the attractiveness of food; (2) modify the activity of the gastrointestinal tract by increasing nutrient absorption (e.g., by decreasing motility) and by inhibiting humoral and neural signals producing satiety in order to prolong eating time; (3) stimulate the transformation of glucose into lipids by acting directly on the liver enzymatic activity; (4) increase the efficiency of lipid synthesis by the liver through a parallel action on the pancreas (stimulation of insulin secretion), and the muscle (inhibition of glucose uptake), in order to create the ideal humoral conditions for this process, i.e., high levels of insulin and glucose; (5) facilitate lipid storage by acting on the adipose tissue, e.g., by facilitating the penetration of fatty acids into the adipocyte, which, especially in humans, is the limiting step of lipids accumulation; and (6) reduce the energy consumption of the organism by reducing energy expenditure, thermogenesis, and mitochondrial activity.

Is the ECS an Exostatic System?

Clearly a system that could exert all the coordinated functions described above would certainly be the ultimate machinery for increasing energy storage. Does it exist? We think that the answer is yes and this system is the ECS, via most of its CB1 receptor-mediated central and peripheral actions.

In order to provide evidence for this statement, we will outline the effects of an activation of CB1 receptors in each of the organs described above: sense organs, the brain, the gastrointestinal tract, the liver, the pancreas, the muscle, and the adipose tissue. The following description specifically addresses the roles of CB1 receptors in mammals because very little is known concerning the metabolic impact of CB1 receptor signaling in other species. However, it is interesting to note that, whereas endocannabinoids are detected in most species, proper orthologs of CB1 receptors are present in vertebrates (Elphick, 2012), which are the ones possessing adipose tissue as a specialized organ to store energy in the form of fat (Birsoy et al., 2013). Therefore, despite the paucity of data, one could speculate that CB1 receptor signaling might be linked to the specialized function of promoting fat accumulation for future use typical of vertebrates. Another aspect that we will not address here because of lack of data in the literature is the interesting question of the role of CB1 receptors in vertebrates that regulate energy balance differently from humans, such as animals very rarely ingesting large amounts of food (i.e., certain reptiles; Astarita et al., 2006), or animals undergoing hibernation (Vaughn et al., 2010). We will limit our discussion to demonstrating the exostatic role of CB1 receptors in rodents and humans which have similar ways of processing and addressing energetic needs.

Impact of ECS Signaling on Sensorial Perception

The ECS plays a role in the modulation of sight, smell, and taste, three senses that promote the perception and the seeking of food sources (Herman and Polivy, 2008).

CB1 receptors are present in the eye, particularly in the retina and ciliary bodies (Yazulla, 2008). Little is known about the physiological impact of ECS activity on vision (Yazulla, 2008). However, anecdotal reports suggest that activation of retinal CB1

receptors might improve night vision in humans (Russo et al., 2004; West, 1991). Interestingly, fishermen from Jamaica use cannabis to increase their ability to see during night fishing excursions, thereby increasing their ability to gather food (Russo et al., 2004; West, 1991). Similarly, very recent animal laboratory experiments have shown that CB1 activation can markedly improve visual contrast sensitivity under low-light conditions (Miraucourt et al., 2016), reinforcing the idea that the ECS might improve vision. It will be interesting to investigate whether this action is particularly strong during active food seeking.

Much more is known concerning the impact of CB1 receptor signaling on taste and olfaction and their relationship to food intake. In simple animals, like the larvae of *Xenopus laevis*, endocannabinoids acting at CB1 receptors promote olfactory perception and food-seeking behavior in deprived conditions (Breunig et al., 2010). Indeed, fasting increases olfactory performance in animals and humans (Cameron et al., 2012; Sengupta, 2013), and we recently showed that olfactory circuits in the mouse are controlled by the ECS, especially during active food search (Soria-Gómez et al., 2014a). Both endogenous and exogenous activation of CB1 receptors in centrifugal fibers regulating odor processing in the olfactory bulb promotes odor perception and food intake (Soria-Gómez et al., 2014a).

Taste is the main sense involved in food intake (Drewnowski, 1995, 1997). Sweet and fat tastes are generally linked to highly energetic foods and, therefore, play a particular role in the exostatic accumulation of energy (Drewnowski, 1995, 1997; Grill and Hayes, 2012). CB1 receptors are present in taste cells, particularly the ones expressing sweet receptors (Yoshida et al., 2010). Activation of these receptors by exogenous or endogenous ligands promotes sweet taste perception in a reciprocal way with leptin, one of the most important anorectic peripheral hormones (Niki et al., 2010; Yoshida et al., 2010). Interestingly, endocannabinoids are also present in human saliva (Matias et al., 2012), and one of their roles could be to participate in the modulation of taste perception and orosensory information. Fat intake affects endocannabinoids levels in tissues (Artmann et al., 2008). Consequently, the levels of fat molecules in the oral cavity might modulate taste signaling during the meal via stimulation of endocannabinoid production. Recent data show that the presence of fat in the oral cavity increases endocannabinoid levels in the gastro-intestinal tract, which, in turn further favor fat intake via efferent vagal signaling (DiPatrizio et al., 2011, 2013; Matias et al., 2008). Thus, the ECS is part of a positive loop mechanism by which the ingestion of fat is self-promoted through interactions involving the mouth, downstream elements of the gastrointestinal tract, and specific neural circuits (DiPatrizio and Piomelli, 2012).

ECS and Brain Control of Food Intake

Two major food-related effects are generally induced by the activation of CB1 receptors in the central nervous system: (1) increase in the sensitivity to appetitive properties of food and (2) stimulation of food intake beyond satiety.

Several studies indicate that alterations of the ECS modify food palatability. CB1 receptor agonists increase the intake of palatable food (Brown et al., 1977; Koch and Matthews, 2001), whereas CB1 receptor blockade reduces it (Arnone et al., 1997; Freedland et al., 2001; Gallate et al., 1999; Simiand et al., 1998). Detailed behavioral procedures showed the positive impact of CB1 receptor activation on the processing of food palatability (Higgs et al., 2003) and on the reinforcing properties of palatable food (Pério et al., 2001). Genetic studies with mice lacking the CB1 receptor gene (CB1-KO) confirmed previous pharmacological data. For instance, CB1-KO mice display reduced sucrose operant responding and this phenotype appears to depend on the rewarding (incentive) properties of sucrose. Indeed, the genotype effect vanishes when the reward is devaluated (adding quinine) and it is independent from the caloric content of the reward (Sanchis-Segura et al., 2004). Different brain regions appear to be the sites where exogenous cannabinoids increase food intake (Mazier et al., 2015). Early studies showed that the hypothalamus plays a key role in these effects (Trojniar and Wise, 1991). This is important in the context of exostatic functions, because increased food intake can be interpreted as a stimulus-bound behavior, i.e., a behavior elicited by the change in the incentive property of external stimuli induced by the activation of the lateral hypothalamus (Berridge and Valenstein, 1991). Other brain regions, such as the limbic system, have been linked to the processing of food palatability by CB1 receptors and the ECS (Jager and Witkamp, 2014; Mazier et al., 2015; Silvestri and Di Marzo, 2013). Also linked to the regulation of incentive properties of food is likely the recently described role of the ECS in olfactory circuits and olfactory bulb, where exogenous and endogenous CB1 receptor agonists increase perception and attractiveness of both odors and food (Soria-Gómez et al., 2014a).

Importantly, this effect on food palatability has been also shown in humans consuming THC, the active component of cannabis. Thus, cannabis or THC intoxication increases the ingestion of milkshake, marshmallows, and other palatable foods (Abel, 1971; Gagnon and Elie, 1975; Hollister, 1971) and induces the subjective feeling of craving "sweet things to eat, like chocolate, more than other foods" (Tart, 1970). The activation of CB1 receptors has been shown to promote food intake in different conditions such as the consumption of regular chow diet in free-fed (Verty et al., 2004) or in fasted animals (Bellocchio et al., 2010; Di Marzo et al., 2001; Soria-Gómez et al., 2014a), or even in operant schedules with standard food pellet (Freedland et al., 2000). This is not surprising based on the assumption that the palatability of all types of food is increased by the ECS.

Activation of CB1 receptors induces a decrease of the release of most major neurotransmitters in the CNS, including glutamate, GABA, serotonin, acetylcholine, noradrenaline, and others (Castillo et al., 2012; Kano et al., 2009; Schlicker and Kathmann, 2001), with one notable exception: CB1 receptor agonists increase the activity of mesencephalic dopaminergic neurons in the ventral tegmental area (VTA), resulting in an increase of dopamine release in target regions such as the nucleus accumbens or the prefrontal cortex (Cheer et al., 2004; Chen et al., 1990; Diana et al., 1998; Gessa et al., 1998; Maldonado et al., 2006; Melis and Pistis, 2012; Patel and Hillard, 2003; Tanda et al., 1997; Wenzel and Cheer, 2014). The specific mechanisms of these effects are not well understood, but evidence suggests that an indirect inhibition of GABAergic transmission controlling VTA dopaminergic neurons is a likely possibility (Maldonado et al., 2006; Melis and Pistis, 2012; Szabo et al., 2002). VTA

dopaminergic neurons are among the major brain systems mediating incentive properties of rewarding stimuli, i.e., the ability of a stimulus to attract and control behavior. The importance of dopaminergic neurons in mediating reinforcement and reward has been known for a long time. Initially, the activity of these neurons was associated with the sensation of pleasure (Berridge and Robinson, 1998; Wise, 2002). However, more recent experimental and theoretical work point to the idea that dopaminergic signaling in mesolimbic circuits is primarily involved in incentive motivation (Berridge and Robinson, 1998; Di Chiara, 1998; Di Chiara et al., 1998; Robinson and Berridge, 1993). In other words, activation of the dopaminergic transmission during motivational processes would mediate the "wanting" for a stimulus and not so much the "liking" of it (Berridge and Robinson, 1998; Robinson and Berridge, 1993). As a consequence, a biological system enhancing the incentive properties of food is expected to increase the activity of dopaminergic neurons. Indeed, recent studies have shown that the ECS controls food-associated activity of accumbal neurons and dopamine signaling (Di Marzo et al., 2009; Hernandez and Cheer, 2012; Melis and Pistis, 2012; Melis et al., 2007; Wenzel and Cheer, 2014). Interestingly, the impact of CB1 receptor signaling in the nucleus accumbens appears to be restricted to the shell portion (Castañeda et al., 1991; Tanda et al., 1997), which is likely the most important region processing incentive values of stimuli (Baldo and Kelley, 2007; Di Chiara and Bassareo, 2007).

CB1 and dopamine receptors seem to interact also at the postsynaptic site of the dopaminergic transmission. For instance, THC-induced activation of extracellular-regulated kinases (ERKs) in the striatum and nucleus accumbens depends on the increase in dopamine release (Valjent et al., 2001). Similarly, CB1 receptor-induced regulation of the adenylyl cyclase pathway depends on the presence and activation of D2 receptors (Jarrahian et al., 2004), which can even determine the direction of these effects (Glass and Felder, 1997), possibly via the formation of heterodimers (Kearn et al., 2005). Consistently, the increase of Fos expression caused by CB1 receptor antagonism in mesocorticolimbic areas (prefrontal cortex and shell of the nucleus accumbens) involves an inhibition of D2 receptors signaling (Alonso et al., 1999).

Brain CB1 receptors can also alter satiety signals, which normally decrease food intake during feeding. For instance, cannabinoid agonists trigger eating in fed rats in a CB1 receptor-dependent manner (Williams and Kirkham, 1999). Interestingly, this effect is stronger when palatable foods are used, indicating that CB1 receptor activation overcomes satiety signals, likely by promoting the incentive value of food (Higgs et al., 2003).

Conversely, CB1 receptor antagonism reduces food intake in free-fed animals, though to a limited extent (Black, 2004; Chambers et al., 2004; Chen et al., 2004; Colombo et al., 1998; McLaughlin et al., 2003). In contrast, larger effects of CB1 receptor antagonists were observed in overeating animals, such as upon fasting conditions, or in obesity models (Hildebrandt et al., 2003; Vickers et al., 2003; Zhou and Shearman, 2004). Interestingly, global CB1-KO mice show slight alteration of food intake under basal conditions, but these effects become much more evident under fasting-induced food intake (Bellocchio et al., 2010; Cota et al., 2003a; Di Marzo et al., 2001).

Eating behavior is under the control of many brain regions. However, a strong consensus exists pointing to the hypothalamus as the major integrative site for this behavior (Morton et al., 2006, 2014; Waterson and Horvath, 2015). Information from other brain regions, such as the ones regulating sensorial and motivational processes, is integrated by the hypothalamus. Peripheral signals such as leptin, glucose, insulin, or ghrelin are first detected by the hypothalamus, triggering the successive activation of other brain regions and peripheral mechanisms determining the ingestion of food and the subjective feelings of hunger or satiety (Morton et al., 2006, 2014; Waterson and Horvath, 2015). Finally, additional peripheral and central signals that reflect the internal state of the individual (in particular stress and physical activity) are also decoded by the hypothalamus, which responds by adapting behavioral and autonomic responses to the specific conditions (Mazier et al., 2015; Morton et al., 2006, 2014; Waterson and Horvath, 2015). The hypothalamus includes several nuclei containing complex neuronal networks, which activate or inhibit each other to finally process the information received and orchestrate proper behavioral, hormonal, and autonomic responses (Morton et al., 2006, 2014; Waterson and Horvath, 2015). Besides their excitatory or inhibitory nature, hypothalamic neurons contain neuropeptides playing key roles in the control food intake (Morton et al., 2006, 2014; Waterson and Horvath, 2015). In respect to this function, hypothalamic neuropeptides can be classified as orexigenic peptides, such as neuropeptide Y (NPY), agouti-related protein (AgRP), melanin-concentrating hormone (MCH), β-endorphin, and orexins/hypocretins A and B, and anorectic peptides such as, α-melanocyte stimulating hormone (α-MSH), corticotropin releasing hormone (CRH), and cocaine- and amphetamine-related transcript (CART).

Pharmacological and functional studies have demonstrated that activation or inhibition of the release of these neuropeptides largely contributes to the final behavioral outcome of feeding circuits (Morton et al., 2006, 2014; Waterson and Horvath, 2015).

Over the last decades, several observations have pointed to the importance of the ECS in the control of food intake in the hypothalamus, which is supported by three lines of observations. First, there is abundant expression of CB1 receptors in the hypothalamic nuclei controlling food intake (Cota et al., 2003b; Fernández-Ruiz et al., 1997; Marsicano and Kuner, 2008; Marsicano and Lutz, 1999; Mazier et al., 2015). Second, hypothalamic endocannabinoid levels are strongly modulated by the feeding status of the animals (Di Marzo et al., 2001; Hanus et al., 2003; Kirkham et al., 2002; Mazier et al., 2015). Finally, direct infusion of endocannabinoids or synthetic CB1 agonists into different hypothalamic nuclei increases food intake (Jamshidi and Taylor, 2001; Mazier et al., 2015; Williams and Kirkham, 1999; but see Soria-Gómez et al., 2014b).

The coordinated modulation of anorectic and orexigenic peptide signaling appears to be a main mechanism of CB1 receptor-dependent regulation of food intake in the hypothalamus. The anorectic peptides CART and CRH, which colocalize with CB1 receptors (Cota et al., 2003a; Di et al., 2003), are downregulated by cannabinoid agonists, whereas the actions of the appetite stimulator orexin-A are facilitated (Hilairet et al., 2003). More recent elegant data have expanded the possible mechanisms by which CB1 receptor agonists can promote food intake in

the hypothalamus. In particular, CB1 receptor agonists can activate hypothalamic proopiomelanocortin (POMC) neurons, which generally inhibit food intake via the release of α-MSH (Koch and Horvath, 2014; Koch et al., 2015). However, stimulation of CB1 receptors on POMC cells by specific doses of agonists favors the processing of POMC toward the production and release of the orexigenic neuropeptide β-endorphin over the appetite-suppressing peptide α-MSH (Koch and Horvath, 2014; Koch et al., 2015). Thus, CB1 receptor signaling can subvert the action of generally anorectic hypothalamic neurons, "transforming" them into orexigenic ones. Although mitochondrial CB1 receptors (mtCB1) and reactive oxygen species (ROS) production have been proposed as cellular mechanisms of this phenomenon (Koch and Horvath, 2014; Koch et al., 2015), further studies will have to identify the precise molecular pathways allowing the "selection" of peptidergic transmission by (endo)cannabinoid signaling within POMC neurons. This ability of CB1 receptor agonists to promote food intake by "reverting" the classical functions of POMC neurons is particularly important, because these neurons together with AgRP-containing neurons of the hypothalamic arcuate nucleus are known to act as a primary integrative locus to match the energy needs of the organism to contextual information (Chen et al., 2015).

As mentioned above, several peripheral hormones target the brain to regulate food intake. In the hypothalamus, the ECS has been shown to mediate the hyperphagic effects of ghrelin. In particular, ghrelin-induced increase of food intake requires CB1 receptor activation, which in turn inhibits the activity of neurons of the paraventricular nucleus (Kola et al., 2008).

Endocannabinoid Control of the Gastrointestinal Tract

All the elements of the ECS are present in the gastrointestinal (GI) tract and CB1 receptor activation in this organ seems to favor energy absorption and storage via coordinate mechanisms (Cani, 2012; Cluny et al., 2012; Di Carlo and Izzo, 2003; Izzo et al., 2001a, 2001b; Maccarrone et al., 2015; Massa et al., 2004; Mechoulam et al., 1995), including control of food intake, GI motility, and inflammation.

Endocannabinoid levels in the GI are increased by fasting (Gómez et al., 2002) and they seem to orient the preference toward food rich in fat (DiPatrizio et al., 2011, 2013; DiPatrizio and Piomelli, 2012; Smeets et al., 2010). Fat intake but not proteins or carbohydrates increase endocannabinoid levels in the jejunum. Blockade of CB1 receptors in this portion of the GI tract prevents further fat intake via vagal activity, suggesting the existence of a positive feedback loop between the ingestion of fatty food, the production of endocannabinoids in the GI tract, and the preference for it (DiPatrizio et al., 2011, 2013; DiPatrizio and Piomelli, 2012). However, how CB1 receptor activation in the GI tract, in turn, triggers brain neural circuits to induce food intake is still the object of speculations. One possibility is given by the control that CB1 receptors have on vagal and/or sympathetic nerve terminals, which provide the major neuronal input from the GI tract to the brain (Burdyga et al., 2004, 2010; Ishac et al., 1996). Another likely mechanism is the stimulation by CB1 receptors in the stomach of the production of ghrelin, the most important orexigenic peptide secreted by the GI tract that particularly favors fat intake (Burdyga et al., 2004; Dockray, 2009; Lin and Chey, 2003; McLaughlin et al., 1999; Müller et al., 2015; Müller and Tschöp, 2013; Senin et al., 2013; Shimbara et al., 2004).

A decrease in GI motility is considered one of the mechanisms through which the body can increase energy absorption (Ruppin, 1985). Several studies demonstrate that this function is increased by endocannabinoid signaling in the GI tract (Di Carlo and Izzo, 2003). Here, CB1 receptor activation reduces gastric emptying and intestinal motility in humans and rodents via modulation of cholinergic (Coutts and Izzo, 2004; Izzo et al., 2015; Izzo and Sharkey, 2010; Pinto et al., 2002) and vagal neurotransmission (Ruppin, 1985; Vianna et al., 2012). The GI tract is continuously exposed to the risk of inflammation, which decreases the efficiency of nutrient absorption. Activation of CB1 receptors in the GI tract has been shown to inhibit inflammatory processes (Alhouayek and Muccioli, 2012; Izzo and Sharkey, 2010; Massa et al., 2004; Nasser et al., 2014). The ECS in the GI tract could contribute to increased energy accumulation also by physiologically protecting the GI tract from inflammation. In line with this observation, recent evidence suggests an interaction between the ECS and the microbiota (Cani et al., 2016), which plays an important role in the regulation of both immune functions and energy balance (Kau et al., 2011; Tremaroli and Bäckhed, 2012).

CB1 Receptors Favor Lipid Synthesis in the Liver

Endocannabinoids and CB1 receptors are present in the liver (Osei-Hyiaman et al., 2008; Tam et al., 2010). One of the major effects of CB1 receptor activation in the liver is the increase of fatty acid synthesis (lipogenesis) (Osei-Hyiaman et al., 2005). Acute in vivo activation of CB1 receptors in wild-type mice fed a regular chow increases the expression of the lipogenic transcription factor SREBP-1c and the enzymes involved in fatty acid synthesis such as fatty acid synthase (FAS) and acetyl-CoA carboxylase-1 (ACC-1) (Osei-Hyiaman et al., 2005, 2008; Tam et al., 2010), whereas this effect is absent in CB1-KO mice (Osei-Hyiaman et al., 2005). Importantly, diet-induced obesity increases hepatic CB1 receptors and endocannabinoids, in particular anandamide, likely due to a decreased activity of FAAH-dependent degradation (Osei-Hyiaman et al., 2008; Tam et al., 2010). A positive loop exists between the ECS and excess energy storage that causes overactivation of the ECS (Auguet et al., 2014; Jourdan et al., 2010; Liu et al., 2012).

It is probably because of this positive loop that specific overexpression or deletion of hepatic CB1 receptors have revealed the key role of ECS activity in causing hepatic and systemic insulin resistance, steatosis, hyperglycemia, and dyslipidemia under high-fat diet conditions (Jourdan et al., 2010; Osei-Hyiaman et al., 2008). Interestingly, these genetic manipulations do not impact body weight under chow or high-fat diet, indicating that hepatic CB1 receptor signaling in the liver triggered by excess energy intake orients hepatic metabolism toward energy storage, but it is not sufficient per se to elicit generalized fat accumulation (Bowles et al., 2015; Dallman, 2010; Jourdan et al., 2010; Osei-Hyiaman et al., 2008).

CB1 Receptors Promote Fat Accumulation in the Adipose Tissue

The discovery of the functional expression of CB1 receptors in adipocytes represented the first step in defining its importance

in peripheral metabolic control (Bensaid et al., 2003; Cota et al., 2003b). Due to strong expression of CB1 receptors in the CNS, they were originally defined, until 2003, as the "brain-type cannabinoid receptors." Since then, CB1 and several other elements of the ECS, including endocannabinoids and the machinery for endocannabinoid metabolism, were described in human and murine adipose tissue (Engeli et al., 2005; Matias et al., 2006a; Roche et al., 2006). CB1 receptor activation in adipocytes favors energy storage by different complementary mechanisms, such as enhancement of fatty acid uptake, stimulation of white adipocyte differentiation and lipogenesis, and inhibition of white adipocyte transdifferentiation.

In vitro studies have demonstrated that CB1 receptor activation in adipocytes promotes the activity of the lipoprotein lipase (heparin-releasable LPL), thereby increasing fatty acid uptake (Cota et al., 2003b). This function is key in the accumulation of energy by adipocytes, because LPL activity mediates the hydrolysis of circulating triglyceride in non-esterified fatty acid (NEFA), the main lipid molecules that can be uptaken by the adipocyte.

CB1 receptors contribute to white adipocyte differentiation and lipogenesis likely through activation of lipogenetic enzymes and inhibition of AMPK (Blüher et al., 2006; Kola et al., 2005; Matias and Di Marzo, 2006). Stimulation of CB1 receptors in white adipocytes promotes adipogenesis and accumulation of triglyceride-rich lipid droplets and inhibits mitochondrial biogenesis (Silvestri and Di Marzo, 2013; Matias et al., 2016). Conversely, pharmacological blockade of CB1 receptors induces fatty acid oxidation, increases mitochondrial biogenesis, and likely helps transdifferentiation of white adipose cells into thermogenic brown-type adipose cells (Perwitz et al., 2010; Tedesco et al., 2010). This last effect seems to occur in vivo because conditional mutant mice specifically lacking CB1 receptors in the adipocyte show altered features of white adipocytes toward a brown phenotype (Mancini et al., 2010). Interestingly, insulin and leptin negatively control endocannabinoid levels in the adipose tissue engaging both local and hypothalamic-dependent long-range mechanisms (Buettner et al., 2008; Matias et al., 2006b), suggesting that development of leptin and insulin resistance might likely promote fat accumulation via activation of the ECS in the adipocyte.

Impact of CB1 Receptor Signaling in the Pancreas and Muscle

An increase in blood glucose levels is one of the first effects of food ingestion. Insulin produced by the pancreas plays a key role in regulating glucose metabolism and fat accumulation, which is enhanced when insulin and glucose levels are high. CB1 receptors seem to assist by decreasing insulin sensitivity and glucose uptake in muscle while increasing pancreatic secretion of insulin.

Studies on isolated soleus muscle from both lean and obese diabetic rats demonstrate that activation of muscle CB1 receptors inhibits both basal and insulin-stimulated glucose transport (Lindborg et al., 2010). Conversely, blockade of CB1 receptors increases glucose uptake in the soleus muscle (Lindborg et al., 2010; Liu et al., 2005). Moreover, recent data suggest that direct actions of CB1 receptor in abdominal muscles might regulate tricarboxylic acid (TCA) cycle and mitochondrial activity under high-carbohydrate diet (Arrabal et al., 2015). The indication of the presence of mtCB1 receptors (Arrabal et al., 2015; Mendizabal-Zubiaga et al., 2016) in skeletal muscle allows further speculating that mitochondrial CB1-dependent downregulation of mitochondrial activity might be part of the more general ECS action aimed at preserving energy.

CB1 receptors, endocannabinoids, and the machinery for endocannabinoid metabolism are present in the pancreas (Juan-Picó et al., 2006; Li et al., 2012). There is evidence that activation of CB1 receptors could stimulate insulin production directly on pancreatic cells (Juan-Picó et al., 2006). In particular, 2-AG seems to play a role in the stimulation of insulin secretion as both mouse MIN6 β-cells and isolated human islets show increased insulin secretion in vitro in response to inhibitors of MGL, the enzyme responsible of 2-AG degradation (Li et al., 2012). Recent data indicate that activation of CB1 receptors in β-cells promotes secretion of insulin via activation of focal adhesion kinases (FAK) and cytoskeletal reorganization (Malenczyk et al., 2013). Conversely, pharmacological inhibition of CB1 in isolated mouse islets from lean mice decreases glucose-stimulated insulin secretion, through a mechanism requiring a functional mTOR pathway (Bermudez-Silva et al., 2016).

CB1-Mediated Effects of Endocannabinoids on Energy Expenditure

Activation of CB1 receptors favors weight gain by tuning down processes under the control of the sympathetic nervous system (SNS), including energy expenditure, brown adipose tissue (BAT) thermogenesis, and white adipose tissue (WAT) lipolysis (Bajzer et al., 2011; Cardinal et al., 2012, 2014; Quarta et al., 2010).

CB1 receptors are expressed in peripheral parasympathetic (Coutts and Pertwee, 1997) and sympathetic terminals (Ishac et al., 1996). Mice with CB1 receptor deletion in the forebrain and sympathetic ganglia are resistant to diet-induced obesity because they display increased lipid oxidation and BAT thermogenesis as a consequence of an enhanced sympathetic tone (Quarta et al., 2010). Similarly, mice with genetic overexpression of the MGL enzyme in the forebrain are resistant to diet-induced obesity through an SNS-dependent mechanism that involves increased BAT thermogenesis and mitochondrial activity (Jung et al., 2012).

CB1 receptors in hypothalamic neuronal circuits also play a critical role in the regulation of these responses. Deletion of CB1 receptors from single-minded homolog 1 (Sim1)-expressing neurons, which constitute the majority of glutamatergic neurons of the paraventricular nucleus (Xu et al., 2013), protects from diet-induced obesity through an SNS-dependent increase in BAT thermogenesis and energy expenditure (Cardinal et al., 2015). Similarly, mice that lack CB1 receptors in steroidogenic factor 1 (SF1)-expressing neurons of the ventromedial hypothalamus have decreased fat mass because of increased BAT metabolism and WAT lipolysis, both consequences of heightened SNS activity (Cardinal et al., 2014). In turn, the diet can impact these responses. While chow-fed SF1-CB1-KO mice are leaner than their WT littermates, when KO mice are fed a high-fat diet, they gain more weight than WT because of a decreased SNS-driven lipolysis (Cardinal et al., 2014). Thus, the ECS regulates the use of energy substrates through the inhibition of SNS activity.

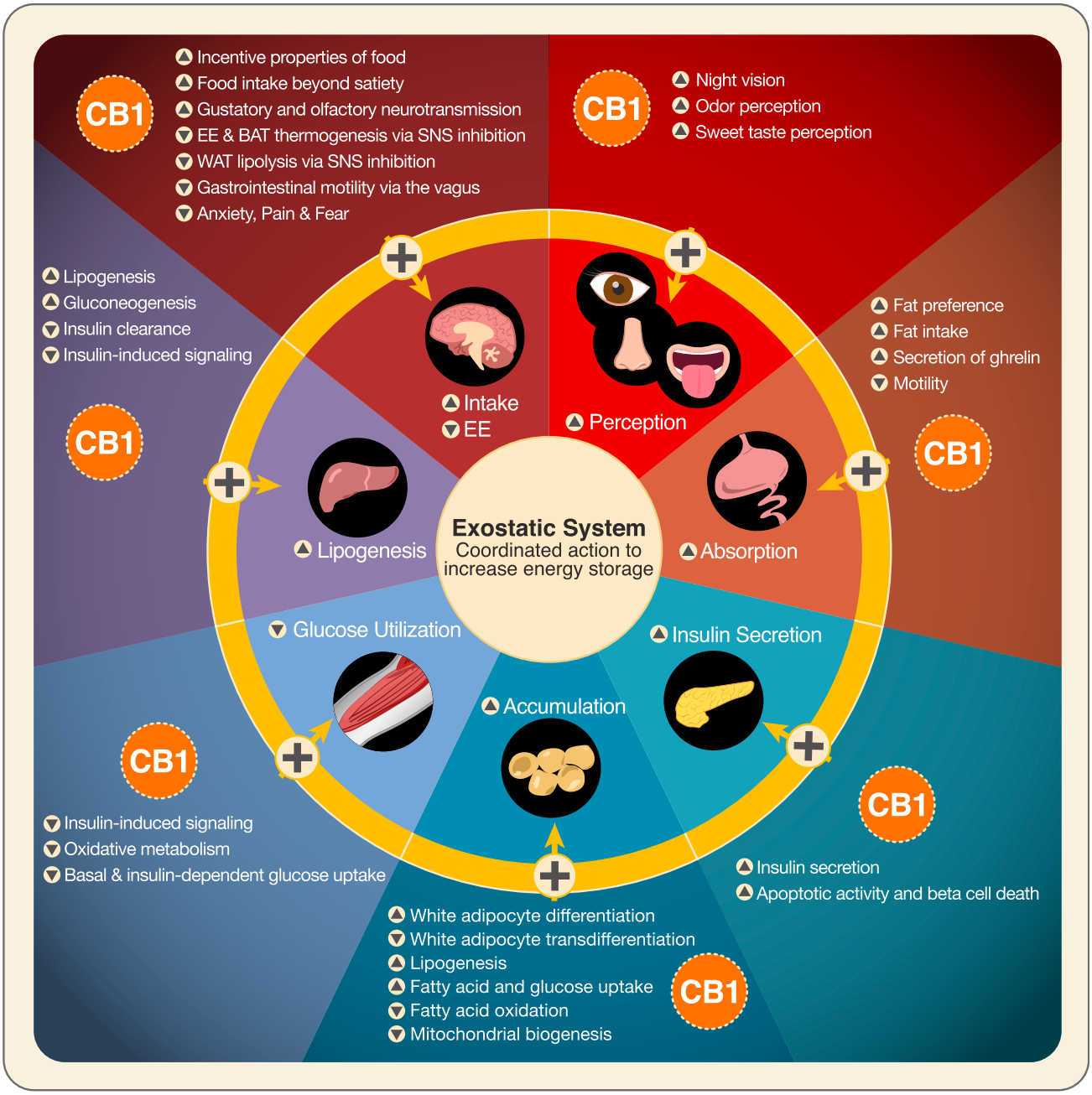

Figure 3. The Endocannabinoid System Is the Prototypical Exostatic System
By exerting coordinated actions at target tissues, CB1 receptor activation favors food intake and energy storage. By acting on the central and the autonomous nervous system, CB1 receptor activation increases food intake while inhibiting energy expenditure and the use of lipids as fuel substrates in peripheral organs. CB1 receptors also modulate olfaction and taste responses and favor fat preference and intake through action on the gastrointestinal tract. Finally, by acting on the adipose tissue, the skeletal muscle, the pancreas, and the liver, CB1 receptors exert a multi-organ action directed toward the increase of energy storage capacity and fat accumulation in the organism. In particular by (1) increasing at the same time insulin and glucose levels, key humoral conditions to promote lipidogenesis in the liver and by (2) facilitating the uptake of lipids by adipocytes, the limiting step in lipid storage.
BAT, brown adipose tissue; EE, energy expenditure; SNS, sympathetic nervous system; WAT, white adipose tissue.

CB1-Mediated Effects of Endocannabinoids and the Pathophysiological Loop of Obesity

The ECS exerts exostatic functions, thereby favoring the development of obesity (Figure 3). By promoting perception, search, palatability, and intake of food, by increasing absorption of nutrients, by favoring energy accumulation under the form of fat and decreasing its use, the ECS plays a key role in establishing obesity (Mazier et al., 2015; Pagotto et al., 2006). Once obesity

has developed, however, whether or not the activity of the ECS is relevant in maintaining this condition needs further discussion.

In obesity, biological mechanisms involved in the control of energy balance undergo resistance, as for example in the case of the actions of leptin or insulin on their target organs, which contribute per se to the maintenance of the pathological state. Conversely, in the case of the ECS, the induction of resistance or tolerance to its actions would result in a reduction of obesity. However, this is not the case.

Under diet-induced obesity in animals or obesity observed in humans, the energy-accumulation properties of the ECS appear to be potentiated. Increased endocannabinoid levels and CB1 receptor expression are hallmarks of obesity in rodents and humans, which strongly contribute not only to the development, but also to the maintenance of the pathology (Mazier et al., 2015; Silvestri and Di Marzo, 2013). Thus, the exostatic roles of the ECS are regulated by positive feedback mechanisms, participating in a loop, by which increased ECS activity leads to higher energy accumulation. This in turn is accompanied by further increased ECS activity. This statement is supported by a very explicit observation made in the liver of conditional mutant mice lacking hepatic CB1 receptor expression (Osei-Hyiaman et al., 2005). In wild-type mice, high-fat diet induces a large increase in liver endocannabinoid levels. This phenomenon is strongly reduced in mutant animals. There is a clear positive feedback relationship between CB1 stimulation and endocannabinoids production, which is the opposite of what occurs in systems regulated through a negative feedback mechanism.

The fact that endocannabinoid signaling is regulated through a positive feedback mechanism suggests that during body weight gain the ECS enters in a pathophysiological loop and can consequently play an important a role in maintaining obesity. One can argue that the ECS plays a physiological role by clearly promoting exostatic processes and energy accumulation, but this function in turn contributes to the pathology of obesity.

Exostasis and Resilience

Although endostatic and exostatic systems are synergistic in ensuring the survival of the individual, they result in opposite and somewhat antagonistic physiological functions. As a result, the endostatic system works to maintain physiological parameters within a pre-set range of values and exerts the prototypical function of a homeostatic system. Exostatic processes help the organism bypass this homeostatic range by actually inducing what could be considered a homeostatic overload. The homeostatic overload induced by exostasis intrinsically induces "unbalanced" cellular and organ activity that could expose the subject to potential dangers. An efficient exostatic system should then also try to protect the individual from the state of overstimulation that it induces. We propose that this is the main function of many of the effects of the ECS that are apparently not directly connected to energy accumulation and exostatic processes.

Research during the last decades clearly points to the involvement of the ECS in the regulation of primary behavioral functions, such as pain perception, stress responses, fear, and anxiety. For the sake of space, we will not go into details of these aspects, and we refer the readers to many recent and comprehensive reviews for more information (Corcoran et al., 2015; Lutz et al., 2015; Maione et al., 2013; Moreira and Wotjak, 2010; Morena et al., 2016; Piomelli et al., 2014; Riebe and Wotjak, 2011). In short, there is high consensus that the ECS is a potent buffer of pain sensations, it controls stress reactions, plays a general anxiolytic role, and reduces fear responses.

All these functions seem to have nothing to do with the exostatic regulation of energy intake and storage. However, from the behavioral point of view, exostasis implies that the motivation to search and ingest food has to overcome to a certain extent the environmental constraints that would decrease such activities. An individual highly motivated to find food sources will have to overcome potential painful, stressful, anxiogenic, and fearful situations. Just as an example, a mouse with high endostatic regulation will not exit the protected nest to venture in search of food if its immediate needs have been fulfilled. Conversely, proneness to explore the environment will increase the chances of an "exostatic" mouse to find additional food sources. Thus, potential adverse environmental stimuli have to be overcome to allow exostatic activities—at least within a certain limit that still guarantees survival of the individual. In this context, it is particularly interesting that interactions among these processes are tightly modulated by the ECS. For instance, there is strong evidence for ECS involvement in stress-induced analgesia (Corcoran et al., 2015; Hohmann et al., 2005; Suplita et al., 2005; Valverde et al., 2000). Animals engaged in a stressful situation will be more resistant to painful stimuli, thereby allowing them to overcome, at least to a certain extent, the behavioral inhibition induced by both stress and pain (Amit and Galina, 1986; Butler and Finn, 2009; Fanselow, 1986). It is interesting to note that the anxiolytic functions of CB1 receptor signaling are "state dependent," in the sense that they are mainly present under highly aversive conditions (Lutz et al., 2015). CB1-KO mice do not show enhanced anxiety-like behaviors under low aversive conditions, whereas this phenotype is evident in more aversive environments (Haller et al., 2004; Lutz et al., 2015). Conversely, inhibition of FAAH or MAGL induces anxiolysis under high, but not low, aversive conditions (Haller et al., 2009; Sciolino et al., 2011; Lutz et al., 2015). The ECS therefore seems to contribute to the mechanisms allowing individuals to extend their options to engage in potentially dangerous activities in anxiogenic environments, such as the search of food.

Similar considerations can apply to the endocannabinoid control of fear and anxiety responses. Low levels of fear and anxiety obviously favor other activities linked to search and exploration, which would eventually increase the chances of finding food. There is wide consensus that ECS signaling generally reduces anxiety and fear responses (Lutz et al., 2015; Moreira and Wotjak, 2010; Morena et al., 2016; Riebe and Wotjak, 2011). Notably, this general function of the ECS applies also to the control of neophobia. Null CB1-KO mice display increased aversion to novel objects and foods (Lafenêtre et al., 2009). In this context, it is interesting to note that the ECS has been proposed to differentially regulate distinct types of fear responses. Mice with constitutive CB1 deletion and conditional mutant mice lacking CB1 in cortical glutamatergic neurons (Glu-CB1-KO) display increased passive and decreased active responses, respectively, in active and passive avoidance and fear conditioning tests (Kamprath et al., 2009; Marsicano et al.,

2002; Metna-Laurent et al., 2012). Data using mutant mice indicate that the general function of the ECS seems to promote active fear responses. Thanks to the ECS, animals exposed to fearful conditions still move and explore the environment, thereby likely increasing the chances of retrieving food.

In summary, the impact of ECS signaling on pain perception, stress responses, fear and anxiety might be inscribed in the general need of maintaining high levels of exploration and "bravery" required by exostatic search of food and energy accumulation.

The observations summarized in the previous paragraph suggest that activation of the CB1 receptor is also a substrate of resilience and give a quite new evolutionary perspective to this precious function that makes individuals able to recover from even the worst traumatic experience. Resilience is in fact difficult to understand in evolutionary terms without the concept of exostasis. Resilience is a function whose primary purpose is to overcome aversive experiences (Aburn et al., 2016). Thus, resilience increases the chances of the individual to be re-exposed to dangers, thereby apparently decreasing the survival of the species. However, in unpredictable environments where dangers are often linked to opportunities, resilience often results in a net increase of chances of survival. Exostatic functions of the ECS, by increasing the search and the consumption of food and by decreasing the responses to stress, pain, and fear clearly contribute to resilience and survival.

The ECS: A Fast Car that Needs Sophisticated Brakes

The ECS comes across as an intriguing system that allows individuals to withstand homeostatic overload and take more risks in order to increase energy accumulation. Such a system can then be quite dangerous if it gets out of control. This is probably why CB1 receptor activity is regulated by sophisticated built-in brake systems that act at both circuit and cellular levels.

At the circuit level, CB1 receptors are present on both glutamatergic and GABAergic neurons in the brain (Katona et al., 2006; Kawamura et al., 2006; Marsicano and Kuner, 2008; Marsicano and Lutz, 1999; Monory et al., 2006), where they can negatively modulate both excitatory and inhibitory neurotransmission (Castillo et al., 2012; Kano et al., 2009). Recent evidence using conditional mutant mice and pharmacological approaches suggests that the overall endogenous or exogenous activation of the ECS in the brain is mediated at first by CB1 receptors expressed in cortical glutamatergic neurons (Bellocchio et al., 2010; Busquets-Garcia et al., 2015; Metna-Laurent et al., 2012; Rey et al., 2012). Indeed, the phenotype of constitutive CB1-KO or Glu-CB1-KO mice are often very similar (Busquets-Garcia et al., 2015), indicating that the general functions of ECS signaling depend on the "glutamatergic" pool of CB1 receptors. These functions correspond to the exostatic ones, because "glutamatergic" CB1 receptors mediate increases in food intake (Bellocchio et al., 2010; Busquets-Garcia et al., 2015; Soria-Gómez et al., 2014a), exploratory activity, and anti-neophobic mechanisms (Busquets-Garcia et al., 2015; Lafenêtre et al., 2009). In addition, it has been shown that a decrease in basal or stress-induced passive fear responses (Busquets-Garcia et al., 2015; Dubreucq et al., 2012; Kamprath et al., 2009) and anxiolytic effects are mediated by low doses of exogenous CB1 receptor agonists (Busquets-Garcia et al., 2015; Rey et al., 2012). However, when CB1 receptor activation goes above a certain threshold, CB1 receptors expressed in GABAergic neurons kick in, exerting opposite effects on the same function. GABA-CB1-KO mice carrying a deletion of the CB1 gene in forebrain GABAergic neurons (Monory et al., 2006, 2007) often display opposite phenotypes as compared to Glu-CB1-KO, indicating that activation of "GABAergic" CB1 receptors actually decreases food intake and exploratory activity (Bellocchio et al., 2010; Busquets-Garcia et al., 2015; Lafenêtre et al., 2009), increases neophobia (Busquets-Garcia et al., 2015; Lafenêtre et al., 2009), and promotes passive fear responses, simultaneously inhibiting active ones (Busquets-Garcia et al., 2015; Lafenêtre et al., 2009; Metna-Laurent et al., 2012). Interestingly, pharmacological studies suggest that, for unknown reasons, low and high doses of CB1 receptor agonists preferentially activate "glutamatergic" or "GABAergic" CB1 receptors, respectively, resulting in opposite effects demonstrating biphasic actions of cannabinoids (Bellocchio et al., 2010; Busquets-Garcia et al., 2015; Metna-Laurent et al., 2012; Rey et al., 2012). One can argue that moderate activation of CB1 receptors likely exerts "exostatic" functions via "glutamatergic" CB1 receptors, whereas excessive presence of ligands activates the "protective" opposite functions of "GABAergic" CB1 receptors.

Negative feedback mechanisms have evolved at the cellular level to reduce deleterious effects of excessive activity of the ECS including the presence of inhibitory CB1 receptor-interacting proteins (Guggenhuber et al., 2016; Smith et al., 2015), or general machineries to induce tolerance/resistance to GPCR signaling (Mackie, 2008; Yao and Mackie, 2009), or the control of excessive excitatory brain activity (Marsicano et al., 2003; Monory et al., 2006). A specific mechanism to control selected signaling aspects of CB1 receptors has been recently discovered. Pregnenolone is a steroid that has been considered for a long time as a neutral precursor of other steroid molecules (Baulieu et al., 2001). Our recent results have revealed that pregnenolone is a very potent signaling specific inhibitor of CB1 receptors that is able to reduce most of the effects induced by cannabinoids (Vallée et al., 2014). Importantly, pregnenolone levels are increased in the brain up to 3,000% as a consequence of CB1 receptor overactivation, thereby reducing CB1-dependent effects (Vallée et al., 2014). It is interesting to note that the production of pregnenolone in the brain seems to depend on the activation of CB1 receptors expressed in GABAergic neurons (Vallée et al., 2014), supporting the idea that this specific pool of CB1 receptors plays an inhibitory role in protecting against the potential dangers caused by the primary exostatic functions of the ECS. In conclusion, the CB1 receptor and the ECS behave like fast cars that need to be manipulated with care and require sophisticated built-in braking system to control potential damages caused by their excessive activation.

How a Physiological Function Can Promote Pathology: Proactive Evolution-induced Diseases

Potent exostatic systems are necessary under conditions with variable energy sources from the environment. One could ask why evolution has selected mechanisms that clearly cause a pre-pathological state like obesity in modern humans. The

answer is quite simple, if we consider the time frame in which foraging conditions have changed (Figure 1).

One could consider that the human species has evolved over a time frame of approximately four million years (Harari, 2015). During almost all of this time, humans did not control their environment and their foraging behavior was one of a hunter or gatherer. It is clear that in such an unstable environment (Harari, 2015), the presence of both individuals with a prevalent endostatic or exosatic system would provide a clear advantage to the species by increasing adaptation to stable and unstable foraging condition, respectively. It is approximately 10–20,000 years ago that humans started crop and livestock farming, thereby stabilizing their energy provisions (Harari, 2015). A little more than one hundred years ago, technological advances promoted a way to produce, store, and conserve food in large amounts, provoking a shift from "stable" to "supra-stable" conditions. Clearly the exostatic system, well adapted to a variable foraging environment, became "pathological" in the supra-stable conditions of present days. Unfortunately, 100 years are insufficient for the selection of a new character (Figure 1), and the human species had no time to adapt to novel environmental conditions.

This observation likely explains the occurrence of the "obesity epidemics" during the last decades. It is not caused by intrinsic changes of human biological properties, but it is the consequence of an unprecedented fast and significant man-made change to his environment. In this sense, obesity can be seen as an example of a new class of diseases that we propose to call "proactive evolution-induced disease" (PEID). The cognitive capacities of humans have inverted the relationship between the organisms and the environment. In the classical evolutionary view, it is the environment that selects the organism more adapted to it via selection mechanisms at different levels (survival, reproduction, etc.), which, however, take a long time to be implemented—a few thousand years are generally necessary to select a new phenotype. During the last 10–20,000 years, humans initiated a process that led to an exponential modification of the environment, inducing what some scientists define as a new epoch called "Anthropocene" (Harari, 2015). In this period, humans were able to select or shape the environmental features that were more adapted to their needs. The short temporal frame of this modification of the environment leaves us with biological systems that have been selected over millions of years by the evolutionary process and are maladapted to the present human-shaped environmental situation. Obesity is likely one of a series of PEIDs ranging from certain types of cancer to neuropsychiatric disorders that may originate from human-induced changes in environmental conditions associated with the presence of physiological systems adapted to other conditions. In the case of a PEID, there is nothing wrong with the functioning of the biological system underlying the disease. It is just the environment that has "suddenly" changed, providing a condition to which biology is not adapted anymore. In fact, physiological "normal" functioning of a biological system is inherently related to a specific environment, it is not an absolute quality. For instance, the lungs are one of the most efficient organs in our body. If you are forced to stay underwater, they do not work so well anymore. Would you then say that drowning reveals a pathological role of the lung? You will certainly not.

This new conceptualization of diseases such as obesity has important implications in terms of therapy. Specifically, one major problem to engage obese patients in lifestyle changes is the sense of guilt felt by these patients, deriving from a negative vision of society on overweight subjects. Although not overtly stated, obese individuals are often considered as subjects who lack control and indulge in a vice. In other words, they are generally considered responsible for their condition. The concept of PEID argues against this stigma for patients. The extremely rapid change in environmental conditions induced by the unique cognitive abilities of our species has left some of us with a biological system ("the exostatic system") that favors obesity in the current environment. This idea may extend to other pathological conditions that might, at least in part, share PEID characteristics. Indeed, we think that it would be better to stay on the watch for other diseases that could arise from the rapid environmental changes induced by the high cognitive abilities that characterize our species.

Conclusions

In this Perspective article, we propose a possible, comprehensive, and theoretical view of different functions of the ECS. We suggest that the ECS and CB1 receptors have evolved in animals and humans as prototypical mediators of exostatic functions aimed at accumulating energy for future use. The ECS fulfills all the theoretical properties of an exostatic system, including its direct roles in energy balance (all pointing to increased intake, absorption, and accumulation of energy) and also its ability to promote resilience. Considering the large scope of the subject, we omitted mention of certain aspects including the role of CB1 receptors in the control of the functions of skin, kidneys, lungs, and other organs, and certainly we did not have sufficient space to mention all the important studies published during the last decades on the ECS. We believe that introducing the concept of exostasis into the field of endocannabinoid functions has the merit to provide a much-needed general theoretical framework. This new theoretical construct will allow for the generation of new hypothesis-driven research that can contribute to this field.

ACKNOWLEDGMENTS

The authors are supported by INSERM, EU–Fp7 (PAINCAGE, HEALTH603191, to G.M.), European Research Council (Endofood, ERC–2010–StG–260515 and CannaPreg, ERC-2014-PoC-640923, to G.M.), Fondation pour la Recherche Medicale (DRM20101220445 and DPP20151033974, G.M.), Human Frontiers Science Program (RGP0036/2014 to G.M.), Region Aquitaine, Agence Nationale de la Recherche (ANR Blanc NeuroNutriSens ANR-13-BSV4-0006, to G.M. and D.C., BRAIN ANR-10-LABX-0043, and ANR Blanc ORUPS ANR-16-CE37-0010-01 to G.M.) and Fondation Francophone pour la Recherche sur le Diabète, which is sponsored by Fédération Française des Diabétiques (AFD), AstraZeneca, Eli Lilly, Merck Sharp & Dohme (MSD), Novo Nordisk, and Sanofi (to D.C.). We thank F. Pamplona, M. Glass, and J. McPartland for useful suggestions. We are particularly thankful to Charlie Padgett for graphical artwork.

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