

Is CB₂R a hidden treasure trove for treating inflammatory diseases?

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Expert scientists working on endocannabinoid system (ECS) trials explain how CB₂R can be used to treat inflammatory diseases

Receptors are important protein structures that allow cells to interact with their environment or control activities within a cell. The largest group of receptors are G-protein-coupled receptors (GPCRs) and encompasses eight hundred members encoded by approximately 3% of the human genome. GPCRs play an important role in multiple physio-pathological conditions throughout the body, including treating inflammatory diseases [1].

Type-2 cannabinoid receptor – A key element of the endocannabinoid system

Type-2 cannabinoid receptor (CB₂R) [2] is a highly important GPCR and represents a promising target for developing novel therapeutics to treat a plethora of diseases linked to its deregulation. CB₂R and the closely related type-1 cannabinoid receptor (CB₁R) [3] are essential elements of the endocannabinoid system (ECS). The ECS plays a key role for human health and disease state and consists of: i) endocannabinoids (eCBs), a class of endogenous CB_{1/2}R ligands, whose main representative members are N-arachidonylethanolamine (anandamide) and 2-arachidonylglycerol (2-AG); ii) receptor targets other than CB₁R and CB₂R that can be bound and activated by eCBs, along with their interacting proteins; and iii) metabolic enzymes and transporters involved in the control of eCB lifespan, and hence biological activity [4].

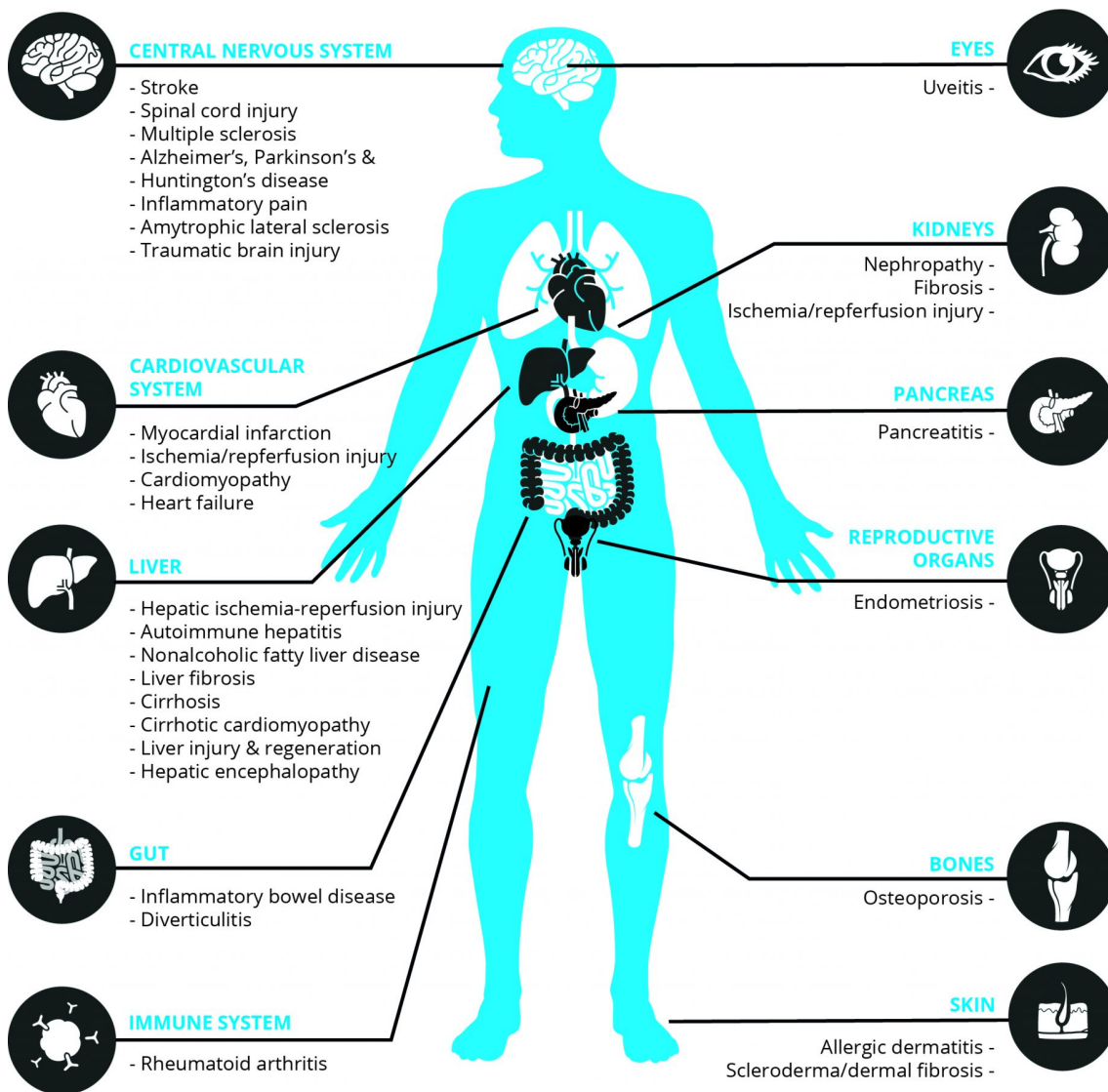


Figure 1: Representative beneficial effects of CB₂R activation for inflammatory/tissue protective pathologies

Where is CB₂R located?

While CB₁R is mainly found in the central nervous system (CNS), CB₂ receptors are primarily expressed in all tissues and circulating cells of the immune system. Furthermore, moderate to low CB₂R expression has been reported in other peripheral districts (e.g. hepatic myofibroblasts, cardiomyocytes, endothelial smooth muscle cells) [5] and in the CNS (e.g. microglial cells and retinal cells) [6]. The degree of CB₂R expression and activity depends on the type and activation of cells, as well as on the stimulus. Under various pathological conditions/disease states CB₂R expression can be markedly unregulated in affected tissues/cells [7]. This is often accompanied by elevated eCB levels as a part of the inflammatory response/tissue injury [7].

How can CB₂R activation treat inflammatory diseases? Increased local eCB levels and CB₂R expression upon inflammation/tissue injury trigger fast signaling responses in immune and other cells leading mostly to a sequence of activities of a protective nature. Furthermore, eCBs and/or synthetic CB₂R activators have been reported to attenuate inflammation and associated tissue injury in a huge number of pathological conditions/

diseases, ranging from cardiovascular, gastrointestinal, liver, kidney, lung, neurodegenerative/neuroinflammatory, skin pathologies, rheumatoid arthritis, endometriosis, to eye diseases [7,8] (Figure 1).

Ligands targeting CB₂R

Due to its enormous therapeutic potential many academic and industry institutions came up with novel ligands targeting CB₂R. First publications and patents appeared in 1991 [9] and 1996 [10], respectively. Since then, more than 750 CB₂R patent applications have been filed, the majority of them describing activators of the receptor. CB₂R molecules can be subdivided into eCBs, plant-derived cannabinoids (phytocannabinoids), cannabinoid-like and synthetic CB₂R ligands. In recent years research efforts concentrated on generating small molecules that are either highly selective against CB₁R or possess limited blood–brain barrier (BBB) permeability, to avoid the psychotropic effects resulting from CB₁R activation in the brain [11], such as for the dual CB₁R/CB₂R agonist Δ^9 -tetrahydro-cannabinol (Δ^9 -THC), the active ingredient of *Cannabis sativa* [12].

CB₂R ligands in clinical trials

Overall more than 20 activators of CB₂R have been or are currently being studied in humans [13]. They cover a broad range of indications encompassing neurological and fibrotic diseases, pain, osteoarthritis and cancer. Three phytocannabinoid-derived dual CB₁R/CB₂R agonists have been launched. Currently, more than 7 CB₂R ligands are under active clinical development. In contrast to first clinically evaluated CB₂R agonists, which often were also activating CB₁R and were designed for pain indications, recent focus shifted toward peripheral indications with an inflammatory and/or fibrotic background.

Future perspectives on the understanding of CB₂R Significant progress in understanding CB₂R expression, mechanism of action and translatability of results toward the human situation has been made in the past years. Furthermore, a multitude of high quality ligands targeting CB₂R have been generated. Applying this knowledge in the right context and condition for attenuating diseases with an inflammatory/tissue injury background holds great promise to guide us to unlock the receptor's full therapeutic potential, ultimately leading to patient benefit.

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