The PPAR-gamma receptor is involved

How Does CBD Regulate Gene Expression?

By Adrian Devitt-Lee and Martin A Lee

There is growing interest among medical scientists in the gene-regulating properties of cannabidiol (CBD), the non-psychoactive plant cannabinoid. Researchers at the California Pacific Medical Center have shown that CBD reduces brain cancer and breast cancer cell proliferation and metastasis by inhibiting the expression of the ID-1 gene. ID-1 expression is implicated in several kinds of aggressive cancer.

In 2012, Israeli scientists identified more than 1,200 genes affected by CBD. Some 680 “gene transcripts” were upregulated (“turned on”) by CBD and 524 were downregulated (“turned off”). The probe focused on CBD’s role in maintaining the right amount of zinc within cells (zinc homeostasis).

In the same study, THC was found to regulate 94 genes. The results show that CBD, but much less so THC, affects the expression of genes involved in zinc homeostasis and suggest that the regulation of zinc levels could have an important role throughout which CBD may exert its antioxidant and anti-inflammatory effects, the researchers concluded.

Mechanism of action

It is well accepted among cannabinoid scientists that CBD has little binding affinity for either the CB1 or CB2 receptor, both of which are activated by THC. Instead, cannabinoid works its magic primarily through receptor-independent actions and by binding with various non-cannabinoid receptors.

Recent studies indicate that CBD influences the expression of some genes by directly activating PPAR-gamma, a non-cannabinoid receptor situated on the cell’s nucleus. (The scientists pronounce it “pea-par.”) CBD’s ability to activate PPAR-gamma has promising therapeutic implications, particularly with respect to cancer and metabolic disorders.

When activated, PPARs bind to certain segments of DNA to promote or prevent transcription of specific genes. What are PPARs?

Peroxisome proliferator-activated receptors (PPARs) are a group of three proteins inside cells—PPAR-alpha, PPAR-gamma, and PPAR-delta (the latter is not yet well-characterized). PPARs are triggered by hormones, endogenous fatty acids, and various nutritional compounds. When activated, PPARs bind to certain segments of DNA to promote or prevent transcription of specific genes. Most genes regulated by PPARs are involved in energy homeostasis, lipid uptake and metabolism, insulin sensitivity, and other metabolic functions.

Big Pharma recognizes the importance of these nuclear receptors. Two classes of pharmaceutical PPAR activators—fibrates and thiazolidinediones—have been approved by the U.S. Food and Drug Administration.

PPAR agonists

Several studies have documented CBD’s role as a PPAR-gamma agonist (activator). Cannabinol also promotes PPAR-alpha activity by inhibiting fatty acid amide hydrolase (FAAH). FAAH is a metabolic enzyme that breaks down several endogenous fatty acid compounds known as endocannabinoids. This important family of endogenous fatty acid molecules includes anandamide, the endocannabinoid that binds directly to the CB1 receptor (which is concentrated in the mammalian brain and central nervous system).

Two other N-acylethanolamides—N-palmitylthanolamine (PEA) and N-oleoylethanolamide (OEA)—bind directly to PPAR-alpha. By upregulating the FAAH enzyme and thereby increasing FAAH and PEA levels, cannabinoids indirectly activates PPAR-alpha. Higher levels of PEA and OEA result in enhanced PPAR-alpha transmission. Deficient PPAR-alpha signaling has been linked to schizophrenia, Alzheimer’s disease, and cancer.

Omega-3s and CBD

Nutritional factors also influence PPAR signaling. The omega-3 fatty acid derivatives docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) directly activate PPAR-gamma. DHA and EPA can be created in the body from the fish oil constituents docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).

At the 2013 International Cannabinoid Research Society conference in Vancouver, Jocelin Meierink from Wageningen University & Research reported that DHEA acts as an inhibitor of the COX-2 enzyme. So does CBD; this is one of the major reasons why cannabinoid has potential anti-inflammatory properties. COX-2 is an enzyme that creates prostaglandins, a class of inflammatory compounds. Aspirin and all the other non-steroidal anti-inflammatory drugs are COX inhibitors.

Regulating angiogenesis

According to a 2008 report by Italian scientists at the University of Rome, both PPAR-alpha and PPAR-gamma regulate angiogenesis, which entails the creation of new blood vessels, particularly capillaries. In cancerous tumors, dysregulated angiogenesis leads to new blood vessels, which provide tumors with nutrients, helping them to grow and metastasize. By directly activating PPAR-gamma and indirectly promoting PPAR-alpha activity, CBD may inhibit tumor angiogenesis.

Three major complications associated with Diabetes Mellitus—retinopathy, neuropathy, and nephropathy—are all worsened by aberrant angiogenesis. Among medical scientists there is great interest in using PPAR agonists to prevent many diabetic complications.

Clinical applications

Obesity and metabolic syndrome, cancer, Alzheimer’s disease, schizophrenia, and diabetes are all worsened by aberrant angiogenesis. Among medical scientists there is great interest in using PPAR agonists to prevent many diabetic complications.

PPAR activation is a promising approach to treating type II diabetes and obesity, cancer, Alzheimer’s disease and schizophrenia.

Sources:


