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Endocannabinoid System and Ocular Vascularization: Systematic Review

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ABSTRACT

This review focuses on the role of the endocannabinoid system in ocular and systemic circulation. By studying different analytic approaches, all of which had been previously proposed in the literature, we explore the importance of the endocannabinoid system on ocular vascularization and its interaction with other anti-inflammatory medication. We focus on the cannabinoids effects on ocular circulation, as well as their implications in visual function. We aim to provide a comprehensive assessment of the endocannabinoid system as a complex neuromodulatory entity that could play an important role in the visual system. Most importantly, modulating the activity of the cannabinoid receptors seems to be very promising from the therapeutic point of view for a wide range of pathological conditions, from anxiety disorders and metabolic syndrome to autoimmune diseases and retina or optic nerve pathology.

Keywords: Cannabinoids, Endocannabinoid system, Ocular vascularization, Visual system

THE ENDOCANNABINOID SYSTEM

Introduction

The endocannabinoid system comprises the cannabinoid receptors, the endogenous cannabinoids (endocannabinoids) and their synthesis/degradation enzymes [1].

The multiple roles of the endocannabinoid system in human physiology have been proven to be very interesting for researchers worldwide, in order to find new perspectives on the use of endocannabinoids as therapeutic goals for new drug development.

Anandamide was the first identified endocannabinoid; the second one was 2-arachidonoyl glycerol. These two cannabinoids belong to a wide spectrum of related bioactive acylethanolamides, being also known as the two major agonists of the CB1 and CB2 receptors. Nonetheless, only 2-arachidonoyl glycerol (2-AG) is considered a full agonist for CB1 and CB2, mediating retrograde signals at the synaptic levels, firmly suggesting 2-AG to be physiologically more valuable than arachidonoyl ethanolamide (anandamide) [1-3].

A particularity of endocannabinoids, comparing with other neuromodulators, is that their precursors are synthetized "on demand", meaning that they exist in the cell membranes and can be cleaved by specific enzymes [3]. The transport of endocannabinoids at the cellular level is facilitated by a specific uptake system and their degradation is managed by the fatty acide amide hydrolase (FAAH) and the monoacylglycerol lipase (MAGL). Fatty acid amide hydrolase is implicated in degradation of anandamide into free arachidonic acid and ethanolamine, while monoacylglycerol lipase manages the degradation of 2-AG into arachidonic acid and glycerol. Oxidation of anandamide and 2-AG may implicate cyclooxygenase-2 and different lipoxygenases [3,4].

CANNABINOID RECEPTORS LOCALIZATION AND VASCULAR IMPLICATIONS

According to International Union of Basic and Clinical Pharmacology classification (IUPHAR), the endocannabinoid system consists of cannabinoid receptors CB1 and CB2, activated by endogenous ligands such as Anandamide and 2-arachidonoylglycerol and inactivated by G-protein coupled receptors. CB1 receptors seem to have a predisposition towards central and peripheral neuronal cells localization, whereas CB type 2 receptors are mainly expressed in immune tissues, presenting a possible immuno-

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immunomodulatory role of the endocannabinoid system [3,5].

Anandamide and 2-arachidonoylglycerol - the two major endocannabinoids - can be found in the adult human retina and also in the retina of adult bovines and rodents. The majority of the studies comparing anandamide with 2-AG expression in the retina pointed out significantly higher levels of 2-arachidonoylglycerol. In humans, 2-AG is mainly produced at the level of the retina, while anandamide is mainly expressed in the iris [6].

In vascular territory, anandamide acts through multiple mechanisms, CB1 dependent and CB1 independent, inducing vasorelaxation. Also, direct activation of vascular CB type 1 receptors has a profound coronary and cerebral vasodilator effect. The hemodynamic profile differences of distinct cannabinoids might be related to quantitative differences in CB type 1 receptor expression in various tissues and the possible involvement of as-yet-unidentified receptors [3].

Another interesting effect of anandamide is the promotion of vasodilation through an indirect mechanism related to arachidonic acid production and secondary cyclooxygenase (COX)-induced metabolism [3]. Relatively recent studies have been shown a rising of cannabinoids levels after non-opioid drug therapy; this effect could be explained by various mechanisms like inhibition of FAAH by some non-opioids (Indomethacin and Ibuprofen included) followed by the inhibition of cannabinoids metabolism or inhibition of cannabinoids metabolism by COX-2.

We might consider though the fact that there are some differences between vasorelaxant effect of anandamide and they are related to tissues and species [3].

CANNABINOID-LIKE RECEPTORS

Recent studies suggested that G-protein coupled receptor 55 (GPR55) acts as a cannabinoid receptor because of its interaction with anandamide and Δ9-tetrahydrocannabinol (THC). Another example of cannabinoid-like receptor presented in the retina is the transient receptor potential vanilloid 1 (TRPV1), which binds anandamide and N-arachidonoyl dopamine. There is also new evidence pointing out the intracellular peroxisome proliferator-activated receptors (PPARs) as targets of cannabinoid ligands [6].

CONCLUSION

Endocannabinoid system represents the newest neuromodulatory system that can regulate inhibitory and excitatory synapses transmission in a short or long-lasting manner. Endocannabinoids are widely spread in neural and non-neural tissues throughout the body, their presence providing a broad spectrum of possibilities for new therapeutic approaches.

Further research is needed, especially because the mechanism of action of the endocannabinoids in the human eye is incompletely known and understood. Yet, considering the neuroprotective properties of the cannabinoids in the retina, we can support additional studies regarding their use in the treatment and prevention of retinal and optic nerve disorders.

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