Pharmacology & Therapeutics 129 (2011) 307–320

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Role of the endocannabinoid system in food intake, energy homeostasis and regulation of the endocrine pancreas

Chen Li, Peter M. Jones, Shanta J. Persaud *

Diabetes Research Group, King's College London, London SE1 1UL, UK

ARTICLE INFO

Available online 3 November 2010

Keywords:
Cannabinoids
Cannabinoid receptors
Food intake
Obesity
Insulin secretion
Islets of Langerhans
β-cells

ABSTRACT

The endocannabinoid system (ECS) is a signalling cascade consisting of CB1 and CB2 receptors, and enzymes for the synthesis and degradation of endogenous ligands for these receptors. Central CB1 receptors have been most widely studied since they play key roles in energy homeostasis and rimonabant, a CB1 receptor antagonist, was used clinically to treat obesity. Less is known about CB2 receptors, but their abundant expression by lymphocytes and macrophages has led to suggestions of their importance in immune and inflammatory reactions. More recently, it has become apparent that both CB1 and CB2 receptors are more widely expressed than originally thought, and the capacity of endocannabinoids to regulate energy balance also occurs through their interactions with cannabinoid receptors on a variety of peripheral tissues. In general, pathological overactivation of the ECS contributes to weight gain, reduced sensitivity to insulin and glucose intolerance, and blockade of CB1 receptors reduces body weight through increased secretion of anorectic signals and improved insulin sensitivity. However, the notion that the ECS per se is detrimental to energy homeostasis is an oversimplification, since activation of cannabinoid receptors expressed by islet cells can stimulate insulin secretion, which is obviously beneficial under conditions of impaired glucose tolerance or type 2 diabetes. We propose that under normal physiological conditions cannabinoid signalling in the endocrine pancreas is a bona fide mechanism of regulating insulin secretion to maintain blood glucose levels, but that energy balance becomes dysregulated with excessive food intake, leading to adipogenesis and fat accumulation through enhanced cannabinoid synthesis.

Contents

Abbreviations: AC, adenylate cyclase; ACEA, N-(2-chloroethyl)5,8,11,14-eicosaetraenamide; AEA, N-arachidonoyl ethanolamine; 2-AG, 2-arachidonoyl glycerol; AM251, N-(piperidin-1-yl)-5-(4-iodophenyl)-1-)2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide; CB, cannabinoid; CCK, cholecystokinin; DAG, diacylglycerol; EC, endocannabinoid; ECS, endocannabinoid system; FAAH, fatty acid amide hydrolase; GABA, γ-aminobutyric acid; GI, gastrointestinal; GPCR, G protein-coupled receptor; HEK, human embryonic kidney; LPC, lysophosphatidylcholine; MAPK, mitogen-activated protein kinase; MGL, monoacylglycerol lipase; NAPE-PLD, N-acyl-phosphatidylethanolamine phospholipase D; PE, phosphatidylethanolamine; PI 3-kinase, phosphatidylinositol 3-kinase; PKA, protein kinase A; PKB, protein kinase B; PKC, protein kinase C; PLC, phospholipase C; PPARγ, peroxisome proliferator activated receptor γ; PTX, pertussis toxin; T2DM, type 2 diabetes mellitus; THC, Δ^9-tetrahydrocannabinol; TRPV1, transient receptor potential vanilloid type 1 receptor; TZD, thiazolidinedione; VGCC, voltage-gated calcium channel; WIN55,212-2, (R)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone mesylate.

* Corresponding author. 2.9N Hodgkin Building, King's College London, Guy's Campus, London SE1 1UL, UK. Tel.: +44 20 7848 6275.
E-mail address: shanta.persaud@kcl.ac.uk (S.J. Persaud).

0163-7258/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.pharmthera.2010.10.006

1. Introduction

Type 2 diabetes mellitus (T2DM) is an increasingly common, chronic disorder of fuel storage and metabolism. It has been estimated that 285 million people world-wide will have diabetes in 2010 and that number is predicted to rise to 438 million by 2030 (Diabetes Atlas, 4th Edition, 2009). The chronic hyperglycaemia associated with T2DM leads to the development of devastating secondary complications in the macro- and micro-vascular systems, and these complications are responsible for reduced quality of life, greatly increased morbidity, premature mortality and considerable health-care costs. T2DM is a heterogeneous disorder in which a combination of genetic susceptibility and environmental factors, particularly obesity, generates a pathology in which the insulin-producing pancreatic β-cells are unable to secrete sufficient insulin to meet the demands of insulin-resistant target tissues. The subsequent failure of liver, muscle and fat to regulate fuel homeostasis leads to hyperglycaemia and dyslipidaemia which, in turn, have further deleterious effects on β-cell function and survival, exacerbating the progression of the disease. The metabolic dysfunctions associated with T2DM therefore involve the functions of many tissues and organs, including the regulation of food intake by the central nervous system, absorption of nutrients from the gastrointestinal tract, and their uptake and storage in liver, skeletal muscle and adipose tissue. In this review we will consider the roles of the endocannabinoid system in these processes, paying particular attention to the β-cells of the endocrine pancreas because of their key regulatory role in fuel homeostasis and because they offer an excellent pharmacological target for the development of new therapies for T2DM.

2. The endocannabinoid system

The physiological effects of *Cannabis sativa* have been known for centuries and it is now clear that they arise from the interaction between Δ^9-tetrahydrocannabinol (THC), the main active constituent of cannabis, and the so called cannabinoid receptors. Three subtypes of cannabinoid receptor have been identified to date: CB1 (Matsuda et al., 1990), CB2 (Munro et al., 1993) and GPR55, which has been classified as a novel cannabinoid receptor (Begg et al., 2005; Baker et al., 2006; Mackie & Stella, 2006; Ryberg et al., 2007). Despite each receptor being highly conserved across species, the amino acid sequences of the cannabinoid receptors show a relatively low level of homology among the receptor subtypes. Thus, CB1 and CB2 receptors only share 44% overall resemblance (68% at the active site) and GPR55 shows a mere 13.5% and 14.4% similarity to CB1 and CB2 receptors respectively (Begg et al., 2005; Lauckner et al., 2008). All three cannabinoid receptors belong to the G protein-coupled receptor (GPCR) superfamily and are expressed by numerous cell populations.

The CB1 receptor, initially identified in rat brain, is one of the most abundantly expressed GPCRs in the central nervous system, particularly in regions such as the cerebral cortex, hippocampus, basal ganglia and cerebellum (Lopez de Jesus et al., 2006). It is also expressed peripherally in organs including the testes, prostate, heart, lung and bone marrow (Howlett et al., 2002). The CB2 receptor, characterised first in human HL60 leukaemic cells, is mainly expressed in immune tissues and cells, such as the marginal zone of the spleen, macrophages, lymph nodes and microglia, with lower expression in non-immune cells (Munro et al., 1993; Walter et al., 2003; Van Sickle et al., 2005). More recently, both central and peripheral mRNA expression of the third cannabinoid receptor, GPR55, has been reported in mice (Ryberg et al., 2007). The wide distribution of cannabinoid receptors is consistent with the suggested physiological functions of the ECS, such as modulation of alertness, cognition, immunosuppression, locomotion and satiety (Dewey, 1986).

Two phospholipid-derived compounds, N-arachidonoyl ethanolamine (anandamide, AEA), extracted from porcine brain, and 2-arachidonoylglycerol (2-AG), from canine intestine, were characterised as having cannabimimetic properties and identified as the endogenous ligands of cannabinoid receptors (Devane et al., 1992; Mechoulam et al., 1995; Sugiura et al., 1995). They are thus known as endocannabinoids. A number of studies have shown that 2-AG and AEA are produced locally in peripheral tissues including adipocytes, hepatocytes, skeletal muscle, the gastrointestinal tract and endocrine pancreas (Sugiura et al., 2000; Di Marzo et al., 2009). They are synthesised on demand by diacylglycerol lipases (DAG-lipases) and N-acyl-phosphatidylethanolamine phospholipase D (NAPE-PLD) respectively, and degraded once the stimulation ceases via the enzymatic activities of monoacylglycerol lipase (MGL) and fatty acid amide hydrolase (FAAH; Prescott & Majerus, 1983; Goparaju et al., 1999). These biosynthetic and degrading pathways enable the system to exert its regulatory activity with spatial and temporal specificity. Collectively, the endocannabinoid system (ECS) is composed of the cannabinoid receptors, their endogenous ligands and the enzymes that are responsible for endocannabinoid metabolism (Fig. 1).

AEA has a greater affinity towards CB1 receptors than 2-AG and lacks CB2 receptor potency, so is therefore generally regarded as an endogenous CB1 receptor ligand (Di Marzo, 1998). However, the content of AEA is ~800 times less than that of 2-AG in rat brain, so endogenous levels of AEA are not considered sufficiently high to activate CB1 receptors in the brain (Sugiura & Waku, 2000; Sugiura et al., 2000). To the contrary, 2-AG, which has been extracted and identified in numerous tissue types, activates both CB1 and CB2 receptors. The relatively higher tissue content of 2-AG may compensate for its lower CB1 receptor potency and it has been suggested that it provides a housekeeping level of endocannabinoid for the maintenance of receptor activity (Sugiura & Waku, 2000). Thus, 2-AG is considered the major endocannabinoid in mammalian physiology. In addition, over the years, several other compounds including 2-arachidonoyl-glyceryl-ether (noladin ether) (Hanus et al., 2001), O-arachidonoyl-ethanolamine (virodhamine) (Porter et al., 2002), N-arachidonoyl-dopamine (Huang et al., 2002) and oleamide (Leggett et al., 2004) have also been reported to exert cannabimimetic activities. These lipid mediators are believed to act, at least in part, through cannabinoid receptors or by inhibiting endocannabinoid degrading enzymes to exert corresponding physiological effects (Smart et al., 2002; Bradshaw & Walker, 2005).

3. Cannabinoid receptor coupling

There is little information available on signalling downstream of GPR55, but it is known that the conventional cannabinoid receptors are coupled to $G_{i/o}$-proteins and their activation can result in inhibition of adenylate cyclase (AC) activity and decreased Ca^{2+} influx through voltage-gated Ca^{2+} channels (VGCCs). The reduction in cyclic AMP generation following inhibition of AC can be dissociated from the decreased Ca^{2+} influx since inhibition of Ca^{2+} currents still occurred in the presence of an exogenous cyclic AMP analogue capable of activating protein kinase A (Mackie et al., 1993). Cannabinoid-induced inhibition of VGCCs is reported to be secondary to decreased excitability following activation of a pertussis toxin (PTX)-sensitive inwardly rectifying K^+ conductance (Mackie et al., 1995). The inhibition of Ca^{2+} channel activity appears to be restricted to CB1 receptors since it was not observed in cells over-expressing CB2 receptors (Felder et al., 1995).

In contrast to the observations that CB1 receptors are coupled to inhibition of Ca^{2+} influx, there are reports that cannabinoids increase intracellular Ca^{2+} ($[Ca^{2+}]_i$). Thus, the endocannabinoid 2-AG induced elevations in $[Ca^{2+}]_i$ in neuroblastoma-glioma hybrid NG108-15 cells via CB1 receptor activation (Sugiura et al., 1996) and in human HL60 cells through CB2 receptor stimulation (Sugiura et al., 2000). Increased Ca^{2+} was also detected in N18TG2 neuroblastoma cells following cannabinoid receptor activation (Sugiura et al., 1997), but not in C6 glioma cells (Sugiura et al., 1997) or CHO cells transfected with CB1 or CB2 receptors (Felder et al., 1992). It therefore appears that the effects of cannabinoid receptor agonists on $[Ca^{2+}]_i$ depend on the cell type and