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Review

Endocannabinoid signaling and food addiction

C. D'Addario[a,e,*], M.V. Micioni Di Bonaventura[b], M. Pucci[a], A. Romano[c], S. Gaetani[c], R. Ciccocioppo[b], C. Cifani[b], M. Maccarrone[d,f,**]

[a] Faculty of Bioscience and Technology for Food, Agriculture and Environment, University of Teramo, Piazza A Moro 45, 64100 Teramo, Italy
[b] School of Pharmacy, Pharmacology Unit, University of Camerino, Via Madonna delle Carceri 9, 62032 Camerino, MC, Italy
[c] "Vittorio Erspamer" School of Physiology and Pharmacology, Sapienza University of Rome, Piazzale Aldo Moro 5, 00185 Rome, Italy
[d] School of Medicine and Center of Integrated Research, Campus Bio-Medico University of Rome, Via Alvaro del Portillo 21, 00128 Rome, Italy
[e] Department of Clinical Neuroscience, Center for Molecular Medicine, Karolinska Institutet, SE-171 77 Stockholm, Sweden
[f] European Center for Brain Research (CERC)/Santa Lucia Foundation, Via del Fosso di Fiorano 64, 00143 Rome, Italy

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ABSTRACT

Overeating, frequently linked to an increasing incidence of overweight and obesity, has become epidemic and one of the leading global health problems. To explain the development of this eating behavior, new hypotheses involve the concept that many people might be addicted to food by losing control over their ability to regulate food intake. Among the different neurotransmitter networks that partake in the reward circuitry within the brain, a large body of evidence supports the involvement of the endocannabinoid system. Indeed, its dysfunctions might contribute to food addiction, by regulating appetite and food preference through central and peripheral mechanisms. Here, we review and discuss the role of endocannabinoid signaling in the reward circuitry, and the possible therapeutic exploitation of strategies based on its fine regulation.

Contents

Abbreviations: 2-AG, 2-arachidonoylglycerol; AA, arachidonic acid; ABA, activity-based anorexia; ACC1, acetyl coenzyme-A carboxylase-1; AEA, N-arachidonoylethanolamine; AN, anorexia nervosa; ARC, arcuate nucleus; BBB, blood-brain barrier; BED, binge eating disorder; BN, bulimia nervosa; CB, cannabinoid; CB1, CB receptor subtype 1; CB2, CB receptor subtype 2; CCK, colecistokinin; CRH, corticotrophin-releasing hormone; DA, dopamine; DAG, diacylglycerol; DAGL, diacylglycerol lipase; DHA, docosahexanoic acid; DMH, dorsomedial hypothalamus; DMS-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; DOP, δ-opioid receptor; eCB, endocannabinoid; EDI-2, the Eating Disorder Inventory-2; EMA, European Medicines Agency; EMT, eCB membrane transporter; EPA, eicosapentaenoic paraventricular nucleus acid; FAAH, fatty acid amide hydrolase; FAA, fatty acid amide; FAS, fatty acid synthase; Fa, fatty acid; FDA, Food and Drug Adminstration; GABA, γ-aminobutyric acid; GI, gastro-intestinal; GPR119, G protein coupled receptor 119; GPR55, G protein-coupled receptor 55; HFD, high fat diet; Icv, intracerebroventricular; LA, linoleic acid; LH, lateral hypothalamus; MAGL, monoacylglycerol lipase; MAG, monoacylglycerol; MCH, melanin-concentrating hormone; MOP, μ-opioid receptor; NAc, nucleus accumbens; NADA, N-arachidonoyldopamine; NAE, N-acylethanolamine; NAPE, N-acylphosphatidyl-ethanolamines; NAT, N-acyltransferase; NPY, neuropeptide Y; OEA, N-oleoylethanolamine; OP, obesity-prone; PE, phosphatidylethanolamine; PEA, palmitoylethanolamine; PET, positron emission tomography; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PLC, phospholipase C; PLD, hospholipase D; POMC, proopiomelanocortin; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acid; PYY, peptide YY; SEA, N-stearoylethanolamine; THC, Δ9-tetrahydrocannabinol; TRPV1, transient receptor potential vanilloid 1; VTA, ventral tegmental area; WAT, white adipose tissue; YFAS, Yale Food Addiction Scale.

* Corresponding author at: University of Teramo, Faculty of Bioscience and Technology for Food, Agriculture and Environment, Piazza A. Moro, 45, 64100 Teramo, Italy. Tel.: +39 0861 266877; fax: +39 0737 403343.
** Corresponding author at: School of Medicine and Center of Integrated Research, Campus Bio-Medico University of Rome, Via Alvaro del Portillo 21, 00128 Rome, Italy. Tel.: +39 06 2254 19169; fax: +39 06 2254 1456.
E-mail addresses: cdaddario@unite.it (C. D'Addario), m.maccarrone@unicampus.it (M. Maccarrone).

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1. The endocannabinoid system

Since the isolation and characterization of the active phytocannabinoids in the cannabis (*Cannabis sativa*) plant, including the most psychoactive ingredient Δ^9-tetrahydrocannabinol (THC) (Mechoulam and Gaoni, 1965; Mechoulam, 1970), and after the identification and cloning of the target of THC, the type-1 cannabinoid receptor (Devane et al., 1988; Herkenham et al., 1991; Matsuda et al., 1990), and of its endogenous counterparts, collectively termed "endocannabinoids" (Devane et al., 1992; Mechoulam et al., 1995; Sugiura et al., 1995), many efforts have been profused to study the different physiological functions modulated by what is known as "endocannabinoid system".

1.1. The endocannabinoids

The endocannabinoids (eCBs) are derivatives of arachidonic acid (AA), resembling other lipid transmitters such as prostaglandins or leukotrienes. They are conjugated with ethanolamine to form fatty acid amides (FAAs), or with glycerol to form monoacylglycerols (MAGs), *N*-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG) so far representing the best studied and most active members of each class, respectively (Devane et al., 1992; Mechoulam et al., 1995). There are also other endogenous FAAs, like the appetite-suppressor *N*-oleoylethanolamine (OEA) (Fu et al., 2008), the antiinflammatory, anticonvulsant and antiproliferative *N*-palmitoylethanolamine (PEA) (Lambert et al., 2001), and the immunomodulator *N*-stearoylethanolamine (SEA) (Maccarrone et al., 2002). The latter are called "eCB-like" compounds, since they do not activate cannabinoid receptors directly but have an "entourage effect" (Ben-Shabat et al., 1998; Lambert and Di Marzo, 1999; De Petrocellis et al., 2004). Moreover, 2-arachidonoylglycerolether (noladin ether) (Hanus et al., 2001), *N*-arachidonoyldopamine (NADA) (Bisogno et al., 2000), and the "inverted anandamide" virodhamine (Porter et al., 2002) also belong to the ever-growing eCBs family. The chemical structures of these substances are shown in Fig. 1.

1.2. eCBs metabolism

eCBs are produced by multiple synthetic pathways from lipid precursors present in cell membranes "on demand", that is when and where needed following physiological or pathological stimuli. However, AEA has been shown to have the potential to accumulate in intracellular stores called adiposomes (or lipid droplets) (Oddi et al., 2008), whereas 2-AG might be pre-formed and sequestered in distinct intracellular pools until needed (Alger and Kim, 2011).

The best known biosynthetic pathway of AEA and other *N*-acylethanolamines (NAEs) occurs in two steps: first a calcium-dependent transacylase (NAT, *N*-acyltransferase) transfers an acyl group from a membrane phospholipid to the *N*-position of phosphatidylethanolamine (PE), to generate *N*-acylphosphatidylethanolamines (NAPEs); then, a NAPE-selective phospholipase D (NAPE-PLD) hydrolyzes NAPEs to release NAEs (included AEA), and phosphatidic acid (Okamoto et al., 2004).

2-AG is mainly synthesized from AA-containing membrane phospholipids through the action of phospholipase C (PLC), leading to the formation of diacylglycerol (DAG), and then through one of two diacylglycerol lipases (DAGLs), DAGLα and DAGLβ (Bisogno et al., 2003).

Inactivation of eCB signaling is achieved by two steps: a rapid removal from molecular targets and subsequent hydrolysis by specific enzymatic systems. eCBs rapid diffusion through the plasma membrane has been shown to be mediated by a selective and saturable transporter, the eCB membrane transporter (EMT), responsible for both AEA and 2-AG uptake by several cells (Di Marzo et al., 1994; Hájos et al., 2004; Chicca et al., 2012). Moreover, an intracellular accumulation of AEA in adiposomes has been also reported (Oddi et al., 2008). Still under debate is whether or not eCB transport and degradation are coupled or independent processes (Fegley et al., 2004).

Once taken up by cells, AEA and 2-AG can be degraded by fatty acid amide hydrolase (FAAH), which breaks the amide or ester bond, to release AA and ethanolamine or glycerol, respectively (Cravatt et al., 1996). Yet, the main responsible for 2-AG metabolism is monoacylglycerol lipase (MAGL) (Dinh et al., 2002). The degradation products are then recycled into the membrane phospholipids, where they produce *de novo* the two eCBs (Bisogno et al., 2005). Moreover, AEA can be hydrolysed also by other enzymes with an "amidase signature", like FAAH-2 (Wei et al., 2006), or that belong to the choloylglycine hydrolase family, like *N*-acylethanolamine-hydrolysing acid amidase (Tsuboi et al., 2005). When MAGL or FAAH activity is suppressed, AEA and 2-AG might become substrates for lipoxygenases (Van der Stelt et al., 2002), cyclooxygenase-2 (Rouzer and Marnett, 2011) or cytochrome P450 (Snider et al., 2010), generating oxidative derivatives endowed with their own biological activities. It has been also reported that AEA and possibly other eCBs are transported intracellularly by distinct carriers, like fatty acid binding proteins (Kaczocha et al., 2009), albumin and heat shock protein 70 (Oddi et al., 2009), or a truncated FAAH termed "FAAH-1-like AEA transporter" (Fu et al., 2011; Leung et al., 2013). Therefore, the intracellular trafficking of eCBs might represent a new dimension to drive distinct signaling cascades of these compounds in the CNS and at the periphery (Maccarrone et al., 2010a,b; Kaczocha et al., 2012).

1.3. Molecular targets and signaling pathways

AEA and 2-AG activate different signaling pathways by binding to (with different affinities) and activating two well-characterized 7-transmembrane G protein-coupled cannabinoid (CB) receptor subtypes: type-1 (CB_1) (Herkenham et al., 1991) and type-2 (CB_2) (Munro et al., 1993). In humans, CB_1 is localized preferentially in the terminals of central and peripheral neurons and glial cells (Egertová et al., 2003), but is also expressed in peripheral tissues like heart, uterus, testis, liver and small intestine, as well as in immune cells (Maccarrone et al., 2001; Nong et al., 2001; Klein

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