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The Role of the Endocannabinoid System in the Pathogeny of Type 2 Diabetes

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1. Introduction

Diabetes mellitus is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both (Bennett & Knowler, 2005). The pathophysiology of type 2 diabetes mellitus (T2DM) includes three mechanisms: insulin deficiency due to insufficient pancreatic insulin production, excessive hepatic glucose release and insulinresistance in peripheral tissues and liver (Gurber, 2010).

Usually, T2DM is associated with a cluster of cardiovascular and metabolic risks including obesity (especially abdominal obesity), decreased levels of high-density lipoprotein cholesterol (HDL), high levels of triglycerides, elevated blood pressure and silent inflammation and diabetes itself is considered to be a cardiovascular disease risk equivalent (Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology and the European Society for the Study of Diabetes, 2007). Taking into account the fact that T2DM is associated with obesity and excess fat accumulation may be the main cause of T2DM, one can evaluate the role of the endocannabinoid system (ECS) assessing (1) its role in the pathogeny of obesity and (2) the role of ECS on hyperglycemia; this last part can be split in (a) the implication of ECS on insulin resistance and (b) its effects on insulin release.

2. The endocannabinoid system

ECS is a very important physiological system involved in appetite stimulation, food intake and energy balance. Besides its metabolic functions, the ECS has also implications upon individual behavior, regarding preferences for sweets or fats, different substances abuses etc.

2.1 The endocannabinoid system – a historical perspective

The history of the discovery of the endocannabinoid system is connected to the history of the human use of the cannabis. A special note is to be mentioned: at first there were discovered the exogenous substances that activate this system and then the receptors and finally the endogenous ligands of this system were described. The first evidence about human use of the plant *Cannabis sativa* comes from fragments of pottery from China almost 10,000 years BC. These fragments appear to have some imprints of a plant that is considered to be hemp. Other proofs come from the cloths found in the Chinese burial chambers of the Chou dynasty (1122-265 BC). Therefore, the first use of cannabis appears to be for the manufacture of cloths, ropes and nets. The first description of the therapeutical effect of cannabis are from the Chinese pharmacopoeia Pen-ts'ao, ca. 1-2 century AD (Iversen, 2000). Nevertheless, it was only in 1964 when Gaoni and Mechoulam described the structure of delta-9-tetrahydrocannabinol (Δ^9 -THC), the main psychoactive substance found in the cannabis plant (Howlett et al., 2004).

The next step was the identification of specific sites for the action of Δ^9 -THC. In 1990, Matsuda et al. cloned the CB1 receptor, the main receptor for THC binding (Di Marzo, 2006). It was obvious that human body did not create cell receptors for exogenous substances only, therefore the endogenous ones had to be found. In 1992, Mechoulam and Pertwee discovered the first CB1 receptor agonist, anandamide, and they proved its THC-like functions. In 1993, Munro et al. cloned the CB2 receptor and two years later Mechoulam et al. and Waku et al. independently identified the second endogenous agonist of the cannabinoid receptors, 2-arachidonoylglycerol (2-AG). In the same year, Vincenzo di Marzo named these endogenous substances "endocannabinoids", after the name given to endorphins and the name given to the entire system derived from here (Di Marzo, 2006).

2.2 The structure of the endocannabinoid system

ECS is composed of cannabinoid receptors CB1 and CB2, their endogenous ligands and the enzymes which mediate endogenous ligands' biosynthesis and degradation (Lutz, 2002).

2.2.1 The cannabinoid receptors

There were identified two types of cannabinoid receptors until now. CNR1 represents the gene coding CB1 and it is localized at 6q14-q15 level. There is a significant similitude between the human CB1 and the one identified in rats or in mice and CB1 receptors were cloned in other species including fish and invertebrates. This receptor has 472 aminoacids and it is a G-protein coupled receptor with seven trans-membrane domains (Demuth & Molleman, 2006).

CB1 receptors are expressed mainly in the brain, but also in other organs involved in energetic homeostasis: adipose tissue, liver, gastrointestinal tract, pancreas and skeletal muscle. There are several endogenous agonists of the cannabinoid receptors, anandamide (N-arachidonyl ethanolamine) and 2-arachidonoylglycerol (2-AG) being the two main important molecules (Demuth & Molleman, 2006).

ECS is considered to link emotional response to stress with appetite and energy balance and it functions like an after stress recovery system which remains inactive in repose physiologic conditions. Activation of the central CB1 receptors is believed to modulate satiety and increase sensitivity to rewarding stimuli, including food (Eggen & Lewis, 2007). On the other hand, activation of CB1 receptors in the adipose tissue and in the liver can regulate metabolism and lipids storage (Jbilo et al., 2005).

The gene of the CB2 receptor is located on gene 1 at p36.11 level and it codes for a protein with 360 aminoacids. It is involved mainly in immunomodulation and its polymorphisms have been associated with autoimmune diseases (Sipe et al., 2005) but also with osteoporosis.

Beside the two cannabinoid receptors, there are other possible targets for the cannabinoids: vanilloid receptors (*transient receptor potential vanilloid type 1* – TRPV1), subtypes of CB1 receptor, CB2-like receptors and possibly other non-CB1, non-CB2, non-TRPV1 receptors that can interact with the cannabinoids (Pertwee, 2005).

2.2.2 The endocannabinoids and the cannabinoid receptor agonists

After the discovery of the two types of cannabinoid receptors the subsequent research focused on the isolation of the main endogenous substances that interact with these substrates. In 1993, anandamide was discovered followed soon after by the isolation of the 2-arachidonoylglycerol (2-AG) the endogenous compound with the most important cannabinoid receptor agonist activity (Lutz, 2002). After their isolation, it was noticed that the two substances were synthesized from the cell membrane-derived phospholipids and due to their lipophilic structure (Fig. 1), they are not needed to be stored in vesicles like other mediators. Anandamide has many biological *in vivo* and *in vitro* functions such as the activation numerous kinases like p38 mitogen-activated protein kinase (p38 MAPK), c-Jun N-terminal kinase (JNK), protein kinase B, the stimulation of arachidonic acid release, appetite stimulation, memory inhibition, pain modulation, vasodilatation, blood pressure decrease and neuroprotection (Onaivi et al., 2005).

Fig. 1. The structure of anandamide and 2-AG (adapted from Doyle, 2011)

Like anandamide, 2-AG has been found in various concentrations in the brain depending on the studied area, age, physiological and pathological conditions. 2-AG has a reduced binding activity compared to anandamide but it acts on both cannabinoid receptors and only on them. This is why some consider it as the only endogenous agonist of the ECS.

Among the two substances, other products have been described as acting on the cannabinoid receptors. Oleamide, noladin ether (2-arachidonoyl glyceryl ether), virodhamine and N-arachidonoyl-dopamine (NADA) can bind to one of the cannabinoid receptors. Their role in the physiology and physiopathology of the ECS has to be determined.

2.2.3 The metabolism of the endocannabinoids

The metabolic pathways of the two best described substances have many common features. Both compounds derive from the enzymatic hydrolysis of the products derived from the membrane phospholipids. Both substances are released and then taken back into the cell by diffusion and they are inactivated by intracellular hydrolysis. There are also some differences between the metabolic pathways of the two substances and this explains why the levels of these substances can vary depending on different physiological conditions (Pertwee, 2005).

The life cycle of the endogenous cannabinoids is different from the one of the other endogenous ligands. Neither anandamide, nor 2-AG is held in vesicles, but they are synthesized “on demand” following the Ca^{2+} influx that determines the activation of the Ca^{2+} -dependent biosynthetic enzymes (Di Marzo et al., 1998). It was shown that endocannabinoids are retrograde signaling molecules that suppress GABA release from presynaptic terminals following depolarization of a hippocampal CA1 pyramidal neuron. This process is known as depolarization-induced suppression of inhibition (DSI) (Wilson & Nicoll, 2001). The synthesis of endocannabinoids is not well understood. The enzymes that mediate this process are still being characterized and it is not possible to localize it to a particular subcellular compartment. Some studies indicate that the endocannabinoids are released from neuronal somata and dendrites (Egertova et al., 1998). Soon after their synthesis in the postsynaptic cell, the endogenous cannabinoids are secreted by simple diffusion or passive (energy-independent) carrier proteins may be required. Afterwards, they bind within the binding site crevice formed by the seven transmembrane helices of CB1 receptor of the presynaptic neuron (Fig. 2). The subsequent activation of CB1 by endocannabinoids results in the inhibition of Ca^{2+} channels in the presynaptic cell. Because the release of cationic neurotransmitters from vesicles (in the presynaptic cell) is Ca^{2+} -dependent, activation of CB1 results in the suppression of neurotransmitter release (Onaivi et al., 2005).

Little is known also about the subsequent events following receptor interaction. It has been proposed that endocannabinoids are released into the extracellular space and then transported by a specific transport protein on both neurons and glia that mediate endocannabinoid uptake (Piomelli et al., 1998). It has also been shown that an antagonist of this transporter, AM404, potentiates the effect of exogenous anandamide on cultured neurons. After being transported into the cell, anandamide is subsequently broken down into arachidonic acid and ethanolamine by a membrane-bound enzyme called fatty acid amide hydrolase (FAAH) (Di Marzo et al., 1998; Piomelli et al., 1998) that is localized to the endoplasmic reticulum (Fig. 3). An alternative mechanism proposed by Deutsch et al. is that anandamide uptake after receptor interaction is a process of simple diffusion (Glaser et al., 2003). The same authors indicated that transport inhibitors such as AM404 are actually inhibitors of FAAH *in vitro*. The mechanism of action for 2-AG appears to be similar.

Fig. 2. The mechanism of action of anandamide

Fig. 3. The uptake and degradation of anandamide

2.2.4 The biology of cannabinoid signaling

Retrograde synaptic signaling is considered a fundamental feature of the nervous system and endocannabinoids are one of the classes of retrograde messengers involved in the regulation of synaptic transmission. Thus, endocannabinoids mediate the rapid retrograde suppression of both excitatory and inhibitory synapses. Functionally, endocannabinoids are released from depolarized postsynaptic neurons in a calcium-dependent manner and act retrogradely onto presynaptic CB receptors to suppress neurotransmitter release.

CB1 and CB2 receptors are coupled with G protein, negatively to adenylate cyclase and positively to mitogen-activated PK. CB1R couples to the G protein signal transduction pathways in presynaptic nerve terminals and transduces the cannabinoid stimulation of MAP kinase and the inhibition of adenylate cyclase, thereby attenuating the production of cyclic AMP. CB1Rs are also coupled to ion channels through G proteins, positively to A-type and inwardly rectifying potassium channels, and negatively to N-type and P/Q-type calcium channels and to D-type potassium channels (Howlett and Mukhopadhyay, 2000). The quantity of cAMP decreases and cAMP-dependent PK (PKA) is inhibited by CB1R activation. In the absence of cannabinoids, PKA phosphorylates the potassium channel protein and exerts decreased outward potassium current. In the presence of cannabinoids

the phosphorylation of the channel by PKA is reduced, which increases the outward potassium current. Moreover, cannabinoids can close sodium channels, but whether or not this effect is receptor mediated has yet to be established. Other cellular responses triggered with CB1 receptor activation include other PK pathways such as the p38 MAKP, JUN N-terminal kinase, (JNK), focal adhesion kinase (FAK), and phosphoinositide-3 kinase (Akt) signaling, which might mediate effects on apoptosis (Molina-Holgado et al., 2002).

Acting on ion channels, the endocannabinoids mediate the rapid retrograde suppression of both excitatory and inhibitory synapses. Functionally, they are released from depolarized postsynaptic neurons in a calcium-dependent manner and act retrogradely onto presynaptic CBRs to suppress neurotransmitter release.

3. The role of ECS in obesity

The pathophysiological role of ECS has been documented on numerous studies involving animal models and also humans. Some of the animals used in the studies developed obesity as a result of leptin gene or leptin receptor gene mutations and others presented diet-induced obesity (DIO). These are the two main representative types of obesity: genetic or diet-induced.

It has been described that ECS plays an important role in the regulation of food intake by homeostatic and non-homeostatic (or hedonic) energy regulation pathways (Matias et al., 2008).

It was noticed that hypothalamic levels of endocannabinoids were increased in all models of leptin deficiency or defective leptin receptors signaling. This study proved the negative regulation of endocannabinoids by leptin. Moreover, leptin treatment for these mice leads to an important reduction of endocannabinoids levels (Engeli, 2008). It was also proved that hypothalamic endocannabinoid levels are decreased after systemic leptin administration in rats, and increased in rodent models of congenital hyperphagia and obesity, such as db/db mice and Zucker rats, where leptin signalling is defective, as well as in ob/ob mice, where leptin biosynthesis is defective and exogenous leptin can restore the normal (low) levels of endocannabinoids.

DIO also has an impact on ECS regulation. There were found increased levels of anandamide after feeding piglets a diet enriched in long-chain polyunsaturated fatty acids (LC-PUFA) like arachidonic acid and docosahexaenoic acid (DHA). These models also presented CB1 receptor downregulation in hypothalamus and the authors explained it as a result of increased levels of anandamide and 2-AG in extra-hypothalamic regions. Lower CB1 density was correlated with cumulative energy intake from the palatable, fat-enriched diet. In contrast, a fish-oil diet was associated with reduced 2-AG levels in the brain (Engeli, 2008).

After food deprivation, endocannabinoids act on CB1 receptors stimulating the central orexigenic system in the hypothalamus, therefore, controlling the homeostatic regulation of food imbalance (Di Marzo et al., 2001). Besides that, ECS may stimulate food intake by reinforcing the motivational processes involving the nucleus accumbens (Matias et al., 2008). Endocannabinoids, directly injected in the hypothalamus or the nucleus accumbens, can induce food-intake in satiated animals (Cota et al., 2006). Therefore, it appears that the ECS participates in the orexigenic hypothalamic network regulated by leptin. Moreover, CB1 receptors are distributed in the hypothalamus in a way suggesting that they regulate directly the expression of orexigenic signals such as agouti-related protein (AGRP), orexins and melanocyte-concentrating hormone (MCH) or anorexic signals such as those produced

from pro-opiomelanocortin (POMC) and the cocaine-and amphetamine-regulated transcript (CART) (Cota et al., 2003).

The ECS is implicated in adipose tissue homeostasis also directly via CB1 receptors located in adipocytes. Cota et al. were the first that suggested the implication of ECS in energy balance regulation by acting directly on peripheral CB1 receptors (Cota et al., 2003). Many researchers started their work to discover the peripheral mode of action of the ECS as a system that reduces energy expenditure and directs energy balance towards energy storage into the adipose tissue. Other organs involved in the process of energy storage are the liver, the skeletal muscle and the pancreas. It is well known that dietary triglycerides are transported to the liver from the intestine via chylomicrons. In addition, hepatic triglyceride synthesis from fatty acids and glycerol takes place under the influence of insulin produced by the pancreas in the postprandial state. Triglycerides are then secreted into blood as very low density lipoproteins (VLDL) that go either to the adipose tissue to be store as re-esterified triglycerides, or are metabolized into fatty acids that will be used as energy source after mitochondrial β -oxidation. Another major energy source in the body is represented by the oxidisable glucose in the skeletal muscle. The muscle will contribute to energy balance also by regulating the circulating levels of nutrients, and in particular of glucose, which can also be transformed into fatty acid precursors in the adipose tissue and the liver.

Several studies demonstrated the presence of endocannabinoid receptors in both animal and human adipose tissue. CB1 receptors are present in white adipose tissue and coupled to stimulation of lipoprotein lipase. These findings suggested that the ECS tonically contributes to fat accumulation, independently from the amount of food ingested and by acting directly on the adipose tissue. Studies carried out in the mouse 3T3 adipocyte cell lines showed that the blockade of CB1 receptors arrests adipocyte proliferation (Gary-Bobo et al., 2006), suggesting that endocannabinoids might stimulate proliferation. Moreover the formation of endocannabinoids precedes pre-adipocyte differentiation into mature adipocytes and chronic stimulation of CB1 receptors during adipocyte differentiation accelerates the appearance of an early marker of differentiation, peroxisome proliferator-activated receptor- γ (PPAR- γ), while inducing accumulation of lipid droplets (Matias et al., 2006). Cota *et al.* showed that CB1 receptor null mice exhibited significantly lower amounts of fat mass and higher amount of lean mass than wild-type mice even when fed with the same amount of food (Matias et al., 2008). Also, CB1 receptor protein expression increased with increasing adipocyte size and adiposity while exercise training inhibited these receptors and the peroxisome proliferators-activated receptor- δ (PPAR δ). PPAR δ tonically inhibits the expression of CB1 in a mouse clonal adipocyte cell line (Yan et al., 2007). When speaking of human studies, one study showed increased levels of anandamide and 2-AG in the plasma of menopausal obese women when compared with lean women of the same age (Engeli, 2008). Anandamide and 2-AG were increased in plasma of obese subjects with diabetes too. In a study that compared lean and obese men and women with either subcutaneous or visceral adipose tissue accumulation, 2-AG plasma levels were clearly correlated with visceral adipose tissue mass and the group with subcutaneous adipose tissue did not differ from the lean control group with regard to 2-AG plasma concentration (Bluher et al., 2006). The same study indicated that women had higher anandamide plasma levels than men, but no relationship with obesity or body fat distribution was found. Another study to support these findings was performed in 62 men and the subjects in the highest tertile of 2-AG levels presented with markedly increased visceral adipose tissue mass despite having almost the same body mass index as those in the lower two tertiles of plasma 2-AG. On the other hand,

anandamide was negatively correlated with visceral fat mass (Cote et al., 2007). Both studies showed that increased plasma 2-AG correlates with markers of metabolic syndrome (such as free fatty acids, triglycerides, HDL cholesterol, adiponectin), and is associated with decreased insulin sensitivity and enhanced glucose and insulin responses during an oral glucose load.

While the role of the brown adipose tissue in humans is less clear, it is known that it importantly contributes to thermogenesis and energy expenditure in small mammals. CB1 receptors are also present in mouse brown adipocytes (Perwitz et al., 2006) and the endocannabinoids might, therefore, regulate thermogenesis in this tissue. It has been demonstrated that CB1 inhibits the uncoupling protein-1 (UCP-1), a thermogenic, mitochondrial, proton translocating membrane protein (Perwitz et al., 2006).

Another mechanism may involve adiponectin, which is a cytokine that reduces the circulating levels of free fatty acids by inhibiting lipid storage stimulating fatty acid oxidation. It was proved that stimulation of CB1 receptors inhibits adiponectin expression in mature adipocyte while their blockade was associated with increased adiponectin expression (Matias et al., 2008). It is possible for CB1 receptors to induce lipogenesis by inhibition of cAMP formation. Matias et al. (Matias et al. 2006) found that, in mature adipocytes, a CB1 receptor agonist inhibited cAMP formation in a way that was significantly attenuated by CB1 receptor antagonists but not by a CB2 receptor antagonist. Inhibition of cAMP and, subsequently, protein kinase A (PKA) might stimulate lipogenesis by inhibiting the AMP-activated protein kinase (AMPK). This enzyme is stimulated by PKA-mediated phosphorylation and plays a key role in energy metabolism because it reduces fatty acid synthesis and stimulates fatty acid β -oxidation in several tissues. Interestingly, other studies demonstrated that Δ^9 -THC decreases AMPK phosphorylation both in subcutaneous and, particularly, visceral adipose tissue (Kola et al., 2005). Because adiponectin stimulates AMPK activity, the CB1-mediated inhibition of adiponectin expression in adipocytes might reinforce this effect (Matias et al. 2006).

Another way for ECS-enhanced lipogenesis in adipocytes might be through their ability to stimulate glucose uptake by these cells via the enhancement of both basal and insulin-induced translocation to the plasma membrane of the glucose transporter 4 (GLUT4) (Gasperi et al., 2007; Pagano et al., 2007). In mouse adipocytes this effect seems to be mediated by CB1-induced stimulation of nitric oxide synthesis (Gasperi et al., 2007), while in human adipocytes CB1 activates the phosphatidylinositol-3-kinase cascade (Pagano et al., 2007). Increased glucose uptake and, subsequently, glycolysis might be the way for *de novo* fatty acid biosynthesis, and this effect might underlie part of the pro-lipogenetic effect of CB1 receptor agonists in these cells (Matias et al., 2008).

A few studies tried to determine the effect of weight loss on ECS in obese subjects (Engeli et al., 2005, Engeli et al., 2008). Unfortunately, in all these studies, circulating anandamide and 2-AG, CB1 and FAAH gene expression in subcutaneous abdominal adipose tissue, were not influenced by weight loss, although metabolic parameters such as fasting insulin and blood pressure were significantly decreased as surrogates of successful therapy. The authors explained that weight loss might not have been large or fast enough and that, probably with a more rigid protocol, an influence on the ECS might have been seen. If weight loss does not influence the ECS in obese subjects, an alternative hypothesis is that genetic modifications could be the cause of dysregulation of the ECS in obesity.

There were several studies concerning the mutations of the CNR1 gene that encodes CB1 receptor. Russo et al. analyzed two variants of exon 4 of CNR1, scanning the gene for

polymorphisms rs12720071 (3813A/G) and rs806368 (4895A/G), in a study carried out on a group of European men. The results indicated that allele 3813G was associated with the growth of abdominal circumference (AC), subscapular cutaneous skinfold and body mass index (BMI). There have been observed no associations between rs806368 polymorphism and the determined variables. The haplotype's analysis consisted in the studying of 3 frequent haplotypes: A3813A4895 (AA), A3813G4895 (AG) and G3813G4895 (GG), haplotype GG being associated with the increase of the abdominal circumference and subscapular cutaneous skinfold (Russo et al., 2007). The polymorphism rs1049353 (1422A/G) was associated in men with a significant increase of the abdominal circumference, waist to hip ratio and of adipose mass after the adjustment for age and BMI. Adipose mass percent was also associated with this polymorphism but the association disappeared after the adjustment for age and BMI (Peters et al., 2007). Another study carried out on Swedish and Danish subjects indicated that polymorphisms rs806381, rs2023239, rs6454674 and rs10485170 associated with an increased BMI (Benzinou et al., 2008).

Fig. 4. The role of ECS in energy balance (adapted after Matias et al., 2008).

Muller et al. studied 8 polymorphisms in German children and adolescents: in region 5' (rs9353527, rs754387, rs6454676), in intron 2 (rs806379, rs1535255), exon 3 (rs2023239), intron 3 (rs806370) and in coding region (rs1049353), but they couldn't find any association with obesity (Muller et al., 2007).

Probably the most important proofs, that ECS is involved in obesity, come from the studies using selective CB1 receptors antagonists such as Rimonabant, where a significant reduction

of body fat was noticed. The Rimonabant in Obesity (RIO) study indicated that 1 year treatment with selective CB1 receptor antagonist, rimonabant 20mg, significantly reduced weight and abdominal circumference compared with diet and lifestyle therapy alone (Di Marzo et al., 2008). The figure 4 describes the ways by which ECS controls the energy balance.

4. The role of ECS in insulin sensitive organs

Adipose tissue. It is well known that adipose tissue is, beside the major energy depot, a very important source of adipokines that play a major role in insulin sensitivity and glucose homeostasis and the role of the ECS in modulating the adipose tissue was already discussed. Adiponectin is one of the adipokines involved in free fatty acid oxidation and hyperglycemia improvement (Kadowaki et al., 2006). It was already mentioned that overactivation of ECS is associated with low adiponectin levels and dysregulation of the adipose tissue.

Liver. Activation of CB1 receptors in mice leads to increased de novo fatty acid synthesis. One of the studies concerning the role of the ECS in the liver demonstrated, in rat hepatocytes, that anandamide inhibits acetyl-CoA-carboxylase activity leading to inhibition of de novo fatty acid synthesis. Furthermore, fatty acid oxidation was found to be increased since carnitine palmitoyltransferase-1 and the rate of ketogenesis from palmitate were stimulated by anandamide. Both effects on fatty acid synthesis and oxidation were prevented by an inhibitor of the anandamide enzymatic hydrolysis via FAAH (Guzman et al., 1995). This study, that presents the role of arachidonic acid originating from anandamide in stimulating the oxidation of fatty acids and inhibiting their synthesis, is of a great importance.

Activation of CB1 receptors in the liver also affects fatty acid homeostasis: CB1 receptors are expressed in hepatocytes, mainly around the centrilobular vein, and CB1^{-/-} mice exhibit lower expression of the important transcription factor SREBP-1c that is implicated in the regulation of fatty acid synthesis (Osei-Hyiaman et al., 2005). Activation of CB1 receptors in the liver enhances the expression of SREBP-1c and of its targets. These effects may explain the stimulatory effect of a CB1 receptor agonist on fatty acid synthesis and lipogenesis in these cells. Measurement of the fatty acids production in the liver after pretreatment of mice with a cannabinoid receptor agonist indicated a twofold increase of fatty acid synthesis (Osei-Hyiaman et al., 2005). An increase of fatty acids synthesis was also noticed in hepatocytes isolated from mice and treated with the same CB1 agonist. The increase in fatty acids synthesis was found neither in the liver nor in isolated hepatocytes from mice pretreated with rimonabant or CB1 receptor knockout (CB1^{-/-}) mice. These mechanisms explain the lipogenetic action of CB1 receptors in these cells.

A great observation was that CB1^{-/-} mice, unlike their wild-type littermates, do not develop hepatic steatosis after several weeks of a high-fat diet, a condition that leads to up-regulation of both hepatic anandamide and CB1 expression levels and down-regulation of FAAH.

In conclusion, the possible mechanism explaining the role of the ECS in the liver is the following: under normal energy homeostatic conditions, the low levels of CB1 receptors and high levels of FAAH increase the arachidonic-acid-mediated stimulation of fatty acid oxidation by anandamide. After several weeks of a high-fat diet the reduction of FAAH activity and the enhancement of CB1 receptors favour instead anandamide and CB1-

mediated hepatic lipogenesis (Matias et al., 2008). It is possible for the endocannabinoids to exert a function on glucose homeostasis in the liver also in healthy animals, because a CB1 receptor blocker was proven to stimulate glycogenolysis in liver in lean normoglycemic rats (Herling et al., 2007).

As it was mentioned, ECS might contribute to the development of diet induced obesity, which is found to be associated with an increase in the hepatic levels of the endocannabinoid anandamide and CB1-mediated fatty acid synthesis in mice (Nogueiras et al., 2008).

Muscle. One of the evidences of the involvement of the ECS in energy expenditure at the level of the skeletal muscle came from the observation that blood anandamide levels were significantly elevated in runners and cyclists but not in sedentary controls following 1h of moderate intensity exercise (Sparling et al., 2003). Other studies indicated that CB1 receptor knockout mice had higher energy expenditure, probably due to the energy combustion produced by fat or carbohydrate oxidation. Recent studies demonstrated that administration of a CB1 receptor antagonist increased energy expenditure in rats. A study about the chronic administration of rimonabant showed enhanced glucose uptake and oxidation by the isolated soleus muscle of genetically obese mice (Liu et al., 2005). Moreover, another study indicated that the very low density of CB1 receptors in the mouse soleus muscle increases when the animals are kept on a high-fat diet (Pagotto et al., 2006). Another study that dealt with the effect of a CB1 receptor antagonist AM251 in an in vitro model of skeletal muscle, indicated that this one increases the expression of AMPK α 1 and decreases that of the pyruvate dehydrogenase kinase-(PDK)4 (Cavuoto et al., 2007). More importantly, anandamide blocked only the effect of AM251 on the expression of AMPK α 1, and not that on PDK4, suggesting that only the former effect, and the subsequent likely activation of lipolysis and fatty acid oxidation, of the CB1 receptor antagonist is CB1 receptor-mediated. PDK4 is known as an important inhibitor of the pyruvate dehydrogenase complex, which links glycolysis to ATP production and to the Krebs cycle and its inhibition by AM251 might stimulate glucose flux into the mitochondria and cause an increase of glucose oxidation in the muscle. The opposite is expected to occur with endocannabinoids (Cavuoto et al., 2007). In leptin-deficient mice that exhibit hyperglycemia and insulinresistance, treatment with selective CB1 receptors antagonists increased basal oxygen consumption and glucose uptake in isolated soleus muscle preparations (Liu et al., 2005).

5. The ECS in the pancreas

Several findings suggest that ECS is involved not only in glucose uptake but also in the control of insulin levels. In pancreatic islets from mice, it was noticed that CB1 receptors are mainly expressed in non- β cells whereas CB2 are expressed in both β and non- β (Juan-Pico et al., 2006). There were seen differences between mice and rats, while in rats and humans both CB1 and CB2 receptors were noticed in both α - and β -cells (Matias et al., 2008; Di Marzo, 2008).

Juan-Pico et al. (Juan-Pico et al., 2006) observed co-localization of CB1 receptors with glucagons predominantly but some co-staining with insulin was also noticed particularly in human islets. Nakata and Yada (Nakata & Yada, 2008) observed co-localization of CB1 receptor with insulin in some but not all β -cells in mouse islets. Another study of Starowicz et al. indicated that CB1 receptors are highly co-expressed with glucagon in both mice and rats with a wider distribution of the CB2R throughout more of the islet cell types (Starowicz

et al., 2008). On the other hand, Li et al. (Li et al., 2010a) showed co-expression of both CB1 and CB2 receptors with insulin but not with glucagons expressing cells in the mouse. A possible explanation for all these contrasting results came from a recent publication that proved that many commercial CB1 receptor antibodies exhibit nonspecific interactions (Grimsey et al., 2008).

There is evidence for the expression in the pancreatic islet of all the molecules requested for the synthesis and degradation of the endocannabinoids (Bermudez-Silva et al., 2008). In conditions of hyperglycemia, over-expression of biosynthetic endocannabinoid enzymes and low levels of degrading enzymes was noticed.

In insulinoma cell lines from rats and also humans islets there were noticed increased levels of the endocannabinoids in response to glucose stimulation (Bermudez-Silva et al., 2008). It is known that β -cells are depolarized and they release of calcium in response to glucose-stimulated insulin release. Therefore, the increased calcium levels stimulate their synthesis in the β -cells.

Two studies (Juan-Pico et al., 2006; Nakata & Yada, 2008) observed a decrease in the amplitude of glucose-induced calcium oscillations in mouse islets in response to treatment with 2-AG (10mmol/l) and anandamide (1mmol/l). A decrease in calcium oscillations would be expected to adversely affect insulin secretion. Juan-Pico et al. noticed a 30% reduction in static insulin secretion by the endocannabinoids and Nakata and Yada observed a concentration-dependent inhibition of insulin release by AEA (1-10mmol/l) in mouse islets. Moreover, Nakata and Yada also noticed a decrease in glucose-induced calcium oscillations and insulin secretion in response to a more specific CB1 receptor agonist. The same authors also showed that a general CB1/CB2 receptor agonist and a specific CB1 receptor agonist, arachidonyl-2-chloroethylamide (ACEA) (100 nmol/l) significantly decreased insulin secretion from mouse islets. All these initial in-vitro experiments in rodents indicate that endocannabinoids and CB1 receptor agonists have deleterious effects on insulin secretion.

Li et al. (Li et al., 2010a,b) showed that treatment with ACEA (10mmol/l) decreased cAMP production in a mouse clonal β -cell and mouse islets. However this same group showed a concurrent increase in calcium levels in, and insulin secretion from, mouse β -cells in response to these cannabinoid receptor agonists in the presence of glucose (Doyle, 2011).

The apparent contradiction to the previous published results and to the fact that cAMP and calcium oscillations following glucose-stimulated insulin secretion are highly interdependent and amplify each other (Ni et al., 2011) was explained by the same author by stating that the stimulatory effect of cannabinoid receptor agonism on intracellular calcium levels overrides the inhibitory effect on cAMP production (Doyle, 2011).

Because ECS appears to modulate glucose homeostasis in both glucose dependent insulin release and glucose uptake from tissues pathways, studies to evaluate the glucose homeostasis *in vivo* were performed. Systemic stimulation of CB1 receptors in lean normoglycemic rats determined slower blood glucose clearance while activation of CB2 receptors improved glucose clearance (Matias et al., 2008).

When anandamide or ACEA were administered acutely to Wistar rats prior to a glucose tolerance test, the rats developed severe glucose intolerance (Bermudez-Silva, 2006). The effect was reversed by the CB1 receptor antagonist AM251, suggesting direct effect on glucose tolerance through this receptor. In this study, the authors did not measure insulin secreted during the glucose tolerance test so it can not be estimated the direct effect on insulin secretion (Doyle, 2011). In another study, they examined glucose tolerance in

response to specific CB1 and CB2 receptors agonists and antagonists and they confirmed the specific effect of the CB1 receptor on glucose intolerance with CB2 receptor imparting a degree of glucose tolerance (Bermudez-Silva et al., 2008). Subchronic administration (18 days) of AM251 (6 mg/kg, interperitoneal) decreased circulating plasma glucose and increased glucose tolerance after a glucose load in ob/ob mice (Irwin et al., 2008). Other studies observed that CB1 stimulation increased insulin secretion. Interestingly, CB1 agonists also enhanced glucagons release from human alpha cells and CB2 agonists reduce both insulin and glucagon release (Di Marzo, 2008). The possible explanation was that CB1 receptors inhibit glucose expenditure by inhibiting insulin utilization in skeletal muscle but enhancing it in the adipose tissue for energy storage into fats (Matias et al. 2008).

Fig. 5. The major mechanisms by which over-activation of ECS may lead to T2DM

The major evidence that dysregulated ECS is involved in glucose homeostasis comes from the clinical studies using CB1 receptor antagonists treatment. The Rimonabant in Obesity (RIO) study indicated that 1 year treatment with selective CB1 receptor antagonist, rimonabant 20mg, significantly reduced weight and abdominal circumference compared with diet and lifestyle therapy alone. The RIO-Lipids trial showed that subjects with dyslipidaemia and body mass index between 27 and 40kg/m² exhibited significant increase in HDL-cholesterol, reduction in plasma triacylglycerol and increase in plasma adiponectin levels. The RIO-Diabetes trial enrolled 1045 overweight/obese subjects with T2DM that received treatment with metformin or sulfonylurea treatment alone. The subjects receiving rimonabant showed significant body weight reduction improvement in glucose control. Approximately 50% of the improvements in HbA1c levels were independent of weight loss (Di Marzo, 2008). The results can be attributed in part to a reduction in insulin resistance in the liver, fat and skeletal muscle, and an increase in lipolysis and direct effects also on the

pancreatic β -cell cannot be ruled out (Van Gaal et al., 2008). In October 2008, rimonabant was withdrawn from market in Europe and it was not approved for use in the USA due to the severe psychiatric side-effects including anxiety, depression, and suicidal ideation (Doyle, 2011). The main mechanisms explaining the implication of the ECS in the pathogeny of T2DM are represented in Figure 5.

6. Future perspectives

Unfortunately, the withdrawal of rimonabant, due to the psychiatric side affects, diminished the interest for investigating the role of ECS in the pathogeny of T2DM. But as previous studies and RIO trials indicated, the ECS has an important role in the pathogeny of T2DM and obesity proving the fact that it represents a physiological system implicated in energy storage, contributing together with other genes and systems at the “thrifty phenotype” that can lead to pathological conditions like T2DM and diabetes when over-activated.

Fig. 6. The possible ways for targeting the ECS (adapted from Patti et al., 2010)

Nevertheless, emerging evidence supported the idea that interrupting endocannabinoid action selectively only in peripheral tissues may be an approach to treat the metabolic consequences of obesity and related diseases, including type 2 diabetes, without causing the undesirable CNS effects that occurred with rimonabant. The studies of Tam and colleagues brought back the attention to the ECS (Tam et al., 2010). Tam et al. first developed a CB1 antagonist (AM6545) that retained binding activity but could not penetrate the brain due to its reduced lipid solubility (Tam et al., 2010). Therefore, it could not block the CB1 receptors

in the CNS. Remarkably, acting only on peripheral CB1 receptors AM6545 reduced body weight and adiposity in mice with diet-induced obesity and also improved systemic metabolism, as indicated by reduced fasting glucose, improved glucose tolerance, reduced insulin and leptin levels, increased adiponectin levels, and reduced hepatic triglyceride content in mice with diet-induced obesity (Patti et al., 2010) (Figure 6). The potency of AM6545 was a bit smaller probably due to additional centrally mediated effects of rimonabant on food intake or metabolism.

The discovery of the ECS represents a great step towards better understanding the pathogeny of obesity and T2DM. Due to its numerous interactions with other physiological systems, it remains an important target for the future treatments of T2DM and not only. In order to clearly elucidate the role of this system and for the development of peripheral selective, nonbrain penetrant, CB1 receptor antagonists, future studies are needed.

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Role of the Adipocyte in Development of Type 2 Diabetes

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Adipocytes are important in the body for maintaining proper energy balance by storing excess energy as triglycerides. However, efforts of the last decade have identified several molecules that are secreted from adipocytes, such as leptin, which are involved in signaling between tissues and organs. These adipokines are important in overall regulation of energy metabolism and can regulate body composition as well as glucose homeostasis. Excess lipid storage in tissues other than adipose can result in development of diabetes and nonalcoholic fatty liver disease (NAFLD). In this book we review the role of adipocytes in development of insulin resistance, type 2 diabetes and NAFLD. Because type 2 diabetes has been suggested to be a disease of inflammation we included several chapters on the mechanism of inflammation modulating organ injury. Finally, we conclude with a review on exercise and nutrient regulation for the treatment of type 2 diabetes and its co-morbidities.

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