THE THERAPEUTIC USE OF CANNABIS

CBD-CANNABIDIOL

AN ENTOURAGE MOLECULE

Cannabidiol can be defined as a multitarget biocompound that leaves no stone unturned, acting as a physiological modulator through a wide range of possible mechanisms that can broken down to the following :

-Receptor binding

-Signaling events

-Intracellular calcium levels

-Gene expression and transcription

- Production of reactive oxygen intermediates

-Other

Receptor binding

The receptor binding is involved in controlling inflammation. Briefly, it can be summarized as follows:

CB1: Antagonist at nano molar concentrations in the presence of THC. Negative allosteric modulator. Actions responsible for the safety profile through controlling the collateral effects of THC

CB2: Inverse agonist. Anti-inflammatory

TPRV-1: Agonist capsaicin like action. Anti- inflammatory

GPR55: Selective antagonist. Anti-inflammatory

A2A: Enhance Adenosine signaling and inhibits uptake. Anti-inflammatory

5-HT1A: Agonist. CBDA even more effective. Anxiety, depression, pain, nausea.

5-HT1A-CB2 dimers: Agonist. Neuroprotection

5-TH2A: Antagonist. Control of psychedelic experience: Headaches, mood disorders, hallucinations

5-HT2A-CB1 dimers: Antagonist. Opposes psychedelic experience

5-HT3A: Negative allosteric modulator. Chemotherapy induced nausea and vomiting

PPAR gamma: Upregulation. Neurogenesis, control of autoimmune inflammation. Neuroprotection in ischemic stroke. Anti cancer effects.

Signaling events

Eicosanoids: Arachidonic acid AA: CBD produces a stimulation of AA release, 1.5 times more potent than THC. Elevation of pro resolving substances like lipoxin A4 and 15d-PGJ2 may explain the anti inflammatory actions.

Cyclooxygenase and products: CBD stimulates COX-2 twice as potently as THC, and has very little effect on COX-1. COX-2 may mediate the synthesis of lipoxin A4 and 15d-PFJ2. CBD has been seen to reduce in a dose dependent manner inflammatory markers like PGE2, COX activity, nitric oxide, lipid peroxide, over activity of glutathione-related enzymes, but not of the common indicators factor-kappa beta and tumor necrosis factor alpha, suggesting that CBD may act by a novel mechanism.

Lipid storage diseases: CBD hydrolytic actions on lipid storage diseases have shown a reduced content of lecithin and sphingomyelin, suggesting a selective action on disease cells.

Cytokines: CBD has been proved to reduce the production and release of pro inflammatory cytokines, such as IL-1beta, IL-6, Interferon-beta; it also reduced the activity of the NF-kappa beta pathway and upregulated

the STAT3 transcription factor. However, different effects on TNF-alpha synthesis, either inhibitory or stimulatory, suggest biphasic responses. CBD may mediate the reduced levels of markers in animal models of Alzheimer´s disease neuroinflammation; and there is compelling evidence for its use both in terms of efficacy and safety in acute ocular inflammation, where retinal microglial activation or macrophage infiltration was prevented at 5mg/kg. Cisplatin-induced inflammation and tissue injury in the kidney as well as several markers of nephrotoxicity were also reduced after treatment with CBD at 10mg/kg.

Intracellular calcium levels*:*

CBD evokes, in a concentration dependent manner a persistent rise of intracellular calcium, and the initiation of the arachidonic acid cascade is strongly dependent on it. This rise in intracellular calcium levels was higher with CBD compared to other phytocannabinoids.

Gene expression and transcription

CBD affects the expression of many more genes than those affected by THC, and it induces a robust response related to oxidative stress and GSH deprivation through

transcription factors. The up and down regulations of different gene expression correlate with the CBD anti-inflammatory actions.

CBD can effectively inhibit beta-amyloid evoked neuro inflammatory reactions and may be effective in the treatment of Alzheimer´s disease through a dose dependent inhibition of glial fibrillary acidic protein mRNA and protein expression as seen in an animal model injected with beta-amyloid.

The reactive gliosis, an important feature of many autoimmune inflammatory diseases is inhibited by CBD through the PPAR-gamma receptor with a reduction in the beta-amyloid induced neuroinflammation and promotion of hippocampal neurogenesis.

Production of reactive oxygen intermediates

Variable effects typical of biphasic responses can be observed, from inhibition to stimulation in the levels of these mediators of inflammation. It is tempting to speculate that CBD may act directly at the level of the mitochondrion or nucleus to oppose oxidative/nitrosative stress. Most probably, CBD therapeutic actions are a result of the fact that inflammation and oxidative stress are intimately involved in many diseases

Other

CBD acts as an inhibitor of fatty acid amide hydrolase (FAAH), the major enzyme for endocannabinoid breakdown. Because FAAH activity correlates with gastrointestinal mobility, CBD may have utility in treating intestinal hypermotility associated with certain inflammatory diseases of the bowel.

At low-micromolar concentrations, CBD was found to inhibit indoleamine-2,3-dioxygenase activity, thereby suppressing tryptophan degradation. Based on this finding, CBD might be useful therapeutically to counter the increased risk of depression in diseases associated with immune activation and inflammation, which often lead to decreased tryptophan, the precursor of serotonin

We should try to remember that we as living organisms have the most sophisticated physiologic system among the species. And as such it is not a fixed and stationary system; it must be regulated and maintained within narrow limits in order for survival to happen. So it is a dynamic machine that reacts to the inner and outer ambient through the production of messenger molecules and receptors on demand.

Basically, this system can be on or off, meaning active or resting, just like day and night, with an excitatory and an

inhibitory neuronal circuit both with a different neurotransmitter, mainly, glutamate and GABA. The endocannabinoid receptors function also in a bidirectional manner, causing both neuronal excitation and inhibition by acting on one circuit or the other. And the cananbinoids show biphasic properties too, where low and high doses result in opposite effects.

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