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THE MAIN ROLE OF DELTA-9-TETRAHYDROCANNABINOL (THC) TO DOWNREGULATE AN EXPRESSION OF CANNABINOID 1 (CB1) RECEPTOR IN CANNABIS WITHDRAWAL SYNDROME

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ABSTRACT

Introduction – Cannabinoids from Cannabis sativa have derived compounds that are the best characterized like delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) as the main psychogenic compounds from Cannabis sativa. In addition, THC is an important agonist for the CB1 receptors and has a responsibility to develop cannabis withdrawal. This paper aims to reveal the role of delta-9-tetrahydrocannabinol (THC) to downregulate an expression of cannabinoid 1 (CB1) receptor and their correlation to developing cannabis withdrawal syndrome.
Methods – A literature review evaluating the role of delta-9-tetrahydrocannabinol (THC) to downregulate the expression of CB1 receptors. The article search strategy is using a *consort statement* with the main keyword **"**Cannabinoid 1 (CB) Receptor", "cannabis withdrawal syndrome (CWS)", "Delta-9-tetrahydrocannabinol (THC)" to get structured and specific results. Data extracted from Science Direct, Springer Link, PubMed, Google Scholar databases and the only papers published from 2010-2021 that are included.
Results – The author reviewed 21 articles that met inclusion criteria based on the consort statement. The psychoactive effect of cannabis results from the binding of delta-9-tetrahydrocannabinol (THC) to the CB1 receptor.
Discuss – Based on some experiments, intensive exposure to THC can decrease the density of CB1 receptors in the tissue by downregulating their expression. A low density of CB1 receptor will suppress the mesolimbic dopamine function that has a main role in the development of cannabis withdrawal.
Conclusion – Intensive exposure to delta-9-tetrahydrocannabinol (THC) as a psychogenic substance of cannabis able to downregulate the expression of the cannabinoid 1 (CB1) receptor. The decrease of CB1 receptor density in the brain is a consequence of the downregulation of CB1 receptor expression. Based on some experiments reveal that decreasing CB1 receptor density will affect to decrease of mesolimbic dopamine function which has a main role in the development of cannabis withdrawal.

Keywords: Cannabinoid 1 (CB) Receptor, cannabis withdrawal syndrome (CWS), Delta-9-tetrahydrocannabinol (THC).

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INTRODUCTION

The criteria for cannabis withdrawal syndrome include both cannabis-related illnesses and cannabis dependence (CWS). Cannabis is a chemical or psychoactive substance that is commonly consumed for recreational purposes worldwide.[1] In Indonesia, based on data from the ministry of health reveal that cannabis use increased year by year from 341 kg in 2012 to 443 kg in 2016.[2] In 2014, Indonesia's National Narcotics Board or BNN reported that there were approximately two million people who used cannabis in Indonesia and making cannabis the most used illicit drug in the country, followed by amphetamine and ecstasy.[3] A cannabis withdrawal syndrome (CWS) is a clinical manifestation of marijuana dependence that occurs when marijuana consumption is abruptly discontinued.[1] Restlessness, cannabis craving, irritability, nervousness/anxiety, insomnia, grumpy, more aggressive, depressed mood, strange/wild dream, decreased appetite, sweating, nausea, stomach ache, headaches, and tremor are all symptoms of CWS, according to the Diagnostic and Statistical Manual of Mental Disorders - fifth edition (DSM-V).[4]
Has been for a long time that *Cannabis sativa* L. is usually used as a medical substance for a pain killer, and usually used for

recreational aim. Cannabis produces over a hundred well-characterized components known as cannabinoids, which are extracted from a cannabis secondary metabolic diterpene molecule.[5] Cannabinoids have derived compounds that are the best characterized like delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), canabigerol (CBG), tetrahydrocannabivarin (THCV), canabichromene (CBC), and canabinol (CBN).[6] The most abundant substance in cannabis, delta-9-tetrahydrocannabinol, is responsible for its psychoactive effects. The psychoactive effects are mediated by the activation of cannabinoid 1 (CB1) and cannabinoid 2 (CB2) receptors.[5] These receptors are G-protein-coupled receptors (GPCR), which are widely expressed in various mammalian cells.[7] Binding between THC and these receptors will activate the cascade by binding the Guanosine Triphosphate to a G protein. Activation of G protein will induce activation of the endocannabinoid system (ECS) and biosynthesis of N-acyl phosphatidylethanolamine-specific phospholipase D and diacylglycerol lipase alpha (DLG-alpha). CB1 receptors are primarily found in the brain and medulla spinalis and are responsible for mediating the central effect of THC and cannabinoids.[8] The endocanabinoid system (ECS) is involved in numerous cellular pathways and is a potential therapeutic target for neuropsychiatric and neurodegenerative disease. Several studies have revealed that THC is the primary ligand for the CB1 receptor; thus, in this paper, we will discuss the relationship between delta-9-tetrahydrocannabinol (THC) exposure and the downregulation of cannabinoid 1 (CB1) receptor expression in mammalian cells.

METHOD

A scientific approach that used in this article is literature review. A literature review is written based on journal resources from search engine such as Science Direct, Springer Link, PubMed, and Google Scholar. The data extracted only from papers published from 2010-2021 that are included.

The article search strategy is using the main keyword such as **"**Cannabinoid 1 (CB) Receptor", "cannabis withdrawal syndrome (CWS)", "Delta-9-tetrahydrocannabinol (THC)" in order to get structured and specific results. This article only uses the journals that fulfill the inclusion criteria such as **1)** journal publication between 2010 – 2021 **2)** the journal's method include clinical trial, case report, and review article.

Based on the article searching, the author obtained 159 articles on identification process and then only 22 articles that met because the articles fulfill the inclusion criteria and consort statement criteria.

RESULT

Cannabis sativa Active Compounds

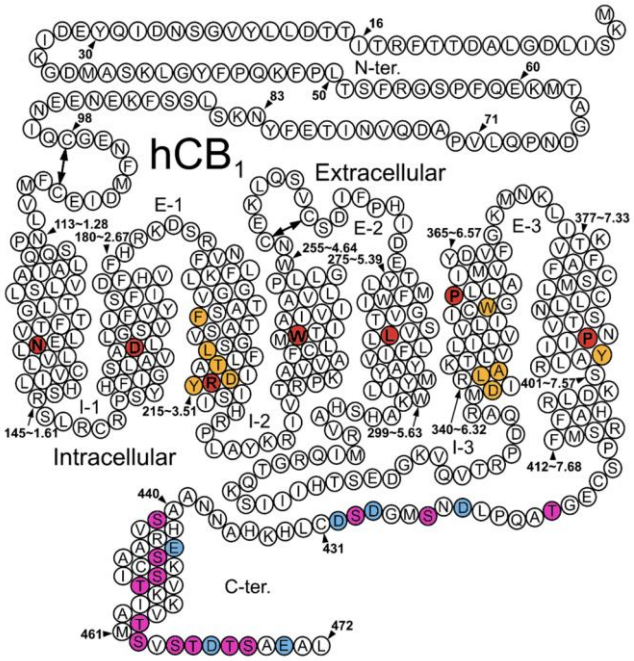
Cannabis sativa L., also known as cannabis, is an annual plant in the Cannabaceae family. This plant has been used as a ritual drug, intoxicant, and medicinal plant. In the twentieth century, structure analysis of *C. sativa* led to the discovery of an unusual class of terpenoid-phenolic compounds known as cannabinoids.[9] Cannabinoid derivatives include delta-9-tetrahydrocannabinol (THC), tetrahydrocannabivarin (THCV), cannabigerol (CBG), cannabinol (CBN), cannabichromene (CBC), and cannabidiol (CBD).[6] THC and cannabidiol (CBD) are both important psychoactive substances that are found in the highest concentrations in cannabis extract.[10] Cannabidiol does not produce the typical behavioral cannabimimetic effects and is not thought to be responsible for marijuana's psychotropic effect.[10] However, based on several clinical trials shown that cannabidiol (CBD) has an anti-inflammatory effect.[10] Delta-9-tetrahydrocannabinol (THC) itself is proven to be the main psychoactive substance.[9] THC is known to be an agonist of the canonical cannabinoid receptors, both CB1 and CB2.[9,10] Therefore, THC has a long story as a biological subject of thousands of experiments concerning therapeutic potential drugs, pharmacology, and toxicity.

Delta- 9-tetrahydrocannabinol (THC) Pharmacodynamic

Delta- 9-tetrahydrocannabinol (THC) therapeutic effects are mainly mediated by two cannabinoid receptors, the cannabinoid 1 receptor and the cannabinoid 2 receptor. Delta-9-tetrahydrocannabinol also connects to other receptors and important neurotransmitters in the cerebral, such as serotonin, glutamate, dopamine, acetylcholine, γ-aminobutyric (GABA), norepinephrine (NE), and peptide opioid.[11] This interaction causes delta-9-tetrahydrocannabinol (THC) to have a potential pharmacological effect as a multifunctional drug for the management of mood, behavior, anorexia, and pain in dementia patients.[11] The binding between delta-9-tetrahydrocannabinol (THC) to their receptor in the brain, especially cannabinoid 1 (CB1) receptors, will activate specific cascade pathways. Activation of the cascade pathway started with the activation of G protein that associated with CB1 receptors.[12] Eventually, activation of the cascade mediated by THC-CB1 receptor will activate some physiologic responses inside the cells.

Cannabinoid 1 (CB1) Receptor

Cannabinoid 1 receptor was first characterized and determined as the main receptor for delta-9-tetrahydrocannabinol from rat cerebral preparation in 1988.[13] Cannabinoid 1 protein receptors expressed from their gene are mostly found in the gray matter of the cerebellum, hypothalamus, hippocampus, ganglia basalis, and medulla spinalis.[11] The CB1 receptor is a transmembrane protein receptor associated with G-protein, with N-terminus of these protein in the extracellular and C-terminus in the intracellular of the cells (Picture 1).[13] When the cannabinoid 1 receptor is activated, it initiates a series of intracellular cascade signals via distinct cellular proteins such as GTP/GDP-protein and beta-arrestin.[13] Each of these signaling pathways influences different pharmacodynamics, which can be used to develop a new therapy for the treatment of a specific disease.



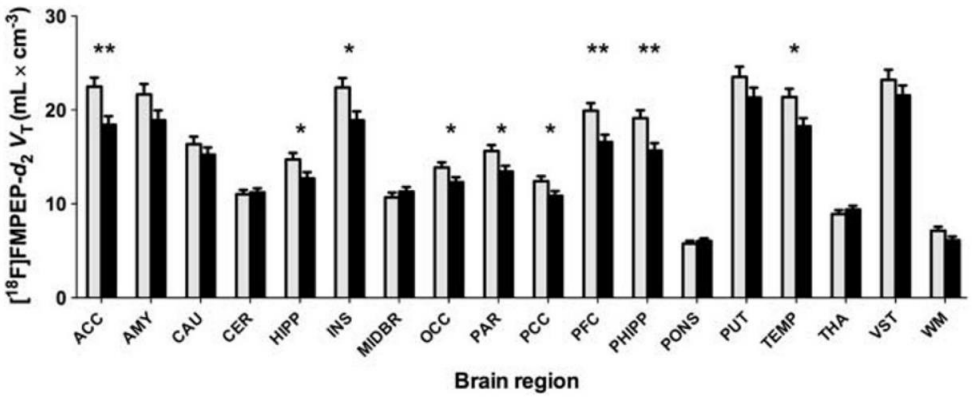
Picture 1. Cannabinoid 1 (CB1) receptor structure.[13]

Cannabinoid 1 receptor activation interferes with forskolin-stimulated adenylyl cyclase by coupling to the pertussis toxin (PTX)-sensitive G-protein and enhances kinase activity of extracellular signal-regulated kinase via GTP-protein dependent and beta-arrestin dependent pathways.[13] Rufaida's in-vitro study reveals the effect of G-protein-coupled receptor kinase (GRKs) and arrestin on CB1 receptor internalization, desensitization, and signalling. In contrast, in-vivo studies using beta-arrestin1 and beta-arrestin2 knockout experimental rats revealed that beta-arrestins regulate cannabinoid sensitivity and activity in an agonist-selective pathway.[13] These findings also show that repeated administration of delta-9-tetrahydrocannabinol to experimental rats decreased the expression of cannabinoid 1 receptor protein, which is associated with GRK4, GRK2, beta-arrestin 1, and beta-arrestin 2 in the CNS.[13]

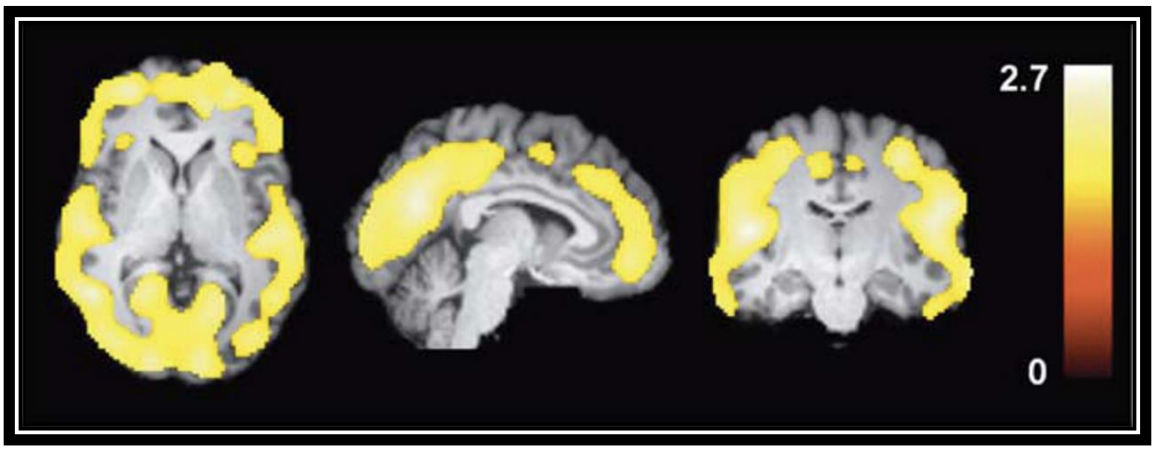
Cannabis Withdrawal Syndrome (CWS)

Based on animals studies reveal that cessation of cannabis has provided evidence of a withdrawal syndrome sign. The effect of cannabis or marijuana cessation on animals included anorexia, aggression, irritability, hyperactivity, and gross motor movement.[14] These withdrawal effects of an animal are almost the same in the human cannabis withdrawal syndrome (CWS). The animal model showed both dependence and tolerance following chronic administration of cannabinoids. Observation of experimental rat cerebral, downregulation of cannabinoid 1 (CB1) receptor signalling is associated with tolerance.[14]

In other human observation, abstinence of delta-9-tetrahydrocannabinol (THC) due to prominent behavior and affective changes. Based on Oleson et. al. studies reveal that the decreasing of mesolimbic dopamine function has a main role in development of cannabis withdrawal.[15] According to Hervonen's research, using 58 men as the subject and divided into two groups (a group is given a daily cannabis smoking intervention and the other is a control group) and evaluated with Positron Emission Tomography (PET) scan for 4 weeks demonstrated a reversible knockdown of cerebral cannabinoid 1 receptor in people who have been smoking marijuana for a long time (Picture 2 and Picture 3).[16]



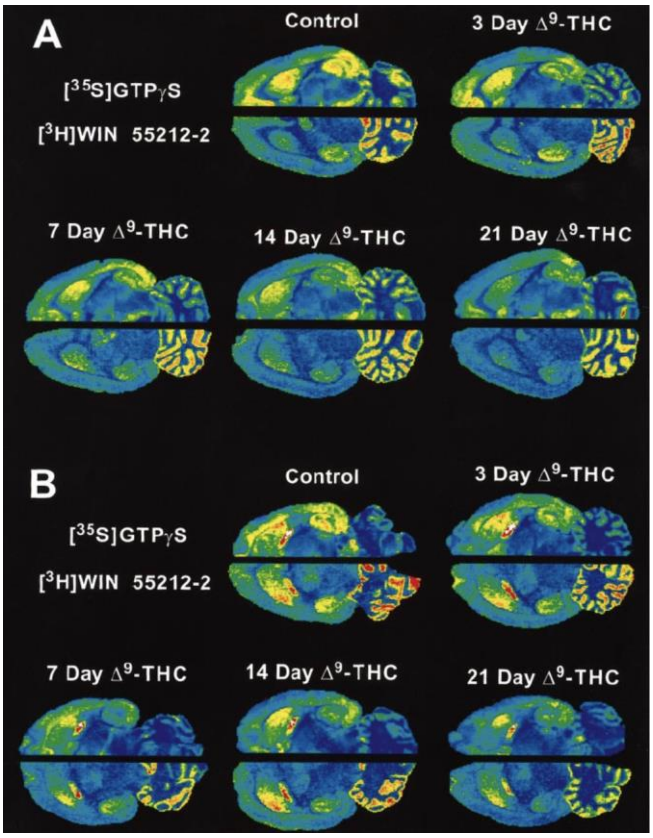
Picture 2. The difference of CB1 receptor distribution volume between control group (grey bar) and intervention group (black bar). Abbreviations: ACC, anterior cingulate cortex; AMY, amygdala; CAU, caudate nucleus; CER, cerebellum; HIPP, hippocampus; INS, insula; MIDBR, midbrain; OCC, occipital cortex; PAR, parietal cortex; PCC, posterior cingulate cortex; PFC, prefrontal cortex; PHIPP, Para hippocampal gyrus; PUT, putamen; TEMP, lateral temporal cortex; THA, thalamus; VST, ventral striatum; WM, white.[16]



Picture 3. Statistical analysis of parametric mapping (SPM) showed lower VT values in chronic daily smokers (n=30) when compared to subjects (n=28) at baseline as a single cluster that also included cortical regions. The colour bar represents the value in each voxel in the cluster that is significant.[16]

Eventually, after 4 weeks of cannabidiol or THC administration cessation, cannabinoid 1 receptors density was restored to the homeostatic levels.[16]

Another study conducted by Christopher S. Breivogel *et. al.* using Sprague-Dawley rat male which divided into two groups (intervention group is given with intraperitoneal diluted THC injection and control group was not given any intervention) for 30 days.[17] Assessment used Autoradiography of Cannabinoid-Stimulated [^{35}S] GTP-gamma-binding and Cannabinoid Receptor Binding as CB1 receptors marker in cerebri.[17] The result of the experiment shows in the picture 4 below.



Picture 4. Autoradiography of Cannabinoid-Stimulated [^{35}S] GTP-gamma-binding and Cannabinoid Receptor Binding imaging.[17]

Picture 4A shows a horizontal section at dorsal and the 4B shows a ventral section. The color fluorescence (the redder) indicates the amount of binding between the marker and the CB1 receptor is getting more intensive, and the darker blue indicates that there is no binding activity between the marker and the CB1 receptor. In other words, there are no CB1 receptors in this area.[17] The conclusion of this research is the more intensive and longer exposure of THC make a decreasing of CB1 receptor density in the cerebri.

DISCUSS

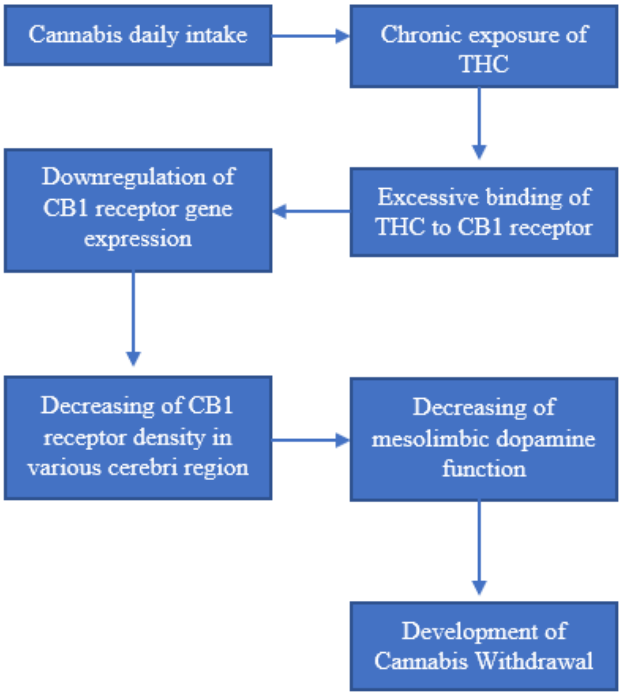
Cannabis sativa for a long time since the twentieth century has been used as an herbal plant for pain killers especially. Nowadays, some of people use cannabis as a recreational without medical reason, eventually they use cannabis without a control and get addiction to the cannabis. Cessation of cannabis usage will appear many symptoms called cannabis withdrawal syndrome. The primary psychoactive in cannabis is delta-9-tetrahydrocannabinol (THC). THC has the capability to attach to their receptor called cannabinoid (CB1) receptors. So, the level of the CB1 receptor could be a precious marker for response to delta-9-tetrahydrocannabinol (THC).[18] The human cannabinoid 1 receptor is a component of the endocannabinoid system, also known as the ECS. The CB 1 receptor is highly regulated in many physiological processes throughout the body, including the digestive tract, reproductive system, urinary tract, and central nervous system.[18]

The psychoactive effects of cannabis are caused by THC binding to the CB1 receptor. Delta-9-tetrahydrocannabinol, in particular, binds to receptors in the ventral tegmental area. Eventually, this interaction between THC and CB1 receptor which inhibits dopamine signaling.[17] Based on Oleson et. al. experiment conducted that development of cannabis withdrawal correlates with a role of decreasing or inhibiting dopamine signaling in the mesolimbic.[15] Based on experiment form Ketcherside et. al. reveal about animal studies examining the expression of CB1 receptor after long-term exposure with delta-9-tetrahydrocannabinol (THC). Their experiment showed a result that delta-9-tetrahydrocannabinol (THC) administration for 10 days in female rats will downregulate the CB1.[18] It impersonate chronically use in human. The cannabinoid 1 receptor was significantly suppressed primarily in the hippocampus, ventral midbrain, and prefrontal cortex.[19] This explanation shows the variable effect of delta-9-tetrahydrocannabinol (THC) throughout the CNS.

An experiment using radioligand to the subject who consumes daily cannabis demonstrated decreasing of radioligand bind to CB1 receptor across all brain regions. This result indicates that density of CB1 receptor lower compared with control.[18] Similarly, a study utilizing positron emission tomography (PET) scan revealed about cannabinoid 1 receptor density inside the brain of heavy marijuana smokers revealed an inverse relation between the density of CB1 receptors in the cerebral with the intensity of THC exposure, as well as the density of canabinoid 1 receptors returns to normal after THC exposure cessation.[20,21]

Even though cannabinoid 1 receptors are most abundant in the central nervous system, they are also found in peripheral tissues.[17] This fact showed that exposure of delta-9-tetrahydrocannabinol (THC) also affect the peripheral system that have CB1 receptors in their cell membrane. Because leucocytes have a cannabinoid 1 (CB1) receptor, exogenous cannabinoid-like delta-9-tetrahydrocannabinol (THC) could influence lymphocyte modifications by activating cannabinoid receptors.[18] Delta-9-tetrahydrocannabinol, in particular, has been proven to suppress pro-inflammatory cytokines in human lymphocytes.[18] It is correlated with an experiment result that chronic exposure to cannabinoid 1 agonists, including delta-9-tetrahydrocannabinol (THC), has been demonstrated to downregulate cannabinoid 1 receptors in peripheral cells such as white blood cells.[18]

An experiment performed by Nicolas J. Schlienz et al. reveals that regular cannabis use may be associated with cannabinoid 1 receptor suppression.[22] Reduction the amount of cannabinoid type 1 (CB1) receptor is associated to increased withdrawal symptoms during early cannabis cessation. In addition, the reduction of cannabinoid type 1 (CB1) receptors reverses with extended abstinence.[22] Decreasing the density of CB1 receptors also contribute to the cannabinoid tolerance, so the heavy daily user usually needs a higher dose of cannabis to obtain the recreational effect.[1] Eventually the correlation between downregulation of CB1 receptor to CWS developmental is explained in the picture 5 below.



Picture 5. The flowchart of Cannabis Withdrawal development.

CONCLUSION

In conclusion, an intensive exposure of delta-9-tetrahydrocannabinol (THC) as an important psychogenic substance of cannabis able to downregulate an expression of cannabinoid 1 (CB1) receptor. Decreasing of CB1 receptors density both in the brain and peripheral tissue are a consequence of downregulation of CB1 receptor expression. Based on some experiments reveal that decreasing CB1 receptor density will affect to decreasing of mesolimbic dopamine function that has a main role in development of cannabis withdrawal.

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