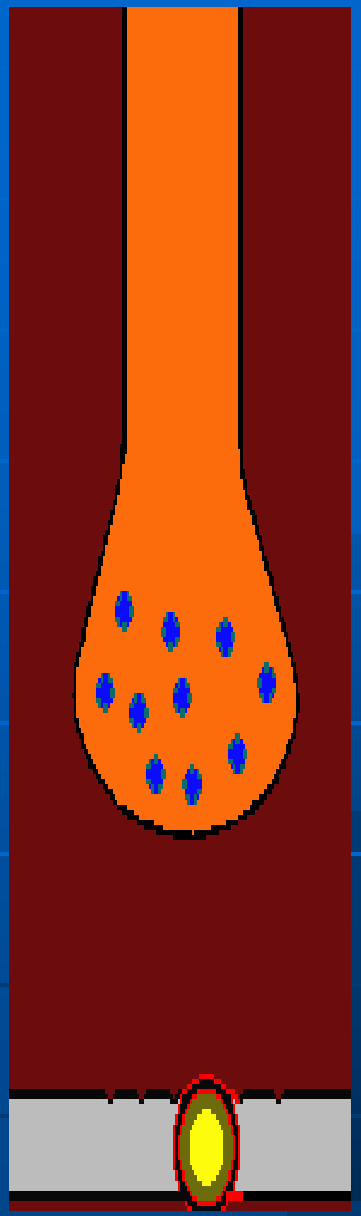
cannabinoid receptors



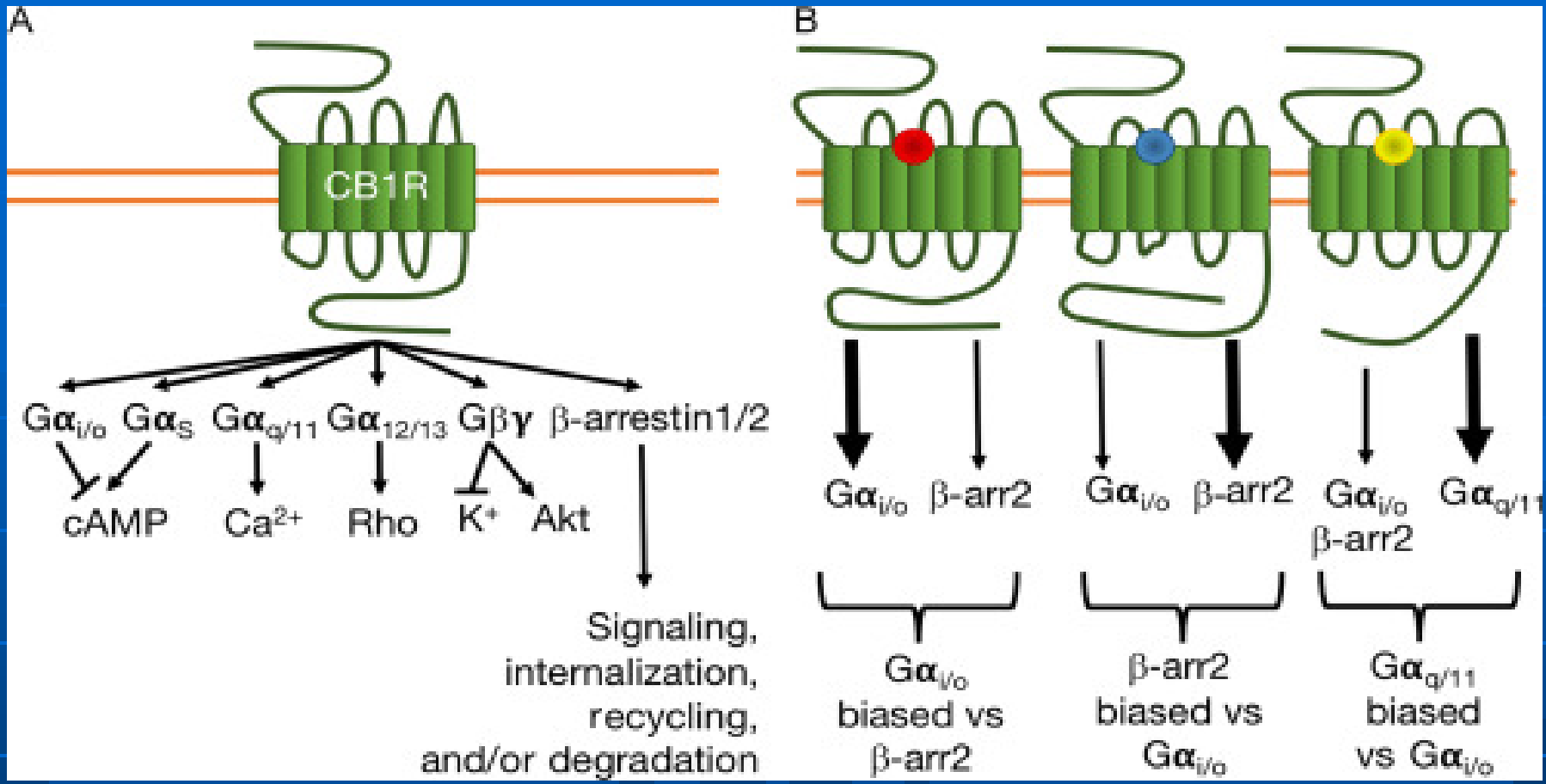
Prof.Dr.Nuray Arı, 2018

Prospects for the Use of Cannabinoid Receptor Ligands for the Treatment of Metabolic Syndrome and Atherosclerosis: Analysis of Experimental and Clinical Data.

Westn Ross Akad Med Nauk. 2017;72(1):59-65. doi: 10.15690/vramn779. Maslov LN, Karpov RS.

Abstract

An antagonist of central cannabinoid CB1 receptors rimonabant causes weight loss in patients with obesity and metabolic syndrome, improves blood lipid parameters, increases the adiponectin level, decreases the rate of glucose and glycosylated hemoglobin in patients with diabetes mellitus type-2. However, rimonabant adverse effects include depression, anxiety, nausea, and dizziness which are apparently due to the blockade of central CB1 receptors. In mice with a high-calorie diet, we defined that the blockade of peripheral CB1 receptors prevents obesity, steatosis of the liver, improves lipid and carbohydrate metabolism. Experimental studies suggest that peripheral CB2 receptor agonists have antiatherogenic effect. To validate the expediency of clinical research of CB2 receptor agonists in patients with atherosclerosis the comparative analysis of antiatherogenic properties of cannabinoids should be performed. In addition, experiments are needed on the combination use of cannabinoids with well-known antiatherogenic agents, such as statins.



CB1R-mediated signaling.

(A) CB1R interacts with multiple effector proteins to produce different intracellular signals. These effector proteins include: $G\alpha_{i/o}$, $G\alpha_{s}$, $G\alpha_{q/11}$, $G\alpha_{12/13}$, Gβγ, and β-arrestins. (B) The binding of different agonists to CB1R stabilizes the receptor in conformations that preferentially enhance coupling to certain effector proteins and diminish coupling to other effector proteins. Consequently, cellular signaling pathways are effectively enhanced or diminished; this describes ligand bias. Here, three theoretical agonists bind CB1R and each facilitates a unique receptor conformation and unique signaling outputs.

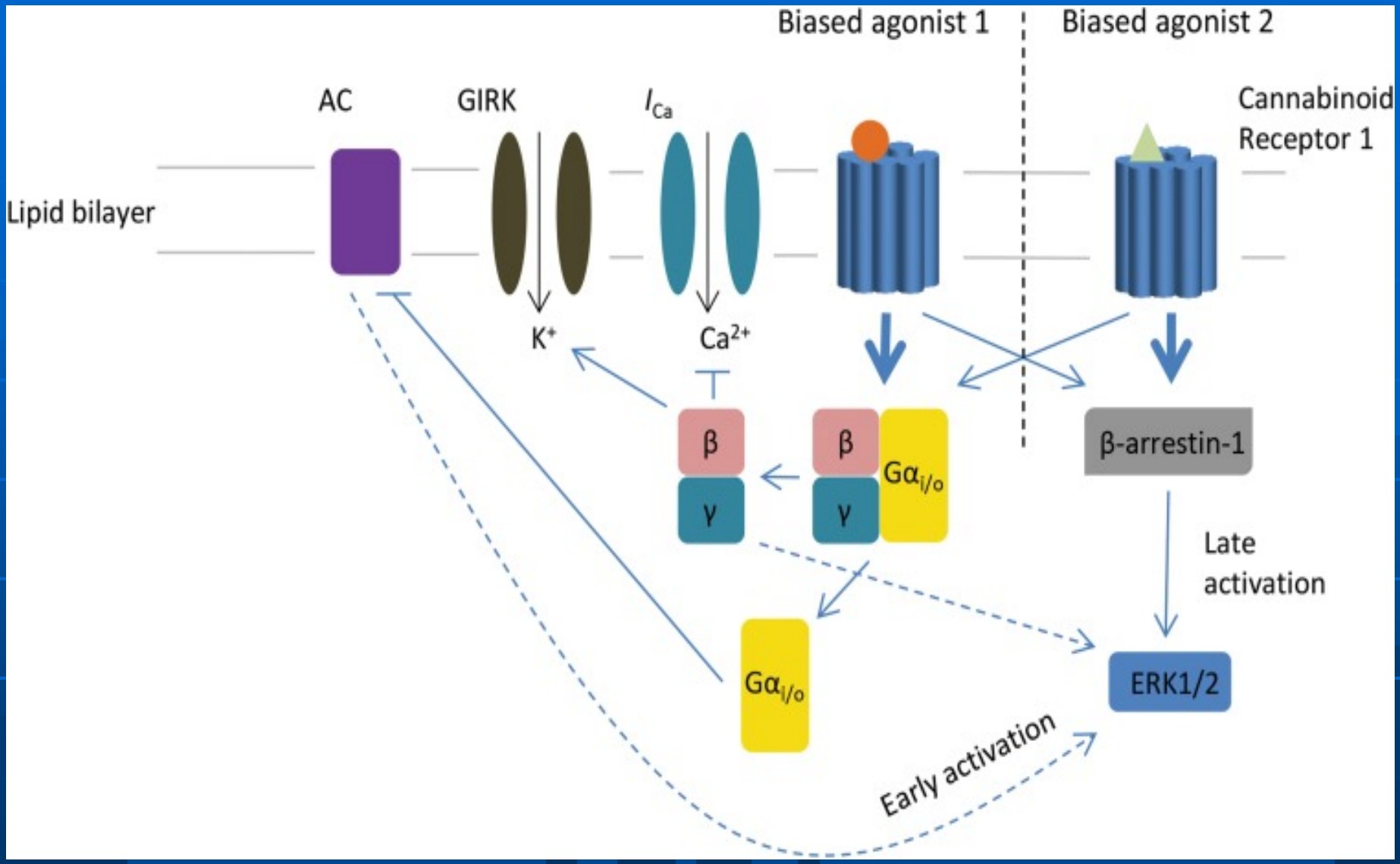
Methods in Enzymology Volume 593, 2017, Pages 259-279 Ch 12 - Approaches to Assess Biased Signaling at the CB1R Receptor Author links open overlay panelRobert B.LaprairieEdward L.StahlLaura M.Bohn

An Update on Non-CB1, Non-CB2 Cannabinoid Related G-Protein-Coupled Receptors.

Cannabis Cannabinoid Res. 2017 Oct 1;2(1):265-273. doi: 10.1089/can.2017.0036. eCollection 2017. Morales P, Reggio PH.

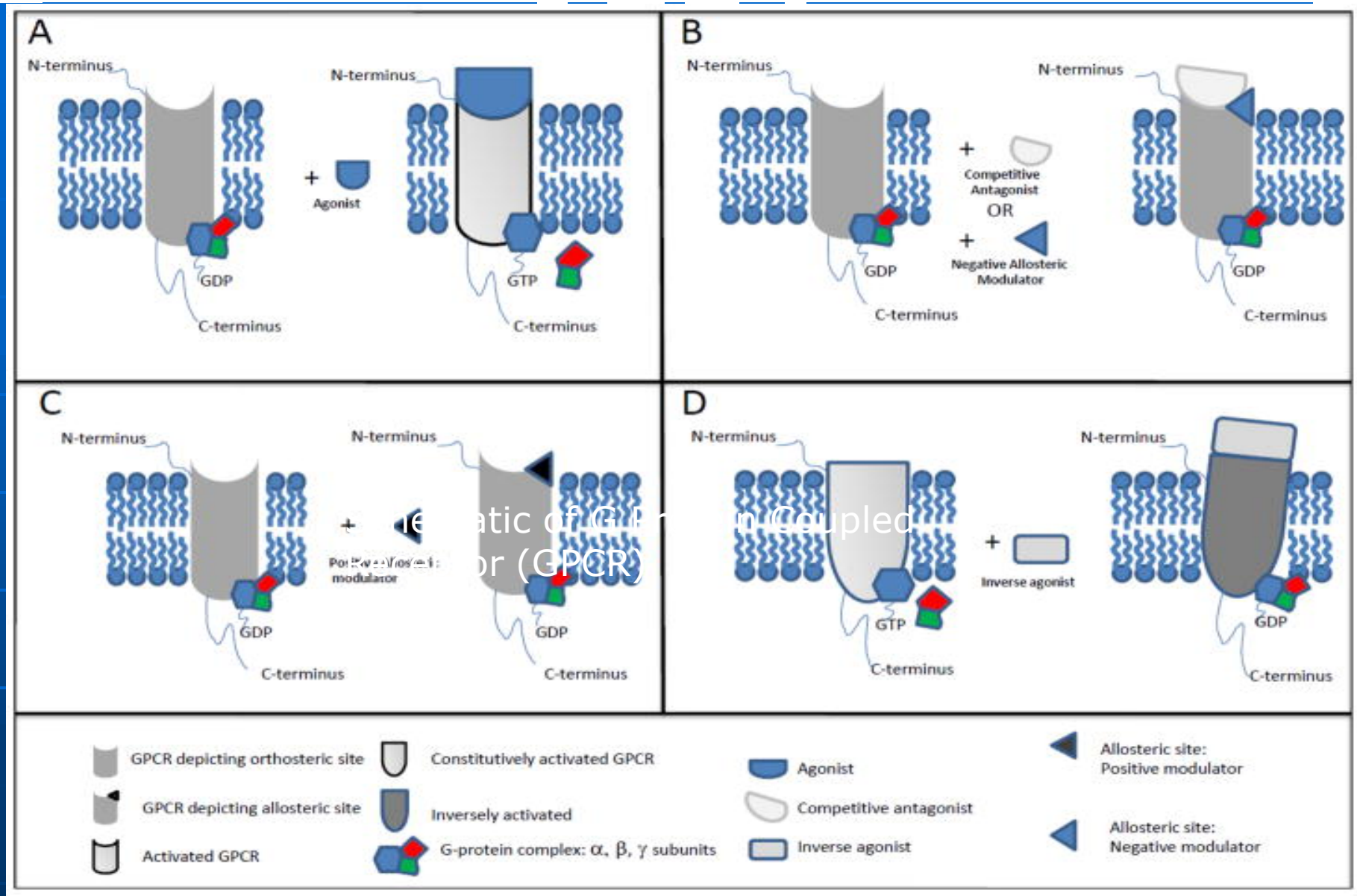
Abstract

The endocannabinoid system (ECS) has been shown to be of great importance in the regulation of numerous physiological and pathological processes. To date, two Class A G-protein-coupled receptors (GPCRs) have been discovered and validated as the main therapeutic targets of this system: the cannabinoid receptor type 1 (CB_1), which is the most abundant neuromodulatory receptor in the brain, and the cannabinoid receptor type 2 (CB_2), predominantly found in the immune system among other organs and tissues. Endogenous cannabinoid receptor ligands (endocannabinoids) and the enzymes involved in their synthesis, cell uptake, and degradation have also been identified as part of the ECS. However, its complex pharmacology suggests that other GPCRs may also play physiologically relevant roles in this therapeutically promising system. In the last years, GPCRs such as GPR18 and GPR55 have emerged as possible missing members of the cannabinoid family. This categorization still stimulates strong debate due to the lack of pharmacological tools to validate it. Because of their close phylogenetic relationship, the Class A orphan GPCRs, GPR3, GPR6, and GPR12, have also been associated with the cannabinoids. Moreover, certain endo-, phyto-, and synthetic cannabinoid ligands have displayed activity at other well-established GPCRs, including the opioid, adenosine, serotonin, and dopamine receptor families. In addition, the cannabinoid receptors have also been shown to form dimers with other GPCRs triggering cross-talk signaling under specific conditions. In this mini review, we aim to provide insight into the non-CB_1, non-CB_2 cannabinoid-related GPCRs that have been reported thus far. We consider the physiological relevance of these molecular targets in modulating the ECS.



Biased agonist 1 or 2 binds to the 7-TM cannabinoid receptor

Cannabis Cannabinoid Res. 2017 Mar 1;2(1):48-60. doi: 10.1089/ can.2016.0037. eCollection 2017.
Cannabinoid CB1 and CB2 Receptor Signaling and Bias. *Ibsen MS[1], Connor M[2], Glass M.*



Schematic of G Protein Coupled Receptor

Prog Neuropsychopharmacol Biol Psychiatry. 2012 Jul 2;38(1):4-15.
Cannabinoid receptors: nomenclature and pharmacological principles.
Console-Bram L, Marcu J, Abood ME.

Adv Pharmacol. 2017;80:207-221. doi: 10.1016/bs.apha.2017.03.005.

Functional Selectivity at Cannabinoid Receptors.

Priestley R, Glass M, Kendall D.

Abstract

It is now clear that, in contrast to traditional descriptions of G protein-coupled receptor signaling, agonists can activate or inhibit characteristic patterns of downstream effector pathways depending on their structures and the conformational changes induced in the receptor. This is referred to as functional selectivity (also known as agonist-directed trafficking, ligand-induced differential signaling, or biased agonism). It is important because even small structural differences can result in significant variations in overall agonist effects (wanted and unwanted) depending on which postreceptor signaling systems are engaged by each agonist/receptor pairing. In addition to the canonical signaling pathways mediated by $G_{i/o}$ proteins, CB_1 and CB_2 receptor agonists can have effects via differential activation not only of $G_i$subtypes but also of G_s and $G_{q/11}$ proteins. For example, the classical cannabinoid HU-210 produces maximal activation of both G_i and G_o proteins, while the endocannabinoid anandamide and aminoalkylindole WIN 55,212 both produce maximal activation of G_i, but submaximal activation of G_o. Cannabinoid agonists can also signal differentially via β-arrestins coupled to mitogen-activated protein kinases, subsequently promoting varying degrees of receptor internalization and agonist desensitization. A recent extensive characterization of the molecular pharmacology of CB_2agonists (Soethoudt et al., 2017) identified marked differences (bias) in the ability of certain agonists to activate distinct signaling pathways (cAMP accumulation, ERK phosphorylation, GIRK activation, GTPγS binding, and β-arrestin recruitment) and to cause off-target effects, exemplifying the need to evaluate functional selectivity in agonist drug development.

Adv Pharmacol. 2017;80:169-206. doi: 10.1016/bs.apha.2017.03.007. Epub 2017 Jun 12.

CB1 and CB2 Receptor Pharmacology.

Howlett AC, Abood ME.

Abstract

The CB_1 and CB_2 cannabinoid receptors (CB_1R, CB_2R) are members of the G protein-coupled receptor (GPCR) family that were identified over 20 years ago. CB_1Rs and CB_2Rs mediate the effects of Δ^9-tetrahydrocannabinol (Δ^9-THC), the principal psychoactive constituent of marijuana, and subsequently identified endogenous cannabinoids (endocannabinoids) anandamide and 2-arachidonoyl glycerol. CB_1Rs and CB_2Rs have both similarities and differences in their pharmacology. Both receptors recognize multiple classes of agonist and antagonist compounds and produce an array of distinct downstream effects. Natural polymorphisms and alternative splice variants may also contribute to their pharmacological diversity. As our knowledge of the distinct differences grows, we may be able to target select receptorconformations and their corresponding pharmacological responses. This chapter will discuss their pharmacological characterization, distribution, phylogeny, and signaling pathways. In addition, the effects of extended agonist exposure and how that affects signaling and expression patterns of the receptors are considered.

Prog Neuropsychopharmacol Biol Psychiatry. 2012 Jul 2;38(1):4-15. doi: 10.1016/j.pnpbp.2012.02.009.

Cannabinoid receptors: nomenclature and pharmacological principles.

Console-Bram L[1], *Marcu J*, *Abood ME*.

Abstract

The CB1 and CB2 cannabinoid receptors are members of the G protein-coupled receptor (GPCR) family that are pharmacologically well defined. However, the discovery of additional sites of action for endocannabinoids as well as synthetic cannabinoid compounds suggests the existence of additional cannabinoid receptors. Here we review this evidence, as well as the current nomenclature for classifying a target as a cannabinoid receptor. Basic pharmacological definitions, principles and experimental conditions are discussed in order to place in context the mechanisms underlying cannabinoid receptor activation. Constitutive (agonist-independent) activity is observed with the overexpression of many GPCRs, including cannabinoid receptors. Allosteric modulators can alter the pharmacological responses of cannabinoid receptors. The complex molecular architecture of each of the cannabinoid receptors allows for a single receptor to recognize multiple classes of compounds and produce an array of distinct downstream effects. Natural polymorphisms and alternative splice variants may also contribute to their pharmacological diversity. As our knowledge of the distinct differences grows, we may be able to target select receptor conformations and their corresponding pharmacological responses. Importantly, the basic biology of the endocannabinoid system will continue to be revealed by ongoing investigations.