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Minireview

The complex modulation of lysosomal degradation pathways by cannabinoid receptors 1 and 2

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ABSTRACT

The two main receptors of the endocannabinoid system, cannabinoid receptors 1 (CB1R) and 2 (CB2R), were described in the early 1990s. Since then, different physiological functions have been revealed that are linked to the activity of these two G-protein-coupled receptors. CB1R and CB2R activities influence signal cascades, which are known to play a role in the regulation of the cellular "self-digestion" process called autophagy. A variety of these signaling pathways are integrated by the mammalian target of rapamycin complex 1 (mTORC1) that acts as an inhibitor of autophagy. Others, like AMP-activated protein kinase dependent signaling pathway, are able to bypass mTORC1 to modulate the autophagic activity directly. In the recent years, several scientific reports demonstrate an involvement of CB1R and CB2R signaling in the control of the autophagic activity in different paradigms. In this review, we summarize the recent literature on this topic, which is in part contradictory and therefore, it is of great importance to illuminate the results of the single reports in the physiological context of the model systems used in these studies. Utilizing CB1R and CB2R as pharmacological targets to modulate the autophagic activity is a promising strategy for the treatment of different patho-physiological conditions and disease.

Contents

1. Introduction

Cannabis sativa has been used as a medical plant for many centuries, but the main psychoactive component, Delta-9-tetrahydrocannabinol (THC), was only identified and synthesized in the 1960s [42]. More than two decades later, two THC-receptors were discovered that belong to the family of G-protein-coupled receptors (GPCRs): the cannabinoid receptor 1 (CB1R — [16,41]) and the cannabinoid receptor 2 (CB2R — [46]). CB1R has been initially described as the neuronal cannabinoid receptor as it is highly expressed in different classes of neurons and is located at the pre-synapse mediating retrograde synaptic signal transduction [74]. Moreover, evidence is rising that CB1R is also participating in the complex communication between neurons and glia cells, including oligodendrocytes, astro- and microglia [24,28,63]. In the meantime, CB1R expression has been found additionally in a number of non-neuronal cell types and tissues (e.g. adipose tissue, pancreas, kidney, hepatocytes [12,31,52]). In these peripheral organs and tissues, the common physiological function of CB1R appears to be the direct modulation of cell metabolism independent of the appetite control system in the CNS [48]. CB2R is primarily expressed in peripheral immune cells (like B cells and natural killer cells) and organs of the immune system (like the spleen or the tonsils) [5,22,54], but CB2R expression is also found in osteocytes, osteoblast and osteoclasts [49].

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In contrast to CB1R, CB2R expression in the CNS is restricted to more distinct cell types like microglia and neurons of the brain stem [69,72].

Interestingly, both subtypes of cannabinoid receptors interfere with a variety of intracellular signaling cascades, which are known to modulate the autophagic activity. Autophagy is a term summarizing a group of evolutionarily highly conserved pathways in eukaryotic cells whereby substrates are finally processed by lysosomal degradation [75]. Microautophagy and chaperone-mediated autophagy (CMA) pathways are characterized by a direct sequestration of autophagic substrates into the lysosomes either by an invagination of the lysosomal membrane or via the lysosomal CMA receptor LAMP2a. The formation of autophagosomes is necessary for the third class of autophagy: macroautophagy (hereafter referred to as autophagy). Here, cytoplasmic proteins, protein aggregates or even defective organelles are enclosed by these double membrane vesicles (autophagosomes) that subsequently fuse with lysosomes [65]. Autophagosome formation is controlled by two major protein complexes, the mammalian target of rapamycin (mTOR) complex 1 (mTORC1) and the coiled-coil myosin-like BCL2-interacting protein 1 (BECLIN1)-complex [44]. mTORC1 is a negative regulator of autophagy as the inhibition of the central kinase mTOR by rapamycin is driving the autophagic flux [9]. The autophagic flux is defined as the amount of autophagic vesicles that are generated by the cell and subsequently cleared via lysosomal degradation in a certain time period. This turnover of autophagosomes is regarded to be synonymous to the autophagic degradation potential [34]. In contrast to mTORC1, the BECLIN1-complex acts as an inducer of autophagy in most physiological situations. Here, the class 3 phosphatidylinositol 3-kinase (PI3KC3) is generating the signal lipid phosphatidylinositol 3-phosphate (PI3) that promotes autophagosome formation and maturation [21,30,32]. In addition to these regulatory complexes, the formation of functional autophagosomes involves the highly organized interplay of more than 30 autophagy-related (ATG) proteins [44] (Fig. 1). Thereby, the conjugation of phosphatidylethanolamine (PE) to autophagic adaptors (ATG8 proteins) like the microtubule-associated light chain 3 protein (LC3) is a crucial step in the maturation of autophagosomes. In contrast to unconjugated LC3 (LC3-I), PE-conjugated LC3 (LC3-II) is specifically localized at the inner and in part also at the outer autophagosomal membrane and is therefore frequently used as a marker for autophagosomes. These adaptor proteins connect the nascent early autophagosomal membrane to their cargo by autophagy receptors (like p62/sequestosome 1, SQSTM1) that simultaneously bind autophagic substrates and the ATG8 proteins attached to the membrane via the LC3-interacting region (LIR) [33,53]. In the last years, evidence is rising that autophagosome formation does not exclusively require the involvement of both mTORC1 and BECLIN1-complex or the intervention of all ATG proteins. These autophagic processes bypassing one or more regulative elements are classified as non-canonical autophagy [13].

CB1R activity influences signaling cascades, which are known to play a role in the regulation of autophagy in addition to its well-described role in retrograde synaptic signal transduction, where CB1R is modulating the permeability of Ca^{2+} and K^{+} channels for these ions. CB1R activation stimulates the class 1 phosphatidylinositol 3-kinase (PI3KC1) and thereby it induces the serine/threonine protein kinase Akt (AKT) activity [7,25,51]. AKT activation subsequently effects mTORC1 [17,44]. In addition, mitogen-activated protein kinase (MAPK) and AMP-activated protein kinase (AMPK) signals are integrated by mTORC1 and CB1R is also a modulator of these intracellular signaling cascades [15,17,66]. It is important to mention that AMPK is also able to influence the autophagic activity bypassing mTORC1 signaling via direct phosphorylation of UNC-51-like kinase 1 (ULK1) the downstream target of mTORC1 [20], which is driving autophagy by activating the BECLIN1-complex [58]. In addition to CB1R, CB2R also interferes with autophagy-regulating intracellular signaling processes. CB2R activity is affecting MAPK, PI3KC1–AKT, and AMPK signaling pathways [1,11,71]. Therefore, CB1R as well as CB2R can be addressed as potential pharmacological targets for the modulation of autophagy, which is of high interest as this cellular process plays an important role in many physiological and pathophysiological states [10,45].

Three physiological aspects of the autophagosomal–lysosomal degradation system are modulated by either CB1R or CB2R activity: the delivery of autophagic substrates to the lysosomes (the autophagic flux), the degradation ability of lysosomes and the control of autophagy-induced cell death as one type of physiological cell death.

2. Cannabinoids modulate autophagy-induced cell death

The translation of the term autophagy from the Greek meaning "self-eating" illustrates the need of a tight regulation of the autophagic

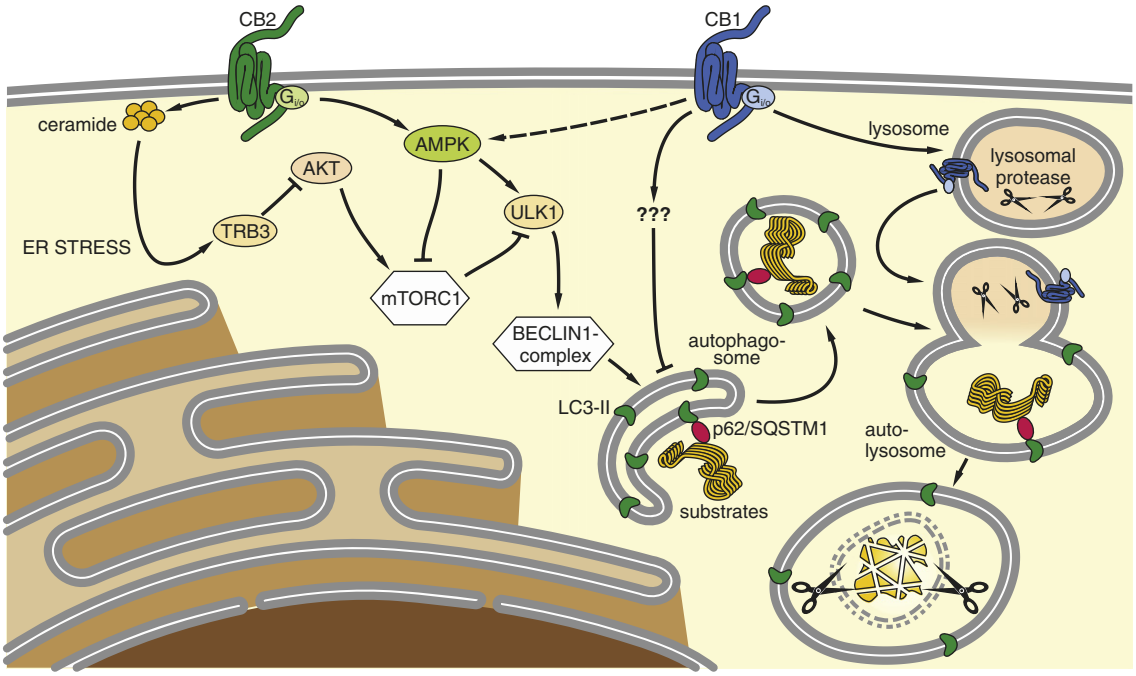

Fig. 1. Schematic overview of the modulation of autophagy by CB1R and CB2R activities.