What is the Endocannabinoid System and What is its Role?

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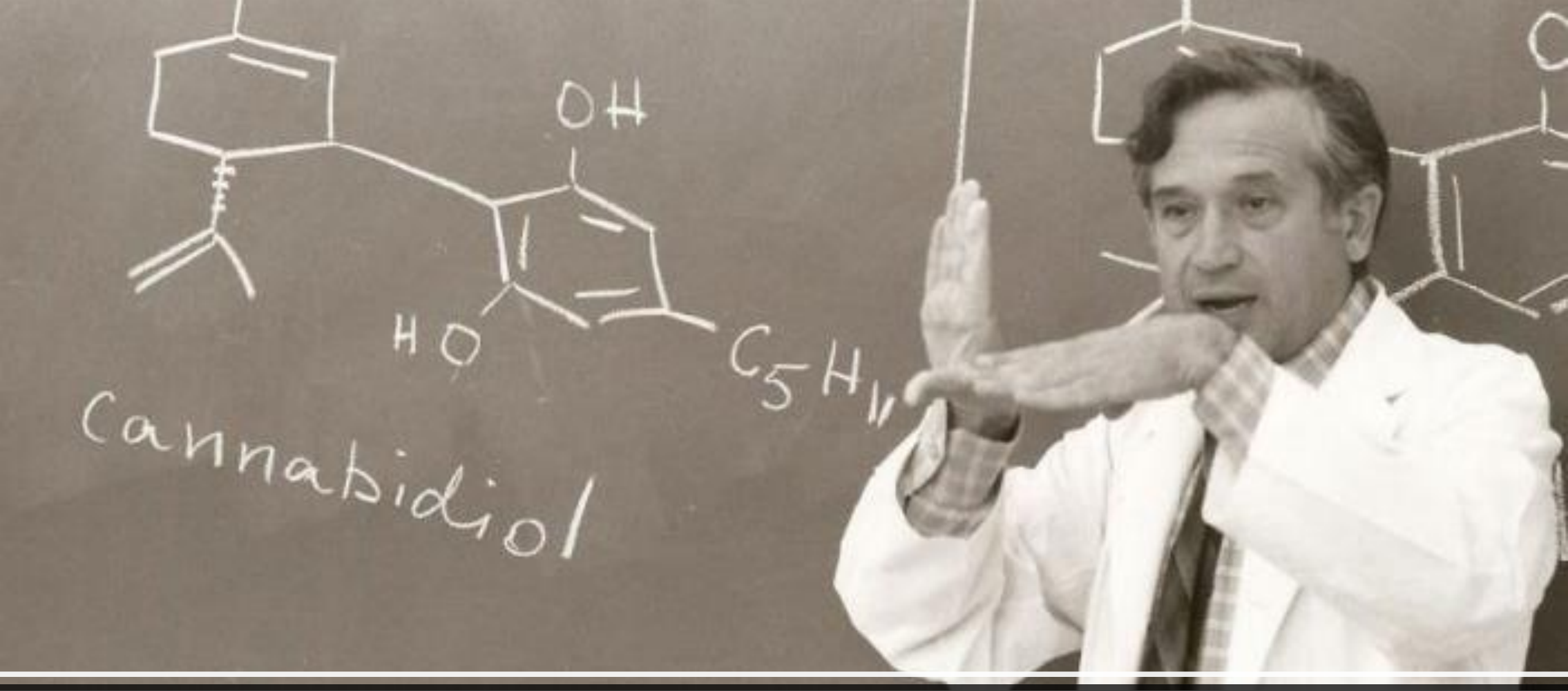
Objectives

- History of cannabis in the USA
- The endocannabinoid system
- Endocannabinoid Deficiency
- Side effects and drug interactions
- CB1 and CB2 Receptors



Raphael Mechoulam

Endocannabinoids: ***Bind CB1 > CB 2***

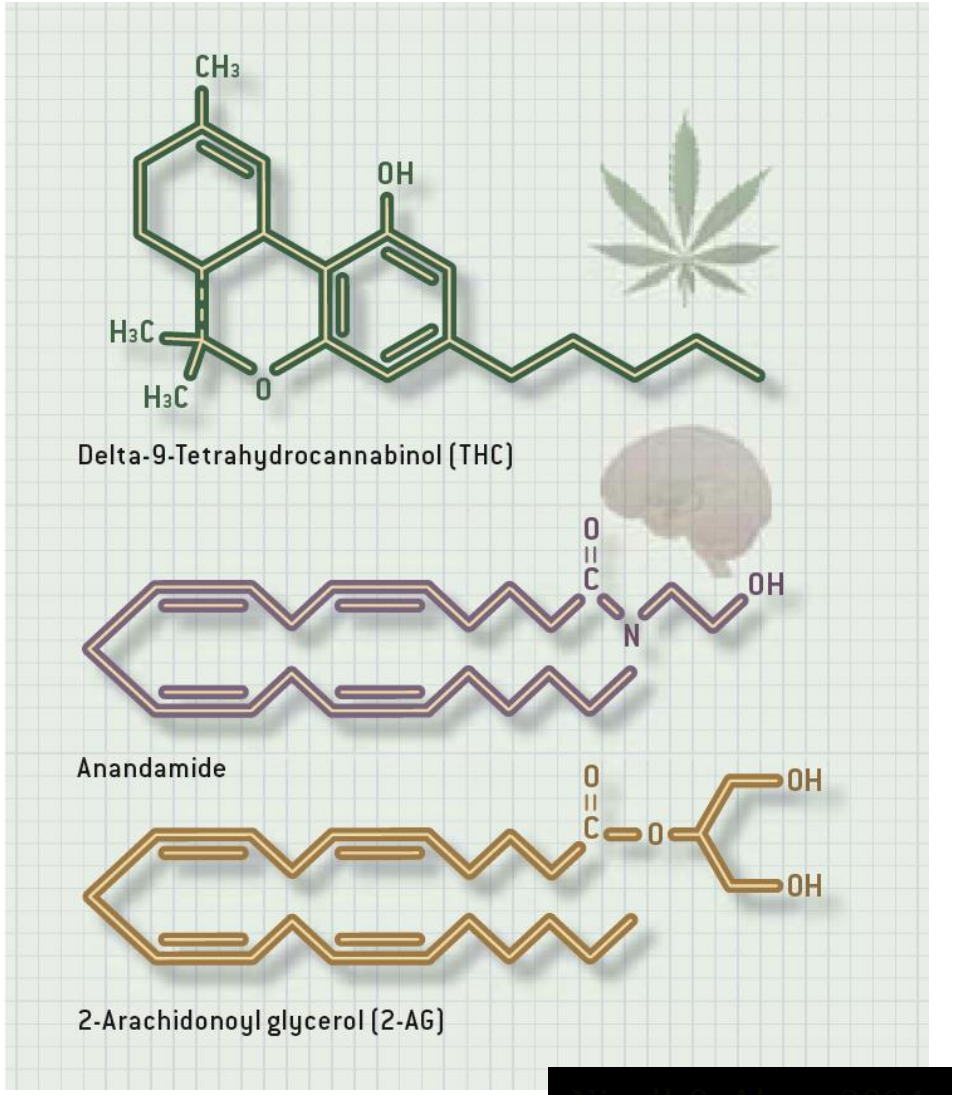
structure, related to prostaglandins

- **Annandamide**

(arachidonyl-ethanolamid)

- **2-Arachidonoyl - glycerol (2-AG)**

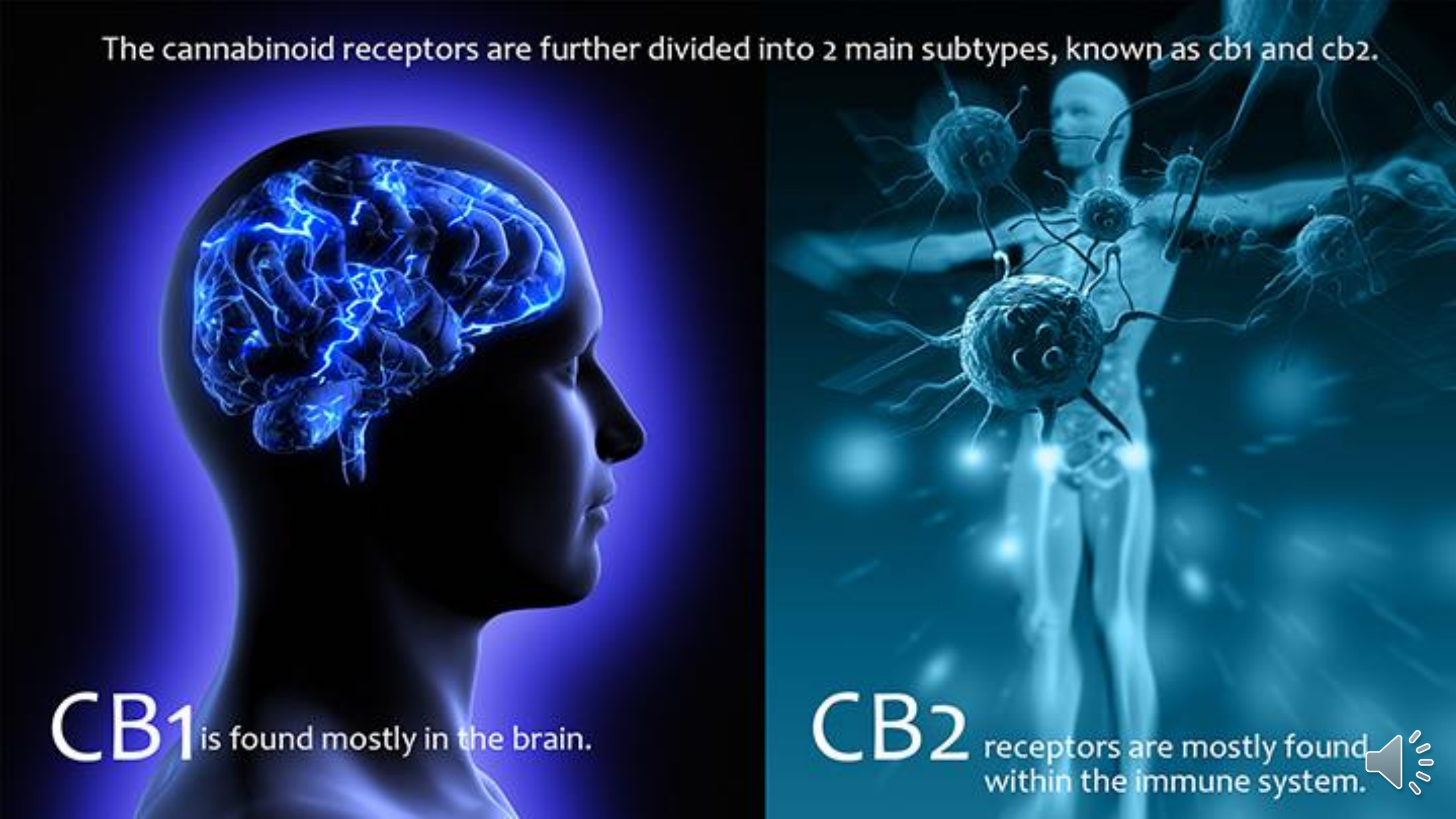
more abundant, less potent



Nicoll & Alger, 2004

Understanding Endocannabinoid Deficiency

The cannabinoid receptors are further divided into 2 main subtypes, known as cb1 and cb2.

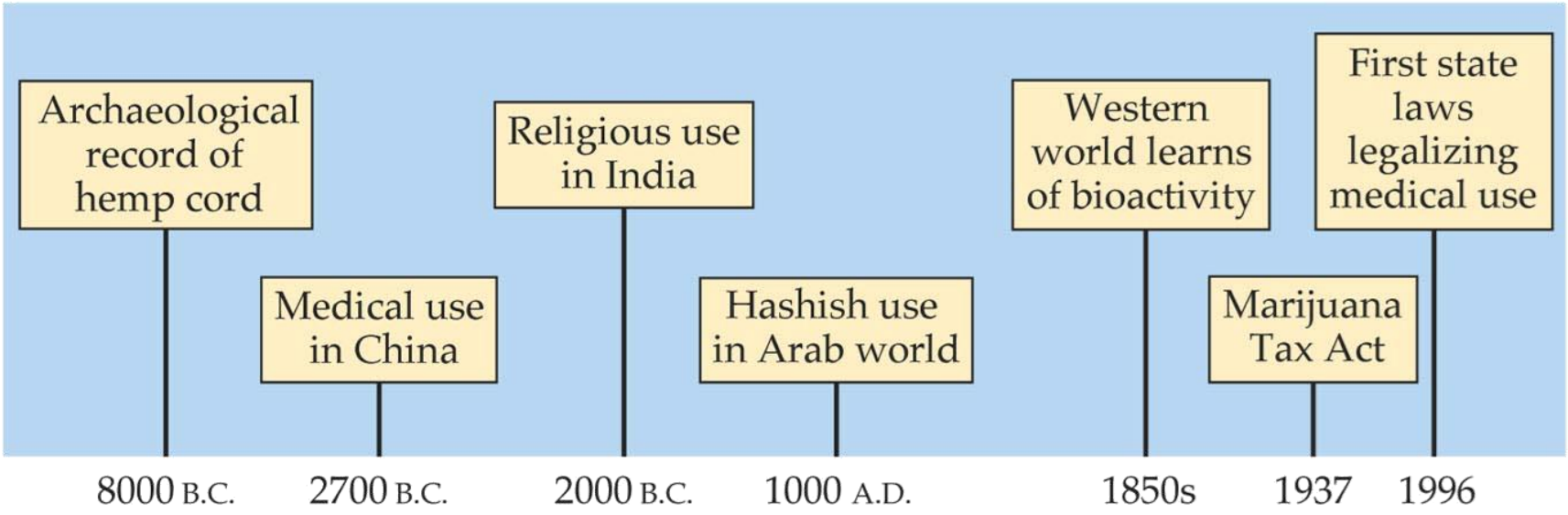


CB1 is found mostly in the brain.

CB2 receptors are mostly found within the immune system.

Background and History

- Cannabis is thought to have originated in central Asia (probably China).
- There is evidence of hemp rope dating back to 8,000 B.C.



Background and History in US

- 1600-1890's Hemp production encouraged
- 1906 Pure Food and Drug Act required labeling of hemp products
- 1900-1920's Mexican use of recreational marijuana
- 1930's Fear of marijuana – Linked to violence and deviate behavior
- 1930 Creation of the Federal Bureau of Narcotics (FBN)
  - Harry J. Anslinger was the first Commissioner of the FBN and remained in that post until 1962

Background and History in US

- 1932 Uniform State Narcotic Act
  - Required States to handle to epidemic
- 1936 Reefer Madness propaganda film
- 1937 Marijuana Tax Act- Congress and the “Evil Weed” for medical and industrial use
- 1944 La Guardia Report finds marijuana less dangerous
- 1940’s- Hemp used for WW2 military equipment

Background and History in US

- 1951-1956- Stricter penalties for possession
- 1960's Counter culture use of marijuana
  - President Kennedy and President Johnson said doesn't lead to other drugs and violence
- 1968 Creation of the Bureau of Narcotics and Dangerous Drugs
  - This was a merger of FBN and the Bureau of Dangerous Drugs of the Food and Drug Administration.

Background and History in US

- 1972 Shafer Commission
  - Decriminalize marijuana but president Nixon rejected the report
- 1973 Creation of the DEA
- 1976 Beginning of parents' movement against marijuana
- 1986 president Nixon – 3 strikes and your out equated marijuana with heroin
- 1996 Medical Use in California

Quick History of the Receptors

1940

CBD identified

1964

THC identified

1988

CB1 receptor discovered

1990

CB1 receptor cloned

1992

Anandamide discovered (Raphael)

1995

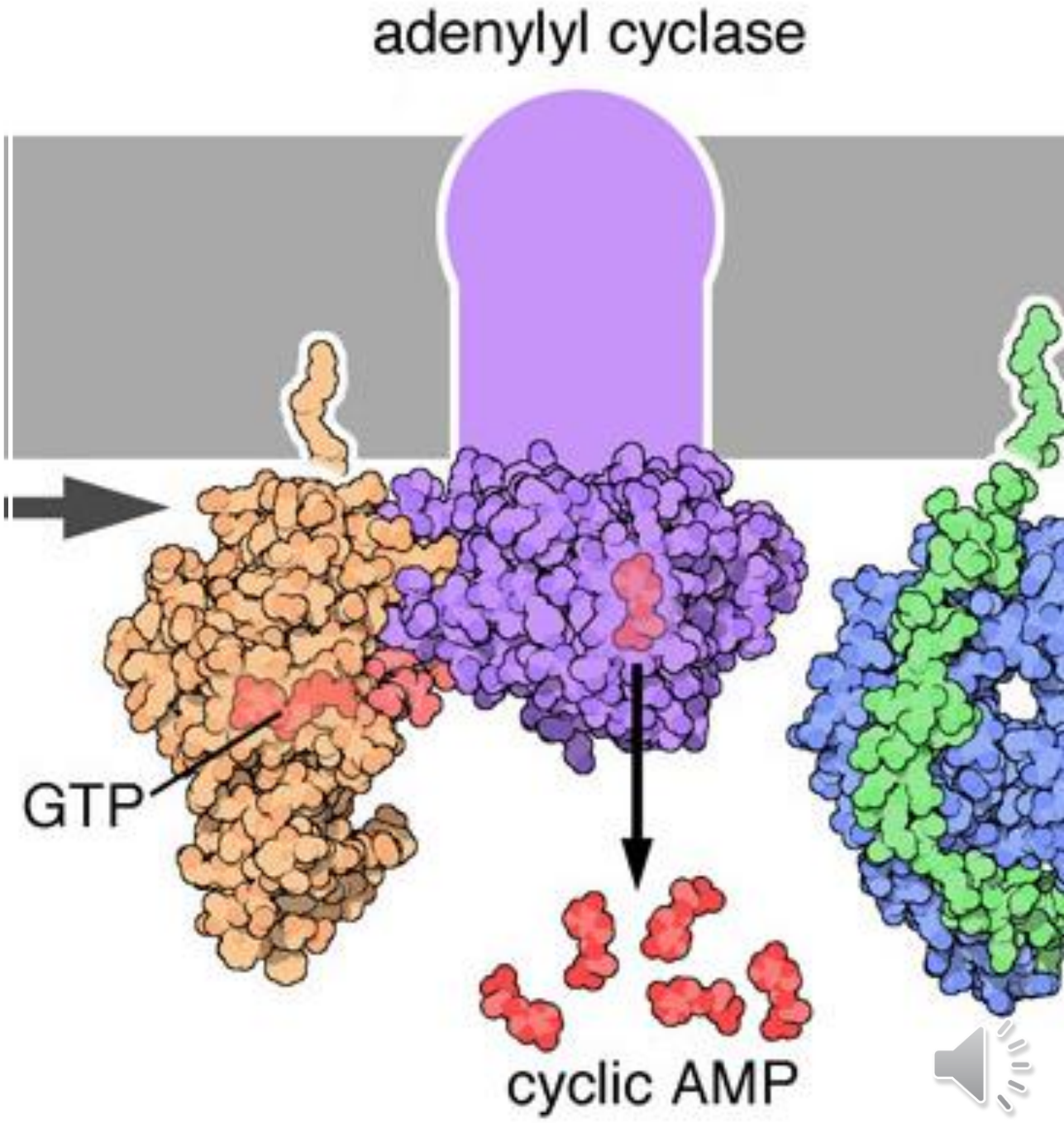
2-AG identified

2001

Discovery of retrograde signaling

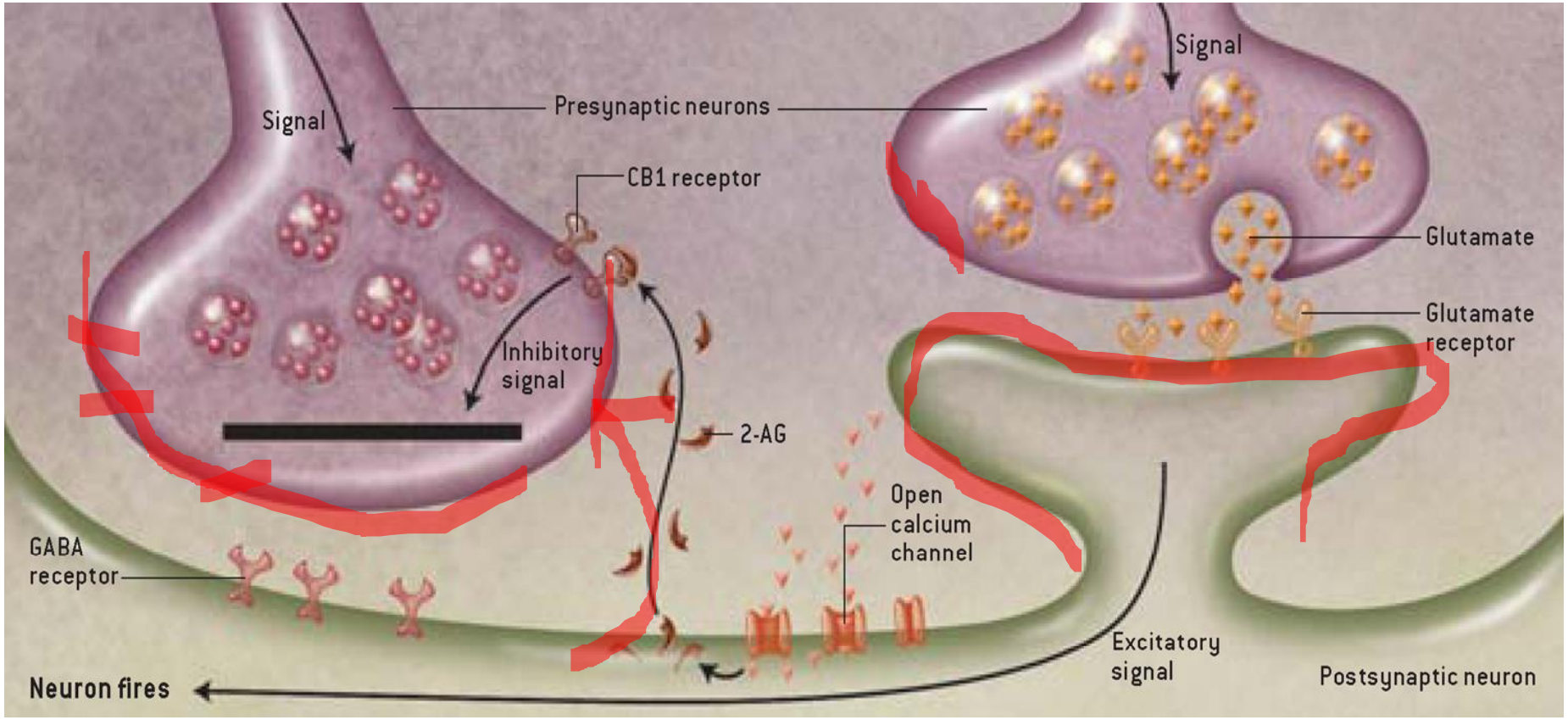
Cannabinoid Receptors
G protein-coupled

- ***CB1***
  - **Brain**, fat cells, liver, duodenum, muscle
- ***CB2***
  - **Lymphocytes**>macrophages>cytokines

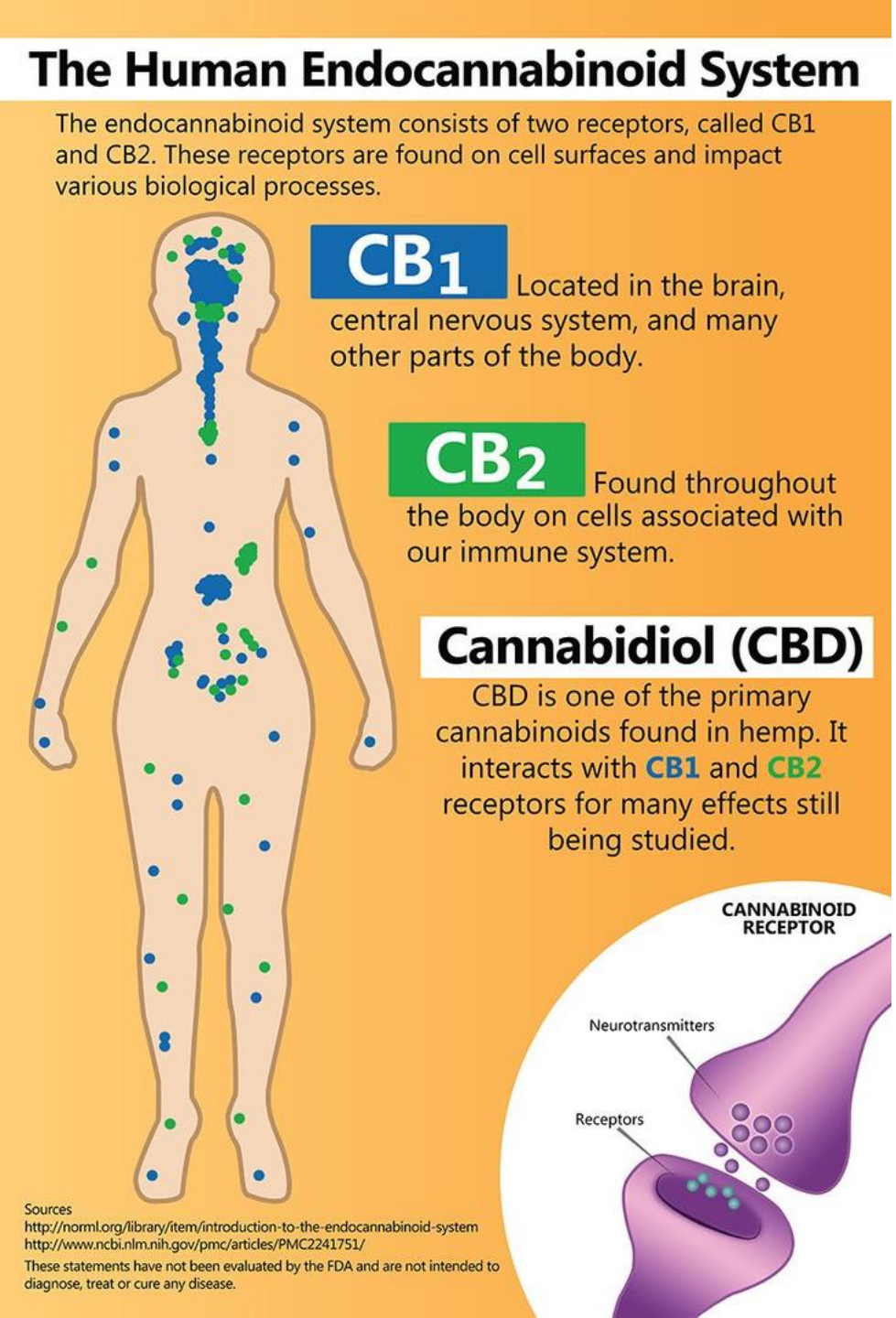


Depolarization-induced suppression of inhibition

POSTSYNAPTIC endocannabinoid release inhibits PRESYNAPTIC GABA and glutamate release



Nicoll & Alger, 2004



Endocannabinoid Overview

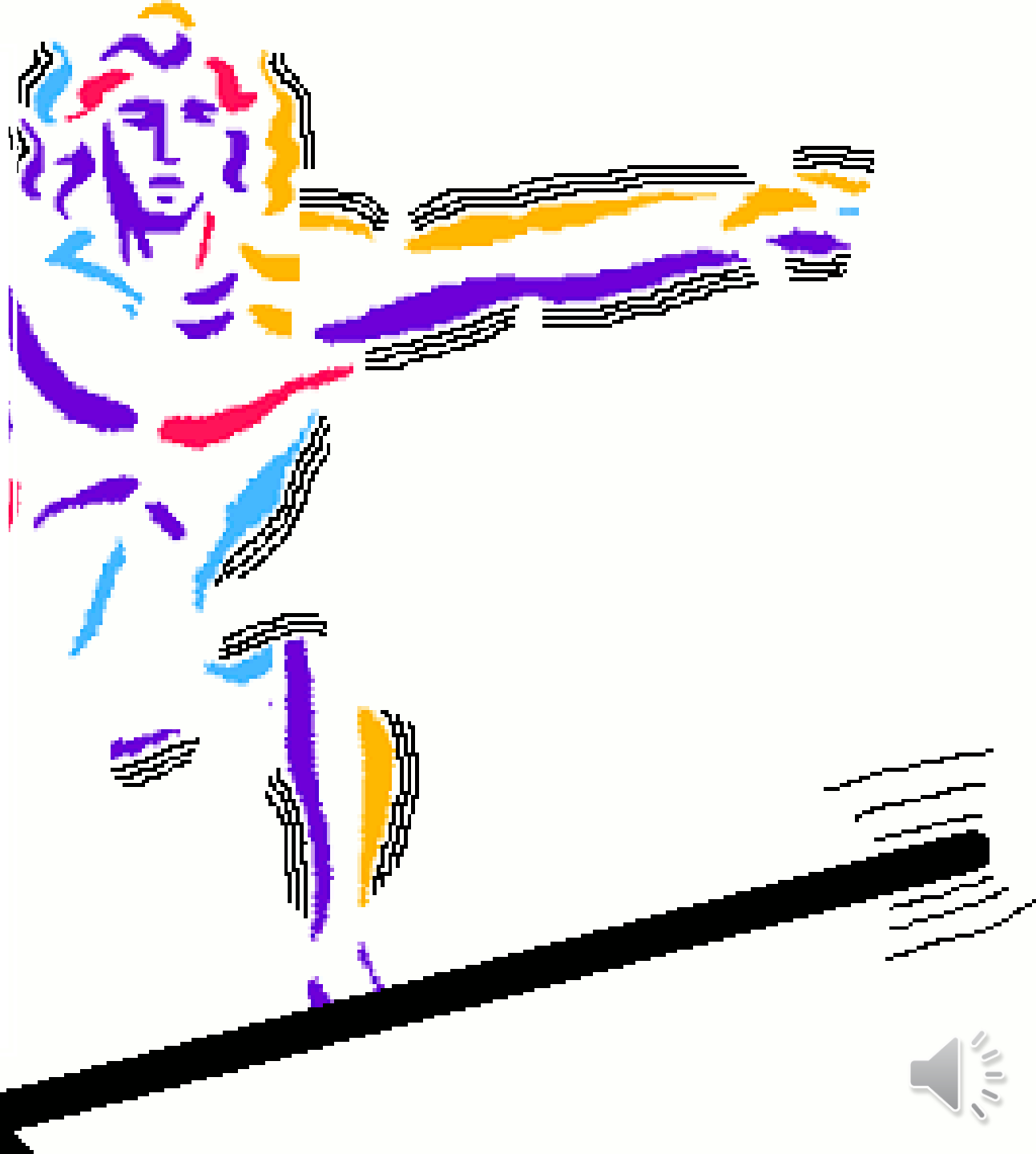
- Endogenous physiologic system
  - Establishes and maintains normal state or homeostasis
  - Key role in food hunger, fat accumulation, glucose and lipid metabolism
- Two well known receptor site
  - CB1 –central and peripheral nervous system
  - CB2 –immune cells
- Endogenous endocannabinoids
  - AEA (Anandamide)
  - 2-AG (2-Arachidonoylglycerol)
- Enzymes degrade AEA and 2-AG

Cannabinoid Receptors:

- CB1
  - THC has high affinity for these receptors
  - Pain , nausea, and depression
  - Arthritis and Lupus
- CB2
  - Receptors part of immune system
  - Great densities found in GI tract
  - Modulate Crohn’s disease and IBS

CB1 physiologic effects

- CB1 blockade helps
  - Regulate energy intake
  - Improves glucose and lipid metabolism
  - Antinociception
  - Motor control
  - Memory and learning
  - Immunity and inflammatory responses
  - Neuroprotection

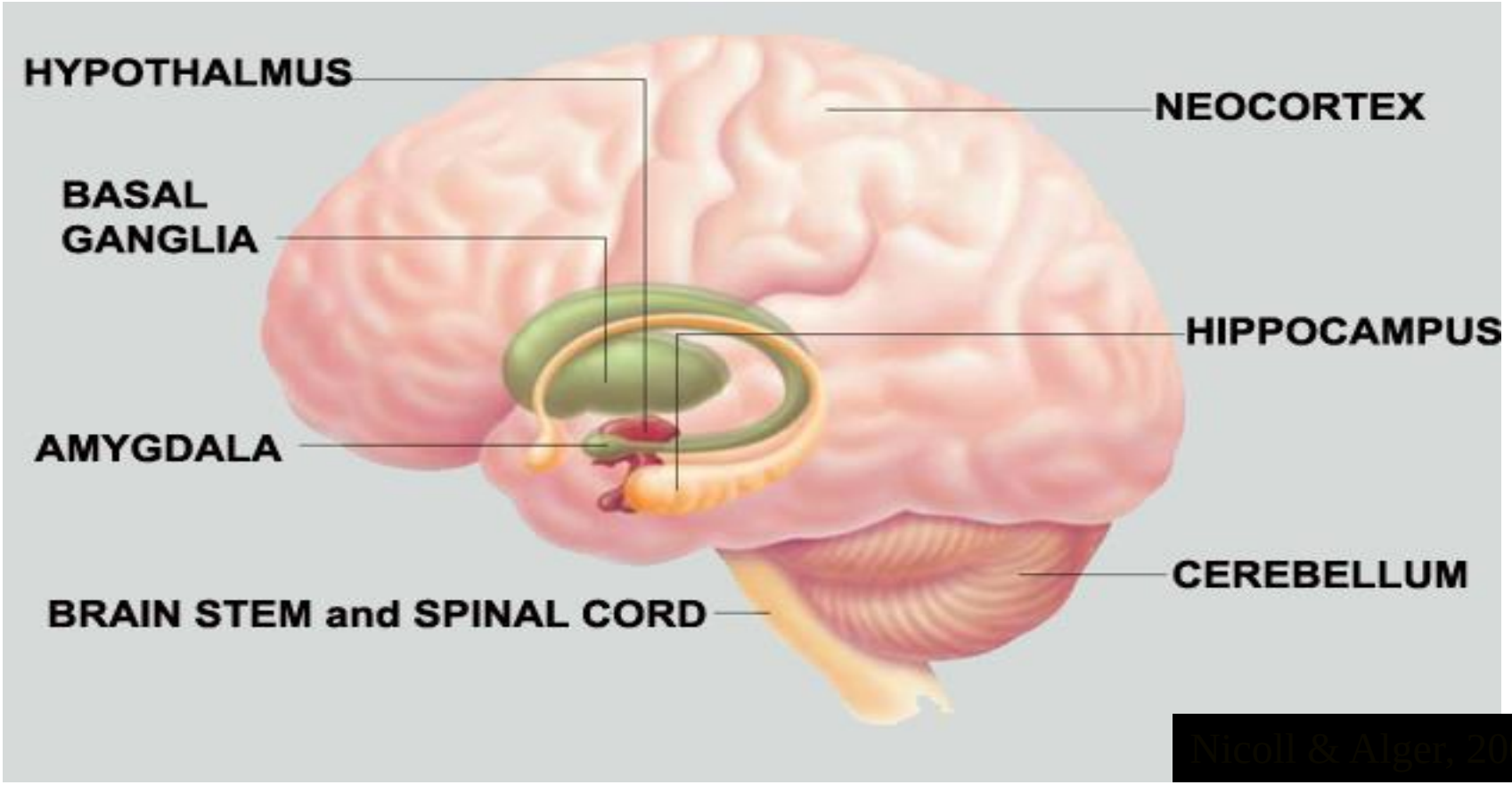


CB1 receptors in the brain

Dense: Basal Ganglia (motor control), Cerebellum (coordination), Hippocampus (Memory and learning)

Middle Prefrontal and Parietal Cortex

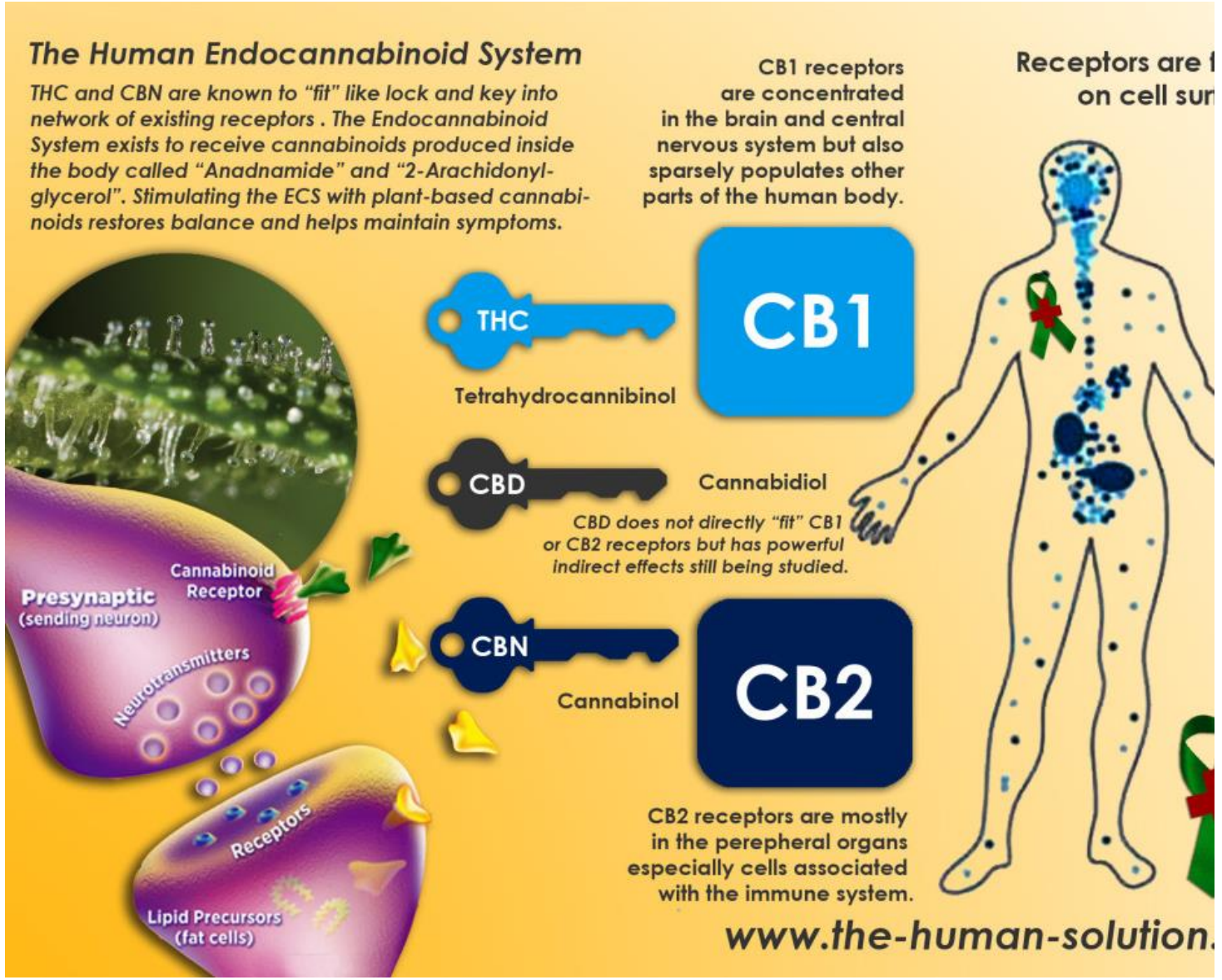
Moderate: Amygdala (Anxiety), Spinal Cord (Pain modulation), Brainstem (Vomiting)



Nicoll & Alger, 2004

CB1 receptors

- Typically the receptors exist on the axon terminal rather than on the postsynaptic cell
  - Affects many neurotransmitter systems
    - Acetylcholine
    - Dopamine
    - Norepinephrine
    - Serotonin
    - Glutamate
    - GABA



Role of CB2 receptors

- Located throughout the immune system and related organs, like the spleen, tonsils, and thymus gland
- Less dense in brain (more CB1)
- Modulate inflammatory responses to intestinal diseases such as Crohns and IBS
- Decreases inflammation in Arthritis and Alzheimer’s

Role of CB2 receptors and pain

- CB2 agonists (AM1241) inhibit nociception without producing CNS effects
  - The effects do not cross-over to morphine effects
- CB2 appears to modulate:
  - Acute pain
  - Chronic inflammatory pain
  - Post surgical pain
  - Cancer pain
  - Pain associated with nerve injury

Role of CBD

- Low affinity for CB1 and CB2 receptors
- Acts as a antagonist on the CB1 and CB2 sites
- Extends duration of Anandamide and 2-AG
- Extend the duration of the effects of THC
  - Via inhibition of the cytochrome P450 enzyme system
- Dravet syndrome
- Other treatment-resistant epilepsies
- Pain
- Cancer
- Inflammation

Endocannabinoid System: Effects of CB_1 Antagonism

	Site of Action	Mechanism(s)	Clinical Implications
	Hypothalamus/ nucleus accumbens	↓ Food intake	↓ Body weight ↓ Waist circumference
	Adipose tissue	↑ Adiponectin ↓ Lipogenesis	↓ Visceral fat ↓ Dyslipidemia ↓ Insulin resistance
	Muscle	↑ Glucose uptake ↑ O_2 consumption	↓ Insulin resistance
	Liver	↓ Lipogenesis	↓ Dyslipidemia ↓ Insulin resistance
	GI tract	↑ Satiety signals	↓ Body weight
	Pancreas	Potential effect on insulin secretion	Potential effect on glucose/insulin metabolism

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Summary

- The endocannabinoid system has been around million of years
- The use of cannabinoids may help chronic disease
- More research is now being conducted
- More to come in the future

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