

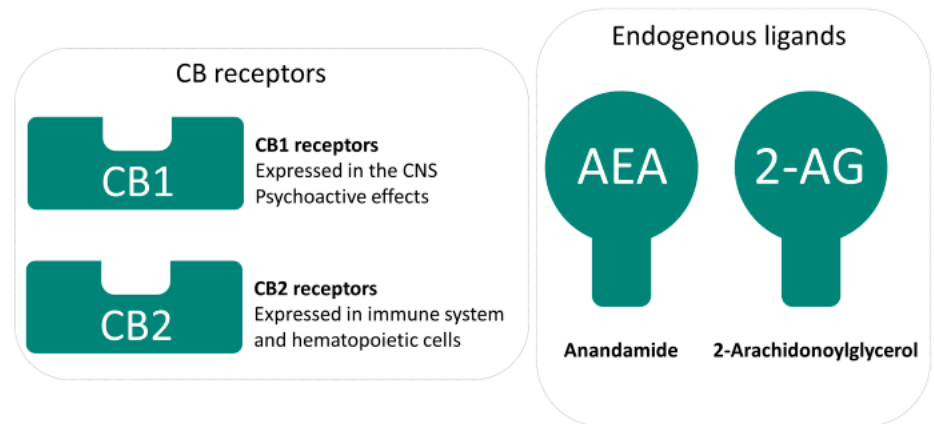
Cannabis and Health

Module 1

Lecture 4: Physiological Effects of Cannabinoids in the Body

Cannabinoid Receptors in the Periphery

- Two main receptors - CB1 and CB2
- **CB1** located primarily in the brain; also found in some peripheral organs and tissues
 - spleen
 - white blood cells
 - endocrine glands
 - reproductive system
 - gastrointestinal tract
 - urinary tract



Mackie, K. (2008, 05). Cannabinoid Receptors: Where They are and What They do. *Journal of Neuroendocrinology*, 20(S1), 10-14. doi:10.1111/j.1365-2825.2008.01671.x

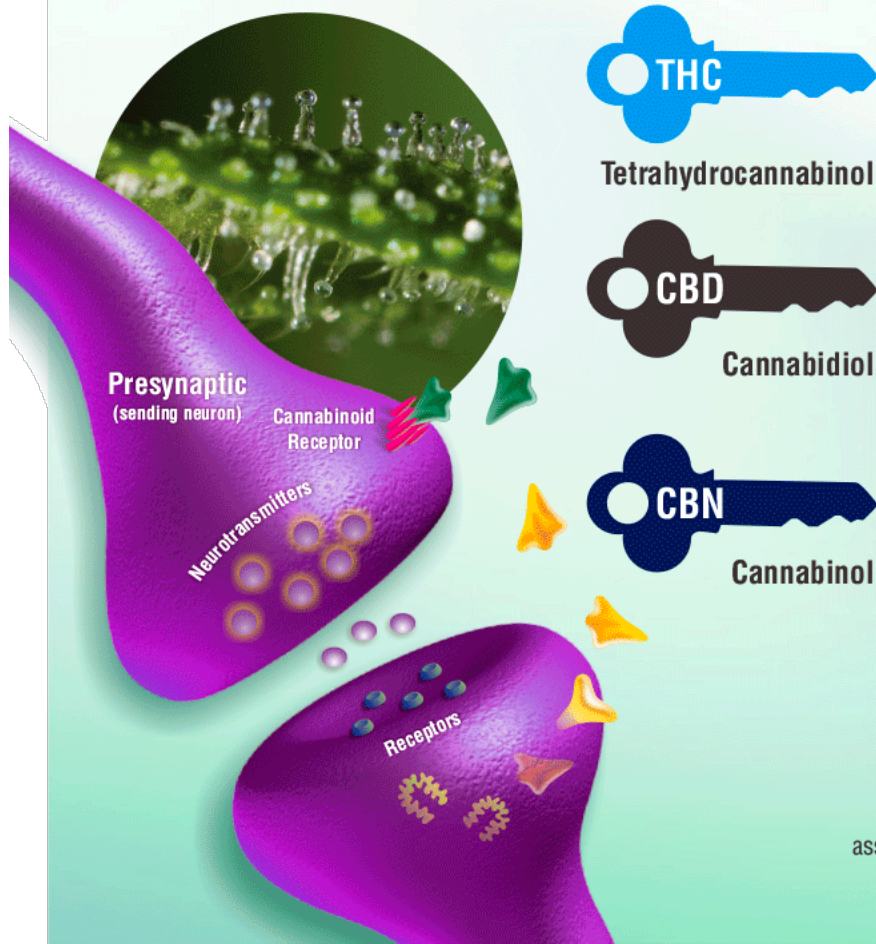
- CB2 receptors found on immune cells
 - B-cells, natural killer cells, monocytes
- CBD a non-competitive CB₁ and CB₂ receptor antagonist
- THC is a partial agonist of CB₁ and CB₂ ; higher affinity for CB₁

The Human Endocannabinoid System

CBD, CBN and THC fit like a lock and key into existing human receptors. These receptors are part of the endocannabinoid system which impact physiological processes affecting pain modulation, memory, and appetite plus anti-inflammatory effects and other immune system responses. The endocannabinoid system comprises two types of receptors, CB1 and CB2, which serve distinct functions in human health and well-being.

CB1 receptors are primarily found in the brain and central nervous system, and to a lesser extent in other tissues.

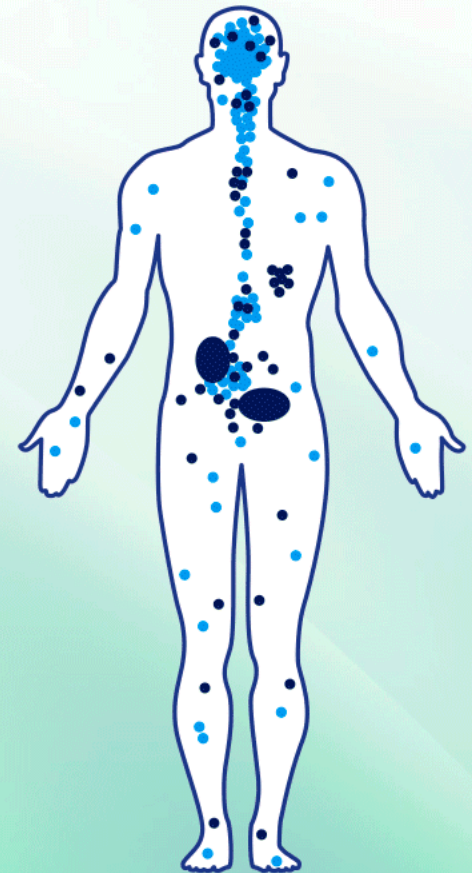
Receptors are found on cell surfaces



CBD does not directly “fit” CB1 or CB2 receptors but has powerful indirect effects still being studied.



CB2 receptors are mostly in the peripheral organs especially cells associated with the immune system.



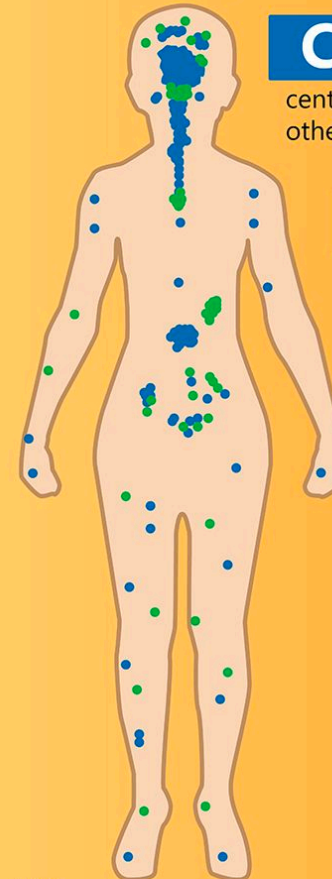
source: www.the-human-solution.org

Major Effects of Cannabis on Human Physiology

- Increased blood flow, increased heart rate
- Respiratory effects
- Stimulates appetite (THC)
 - “Munchies”
 - Therapeutic use
- Effects on the immune system
 - Inflammation
 - THC vs. CBD
- Effects on the digestive system
 - Intestinal permeability
 - Gut microbiome
 - Treating GI disorders
- Likely many other physiological effects

The Human Endocannabinoid System

The endocannabinoid system consists of two receptors, called CB1 and CB2. These receptors are found on cell surfaces and impact various biological processes.



CB1

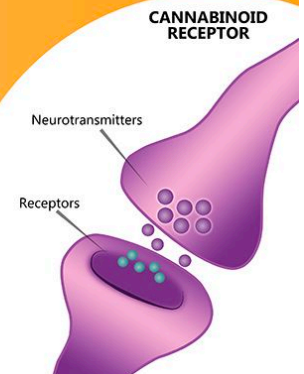
Located in the brain, central nervous system, and many other parts of the body.

CB2

Found throughout the body on cells associated with our immune system.

Cannabidiol (CBD)

CBD is one of the primary cannabinoids found in hemp. It interacts with **CB1** and **CB2** receptors for many effects still being studied.



Sources

<http://norml.org/library/item/introduction-to-the-endocannabinoid-system>
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2241751/>

These statements have not been evaluated by the FDA and are not intended to diagnose, treat or cure any disease.

Cannabinoids and the Digestive System

- Preclinical studies indicate that *endocannabinoids* are involved in many digestive functions:

- nausea and emesis
- food intake
- gastrointestinal motility
- hepatic fibrogenesis,
- intestinal inflammation
- intestinal permeability
- gut microbiome
- gut-brain signaling

Table 1. Randomized controlled trials evaluating the impact of marijuana on gastrointestinal function, symptoms, or disease

First author	Year	Function or disorder studied	Treatment	Subjects	Outcome
Foltin	1988	Appetite	Smoked marijuana (2.3% THC); placebo	6 Healthy adult males	40% Increase in daily caloric intake because of more frequent snacking with marijuana
Haney	2005	HIV	Smoked marijuana (1.8, 2.9, 3.9% THC); dronabinol; placebo	30 HIV+ patients	Comparable increases in caloric intake for marijuana and dronabinol over placebo
Strasser	2006	Cancer-related anorexia–cachexia	Oral cannabis extract (2.5 mg THC, 1 mg CBD); oral THC; placebo	164 Cancer patients	No difference in appetite or quality-of-life outcomes
Haney	2007	HIV	Smoked marijuana (2.0, 3.9% THC); dronabinol; placebo	10 HIV+ patients	Dose-dependent increase in caloric intake and body weight for marijuana and dronabinol over placebo
Naftali	2013	Crohn's disease	<i>Cannabis sativa</i> cigarette (23% THC, 0.5% CBD); placebo	21 Patients with moderately active Crohn's disease	Significant clinical response but no decrease in inflammatory markers with marijuana

Gerich et al., 2015

- What about cannabis?
 - Lack of clinical data
 - many myths from popular media

CBD and the Digestive System

- CBD reduces intestinal inflammation via neuroimmune effects
 - Study of humans with ulcerative colitis and mice with LPS-induced intestinal inflammation
- CBD may be promising treatment for inflammatory bowel disease
 - slow the course of disease
 - ameliorate symptoms
 - potentially increase efficacy of drugs available for gut disorders (UC or Crohn's disease)
- However, according to the National Academies Report:
 - Limited human research
 - Insufficient evidence to support or refute the conclusion that cannabis is an effective treatment for the symptoms of irritable bowel syndrome

References:

Esposito et al., 2012, Phytotherapy Research
de Filippis et al., 2011, PLoS ONE

Cannabis and the Immune System

From National Academies Cannabis and Health Report:

- Not much data on the effects of cannabis or cannabinoid-based therapeutics on the **human immune system**.
- Insufficient data to draw overarching conclusions concerning the effects of cannabis smoke or cannabinoids on immune competence.
- Limited evidence to suggest that regular exposure to cannabis smoke may have anti-inflammatory activity.
- Insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and adverse effects on immune status in individuals with HIV.

Cannabis and the Immune System

- Insights from preclinical research
- Immune cells express CB2 receptors and probably CB1 receptors
- Endocannabinoids proposed as native modulators of immune functions through cannabinoid receptors
- Exogenously introduced cannabinoids may disturb homoeostatic immune balance.
- Cannabinoids may affect immune responses and host resistance via perturbing balance of T helper (Th)1 pro-inflammatory versus Th2 anti-inflammatory cytokines

References:

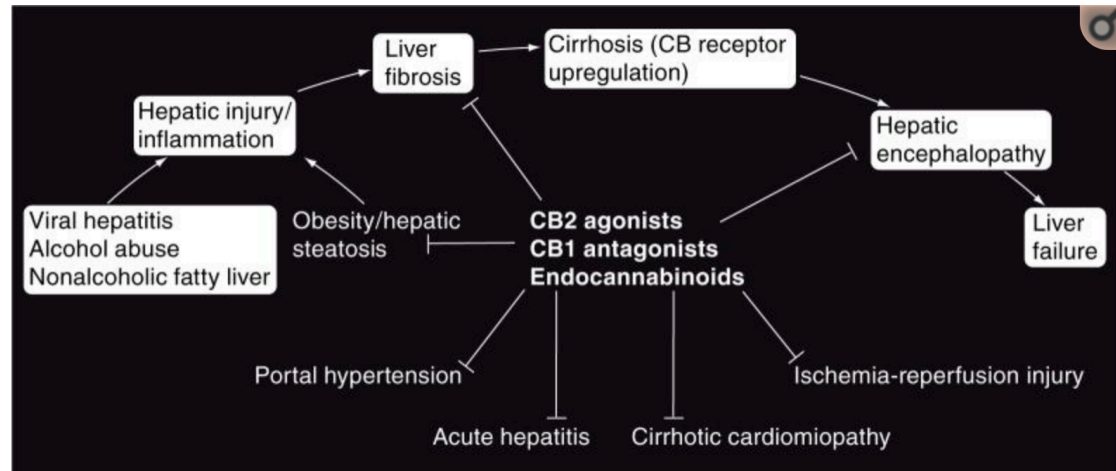
Klein et al., 2003, Journal of Leukocyte Biology

Cabral & Staab, 2005, Handbook of Experimental Pharmacology

Cannabis and the Immune System: Treatment Potential

Non-human evidence base for:

- Liver Injury
- Rheumatoid arthritis
- Colitis
- Multiple Sclerosis
- Cancers
- Other inflammatory disorders



Nagarkatti et al., 2009, *Future Med Chem*

Cannabis Effects on the Respiratory System

National Academies Cannabis and Health Report found:

- Substantial evidence of a statistical association between cannabis smoking and worse respiratory symptoms and more frequent episodes of chronic bronchitis
- Moderate evidence of a statistical association between cannabis smoking and improved airway dynamics with acute but not chronic use
- Moderate evidence of association between cessation of cannabis use and improved respiratory symptoms
- Limited evidence of an association between cannabis smoking and increased risk of COPD when controlling for tobacco use
- No or insufficient evidence of an association between cannabis smoking and hospital admissions for COPD or asthma development or exacerbation

Cannabis Effects on the Respiratory System

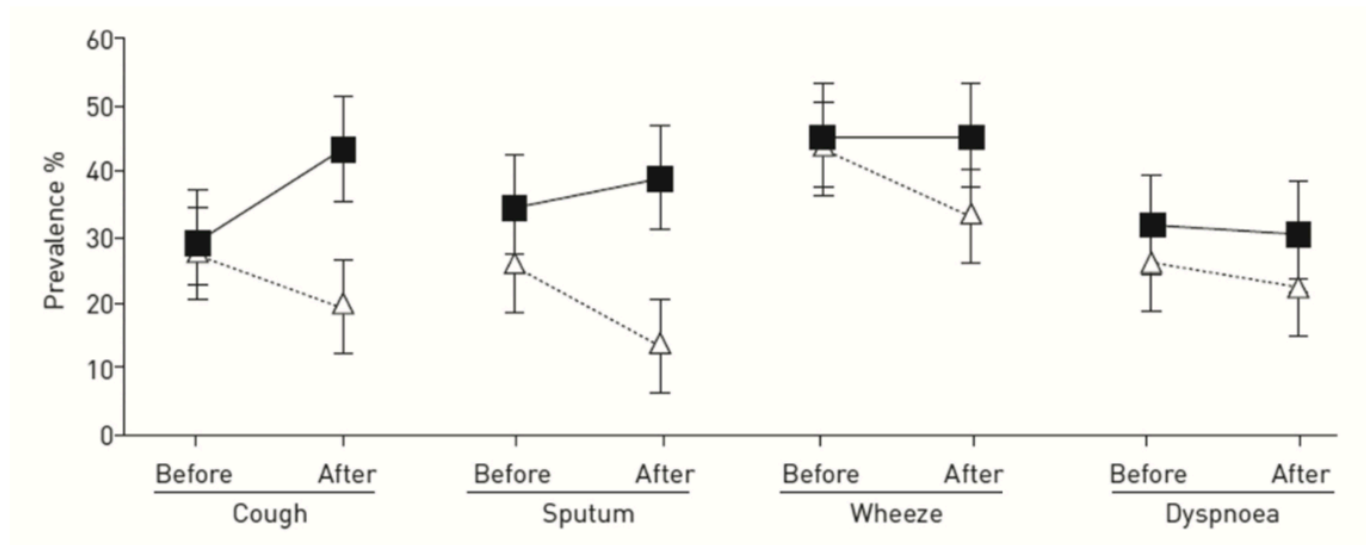


FIGURE 7-1 Prevalence of symptoms before and after quitting regular cannabis use (open triangles) and among those who used cannabis for two consecutive phases (solid squares). Vertical bars show 95% confidence level.

SOURCE: Hancox et al., 2015.

Cannabis and appetite

National Academies Cannabis and Health Report:

- Limited evidence that cannabis and oral cannabinoids are effective in increasing appetite and decreasing weight loss associated with HIV/AIDS
- Insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for cancer-associated anorexia-cachexia syndrome and anorexia nervosa
- Contrary to popular perception
 - Different cannabinoids may differentially impact appetite?

Cannabis and Appetite: Applications for Obesity

- Prevalence of obesity lower in cannabis users than nonusers
 - Results from representative national surveys
 - Also true of young adults
- Possible explanations
 - effects of other cannabinoids: TCHV, CBD (alone or in addition to THC)
 - reduced stress
 - mixed findings regarding the role of insulin resistance
 - positive effects of cannabis before exercise or on exercise recovery

References:

Le Strat & Le Foll, 2011, *Am Journal of Epidemiology*

Hayatbakhsh et al., 2010, *Am Journal of Drug and Alc Abuse*

Ngueta et al., 2015, *Obesity*

Cannabis and the Reproductive System

Adverse effects of cannabis use during pregnancy:

- High doses cause growth retardation and malformations in animals
- Epidemiological studies: scarce evidence for an increased risk of birth
- Effects in women who use cannabis during pregnancy
 - Possibly mild developmental abnormalities
 - Reduced birthweight is most consistent adverse effect observed
 - Mixed evidence on childhood IQ and behavior problems
 - Difficult to disentangle effects of other co-used substances

References:

Hall & Degenhardt, 2009, *The Lancet*

Important Remaining Questions

- Dose effects
- Effects of different strains, potencies, cannabinoid combinations
- Routes of administration
- Differences between synthetic and plant-derived cannabis
- Effects in combination with other substances (e.g., alcohol, opioids)
- Effects on special populations
- Treatment possibilities
 - obesity
 - immune disorders
 - digestive disorders

Summary

- CB1 and CB2 receptors are found in the periphery
- These receptors bind endocannabinoids 2AG and AEA
- These receptors play an important role in a number of systems (immune, digestive, reproductive)
- The action of THC and CBD in the periphery may be related to some of the purported effects on disease states like RA, IBS, liver inflammation, and other inflammatory states
- The endocannabinoid system and the effect of cannabinoids on these disease states will be discussed in greater detail in upcoming lectures