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Feature Review

The Endocannabinoid System: Pivotal Orchestrator of Obesity and Metabolic Disease

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The endocannabinoid system (ECS) functions to adjust behavior and metabolism according to environmental changes in food availability. Its actions range from the regulation of sensory responses to the development of preference for the consumption of calorically-rich food and control of its metabolic handling. ECS activity is beneficial when access to food is scarce or unpredictable. However, when food is plentiful, the ECS favors obesity and metabolic disease. We review recent advances in understanding the roles of the ECS in energy balance, and discuss newly identified mechanisms of action that, after the withdrawal of first generation cannabinoid type 1 (CB_1) receptor antagonists for the treatment of obesity, have made the ECS once again an attractive target for therapy.

From the 'Munchies' to the ECS

The ECS exerts regulatory control essentially on every aspect related to search, intake, metabolism, and storage of calories, and it has been thus recognized to have a crucial role in the regulation of energy balance. This system, which is particularly well preserved across species [1], seems to have been selected by evolution to maximize intake and conservation of energy, likely to increase survival in times of scarcity [2,3]. Accordingly, activation of the ECS promotes consumption of palatable food, stimulates fat mass expansion and calorie preservation, while inhibiting energy expenditure and **thermogenesis** (see Glossary). However, in modern society where food is plentiful, excessive ECS activity is a landmark feature of obesity and metabolic disorders [4,5].

The first reports of increased appetite induced by **cannabis** (also known as marijuana) in humans were documented in AD 300 [6]. However, understanding the biological mechanisms underlying the '**munchies**' started only after the discovery of specific G-protein-coupled **cannabinoid receptors**, CB_1 and CB_2, followed by the identification of endogenous lipid-derived ligands, termed **endocannabinoids**, and elucidation of their biosynthesis and degradation pathways [7,8] (Box 1). The best-characterized endocannabinoids are *N*-arachidonoylethanolamide (anandamide, AEA) and 2-arachidonoylglycerol (2-AG). Both AEA and 2-AG increase food intake, usually through the activation of CB_1 receptors (CB_1Rs). These receptors are abundantly expressed throughout the central nervous system (CNS) in areas controlling food intake and energy expenditure (hypothalamus, brainstem) and reward-related responses (nucleus accumbens), as well as in the peripheral nervous system, and in organs affecting metabolic homeostasis, such as the gastrointestinal tract, adipose tissue, liver, and muscle. Central and peripheral inhibition of CB_1R activity, and more generally of the ECS, is beneficial for the treatment of obesity and metabolic disorders [4,5]. Rimonabant, an anorectic drug and

Trends

The endocannabinoid system (ECS) exerts a multi-organ energy-stowing function by promoting consumption of palatable food, stimulating fat mass expansion, and inhibiting energy expenditure and thermogenesis.

The ECS adjusts behavior and metabolism to food availability. Its activity is advantageous when access to food is limited or cannot be predicted, but becomes harmful when food is abundant, favoring the development of obesity and metabolic disease.

Inhibition of ECS activity has beneficial metabolic consequences by reducing adiposity, dyslipidemia, insulin resistance, and hepatic steatosis.

After the withdrawal of the first generation of cannabinoid type 1 receptor antagonists for the treatment of obesity and metabolic disease, newly identified mechanisms point again to the ECS as attractive therapeutic target.

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Box 1. Endocannabinoid Synthesis and Degradation

Within the CNS, endocannabinoids are synthesized and released on demand, and classically act on CB_1Rs that are mainly located presynaptically to inhibit neurotransmitter release, and are thereafter immediately metabolized [7,31,124] (Figure I).

AEA synthesis takes place through the hydrolysis of the membrane phospholipid precursor *N*-acylphosphatidylethanolamine (NAPE) by NAPE-selective phospholipase D (NAPE-PLD) [7] (Figure I). The production of 2-AG depends on the activation of phospholipase C (PLC), which generates 1,2-arachidonoylglycerol that is then cleaved by diacylglycerol lipase (DAGL) α or β to produce 2-AG [7]. Endocannabinoid degradation requires cellular reuptake and enzymatic hydrolysis, which is under the control of a fatty acid amide hydrolase (FAAH) for AEA, and a monoacylglycerol lipase (MAGL) for 2-AG, resulting in the release of ethanolamine or glycerol, together with arachidonic acid [7]. The transport of AEA from the extracellular space to the intracellular space may be facilitated by a FAAH-like anandamide transporter (FLAT) [125], although recent studies have questioned the possible role of FLAT as an AEA intracellular carrier [126]. In addition to AEA and 2-AG, other putative endocannabinoids have been identified [127], but their physiological function remains largely unknown. The canonical receptors for AEA and 2-AG are CB_1Rs and CB_2Rs, which classically act through $G_{i/o}$ proteins to inhibit adenyl cyclase and various voltage-gated Ca^{2+} channels, leading to lower cAMP levels and activation of some types of K^+ channels, as well as mitogen-activated protein kinase (MAPK) and phospholipase pathways [128]. In the CNS, apart from their localization on the neuronal cell membrane, CB_1Rs have been also identified on astrocytes [129,130] and intracellularly on mitochondria [41]. AEA and 2-AG can also bind to non-CBRs, such as the transient receptor potential vanilloid 1 (TRPV1), whose activation sometimes opposes the effects of CB_1R or CB_2R activation [122]. In addition, AEA can bind to the peroxisome proliferator-activated receptor γ (PPARγ), thus inducing adipocyte differentiation through this mechanism [121]. Finally, endocannabinoid-related compounds, such as OEA, PEA, and 2-oleoylglycerol, are synthesized and degraded through the same enzymatic steps illustrated above for AEA and 2-AG, but do not bind to CB_1Rs or CB_2Rs and often have actions opposite to those of endocannabinoids.

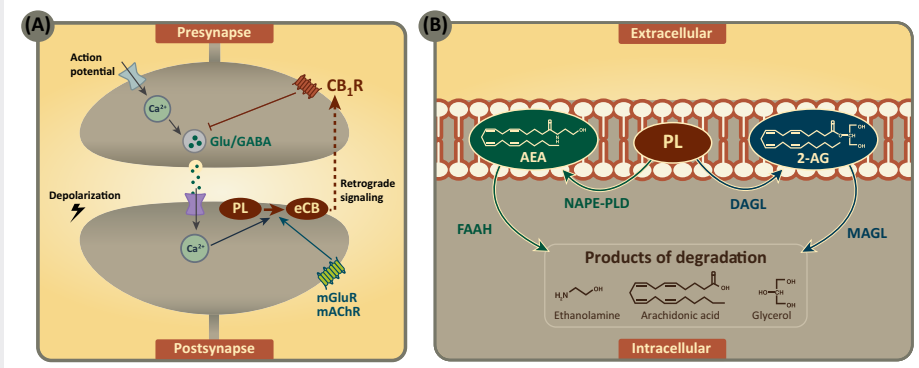

Figure I. Endocannabinoid Signaling at the Synapse and their Synthesis and Degradation within the Cell. (A) Retrograde endocannabinoid (eCB) signaling at the synapse. eCBs are mobilized from postsynaptic neurons and target presynaptic CB_1Rs to suppress neurotransmitter release. (B) Main enzymatic steps involved in the formation and hydrolysis of AEA and 2-AG within the cell. Abbreviations: mAchR, muscarinic acetylcholine receptor; mGluR, metabotropic glutamate receptor; PL, phospholipids.

systemic CB_1R **inverse agonist** developed by Sanofi-Aventis, was approved as anti-obesity therapy in Europe, but in late 2008 it was withdrawn because of its psychiatric side effects[i]. This event profoundly affected further drug development efforts by the pharmaceutical industry, causing the termination of all clinical programs involving rimonabant-like CB_1R antagonists in development. Nevertheless, studies published during the past 5 years have not only provided information on new physiological roles played by the ECS in the context of energy balance but have also identified novel mechanisms of action that make the ECS once more a very attractive target for therapy. We therefore believe it is timely to review these recent advances, which clearly designate the ECS as a '*chef d'orchestre*', strategically positioned to regulate every step affecting the intake and use of calories, while discussing evidence that brings this system back at the center stage in the treatment of obesity and metabolic disease.

Glossary

Allosteric modulator: a compound that binds to a receptor at a site distinct from the active (or orthosteric) site and induces a conformational change in the receptor, thereby increasing or reducing the affinity of the receptor for its ligands.
Cannabinoid receptors (CBRs): a class of G-protein-coupled receptors activated by endogenous or exogenous cannabinoids. Two CBR subtypes have been cloned and characterized so far: the CB_1R and the CB_2R.
Cannabis: a preparation of the *Cannabis sativa* plant used as a psychoactive drug or medicine. The main psychoactive component of cannabis is tetrahydrocannabinol (THC).
Cephalic-phase responses: anticipatory responses elicited by the autonomic nervous system to enhance digestion and metabolism of a meal. Cephalic-phase responses can arise from cognitive or sensory stimuli regarding food.
Endocannabinoids: endogenous lipid-derived agonists for G-protein-coupled CBRs. They include anandamide (AEA) and 2-arachidonoylglycerol (2-AG).
Hemopressin: a bioactive peptide fragment derived from the hemoglobin α1 chain which has been proposed to work as an endogenous allosteric modulator of CB_1R.
Inverse agonist: a compound that has effects similar to those of an antagonist, but also causes a distinct set of downstream biological responses. Inverse agonists not only block the effects of binding agonists like a classical antagonist, but also inhibit the intrinsic or basal activity of the receptor.
Leptin: a hormone produced mainly by adipocytes that regulates energy balance, metabolism, and immune and reproductive functions.
Melanocortin system: a system crucially involved in the regulation of energy balance that in the CNS includes POMC and AgRP neurons of the hypothalamic arcuate nucleus, which respectively produce melanocortin agonists and antagonists acting on melanocortin receptors in target brain areas.
Munchies: a typical craving for palatable food after consuming marijuana-containing products.

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