Endocannabinoid Physiology and Cannabinoid Pharmacology

Dustin Sulak, D.O.

The 15th National Clinical Conference on Cannabis Therapeutics

Disclosure

- Healer: equity owner and employee
  - patient education, cannabis and hemp products, industry training, consulting, extraction/formulation
- Forian: former paid scientific advisor
- Society of Cannabis Clinicians: unpaid member of board of directors
- Author of "Handbook of Cannabis for Clinicians: Principles and Practice" published by Norton Professional

Overview

- Cannabinoid receptors
- Endogenous cannabinoids
- A tour of ECS activity
  - Nervous system
  - Pain signaling
  - Immune system
  - Gastrointestinal system and metabolism
- ECS dysfunction
- Pharmacology of THC, CBD, THCA, CBDA, CBG, THCV

Health Conditions Influenced By Cannabinoids

ADD/ADHD
ALS
Alzheimer's
Anorexia
Anxiety
Asthma
Ataxia
Bipolar
Cachexia
Cancer
Chronic fatigue
Chronic pain
Cramps
Crohn's
Diabetes
Depression
Epilepsy
Fever
Fibromyalgia
Glaucoma
Hepatitis
HIV/AIDS
Incontinence
Insomnia
Migraine
MRSA
Multiple Sclerosis
Nausea
Neuralgia
Neuropathy
Parkinson's
PMS
PTSD
Rheumatoid Arthritis
Seizure disorders
Sickle cell anemia
Spasms
Spinal injury
Stroke
Tourette's
Vomiting

Pacher & Kunos, 2013

Why does one herb help so many different conditions?

The Endocannabinoid System

The Endocannabinoid System (ECS)

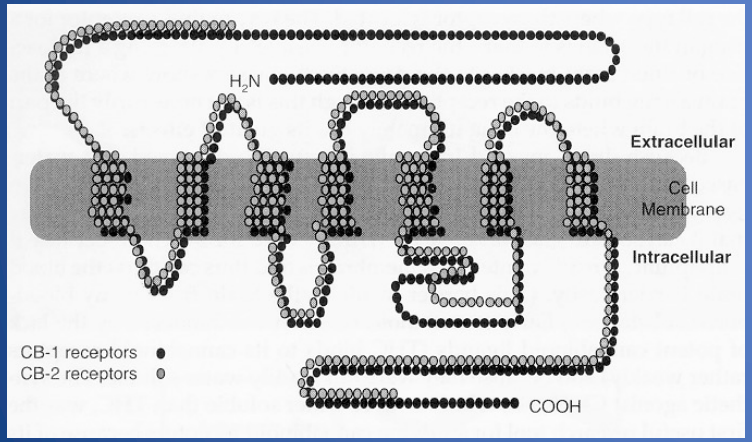
- The ECS is a homeostatic regulatory system active throughout the body.
- Endocannabinoid synthesis is an adaptive response to cellular stress, aimed at re-establishing cellular homeostasis.

- Pubmed search results for "endocannabinoid"
  - 1993: 10 citations
  - 2022: 11,800+ citations

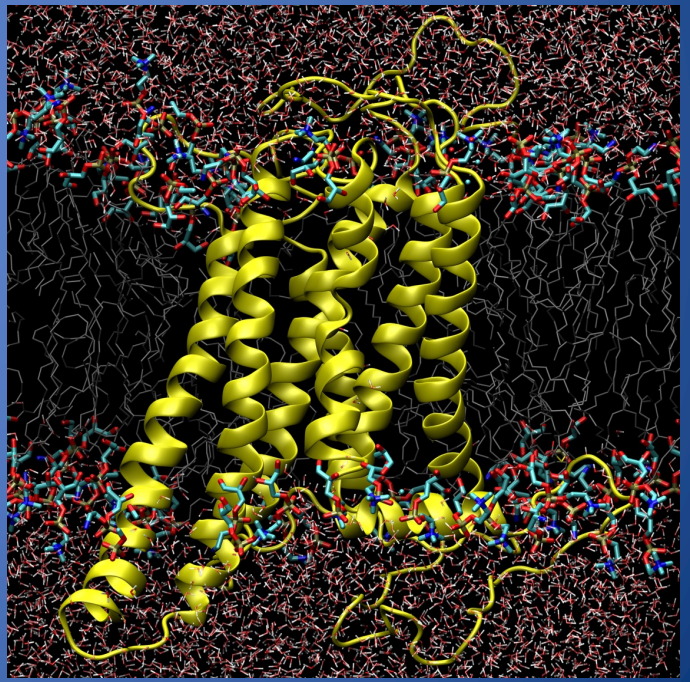
Cannabinoid Receptors

The Cannabinoid Receptors: CB1 and CB2

secondary structure



tertiary structure



Cannabinoid Receptors

CB1 located in:

- Central and peripheral nervous systems
- Fascia
- Adipose tissue
- Skeletal muscle
- Smooth muscle
- Liver
- Lungs
- Pancreas
- Kidneys
- Adrenal glands
- Heart
- Thymus
- Tonsils

CB2 located in:

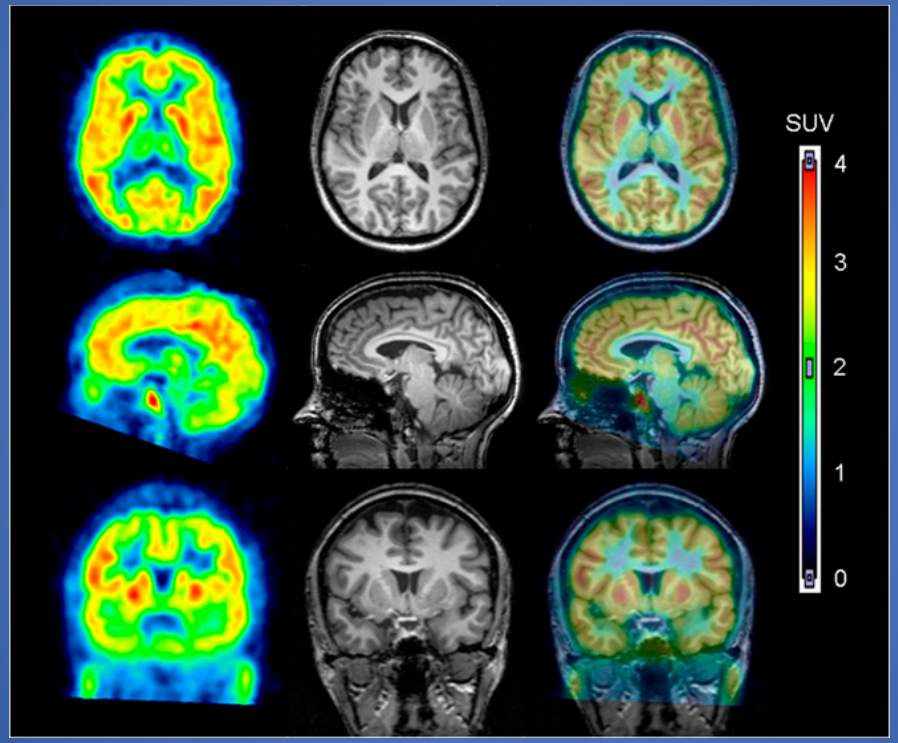
- Monocytes
- Macrophages
- B-cells
- T-cells
- Liver
- Spleen
- Tonsils
- Osteoblasts
- Osteoclasts
- CNS
- Enteric nervous system

Cannabinoid Receptors

- In addition to the outer cellular membranes, cannabinoid receptors have been found in intracellular compartments
  - Mitochondria (regulate ATP production and cellular respiration)
  - Endoplasmic reticulum, endosomes, lysosomes, cell nuclei

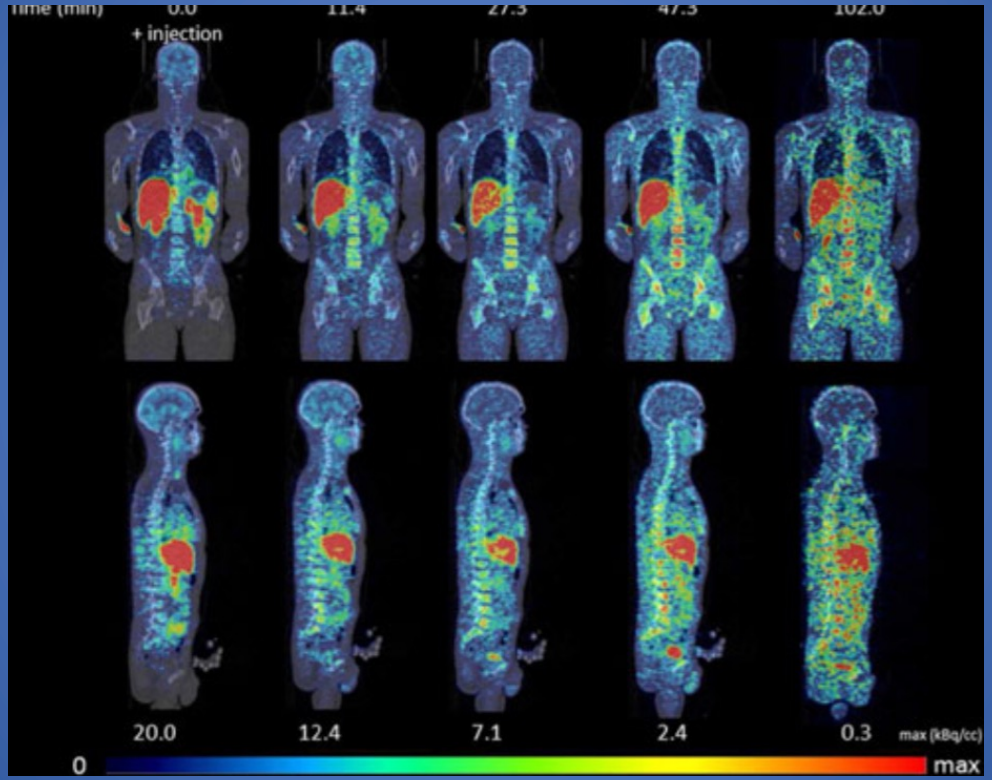
Hebert-Chatelain et al., 2017

CB1 Receptor Distribution in Human Brain



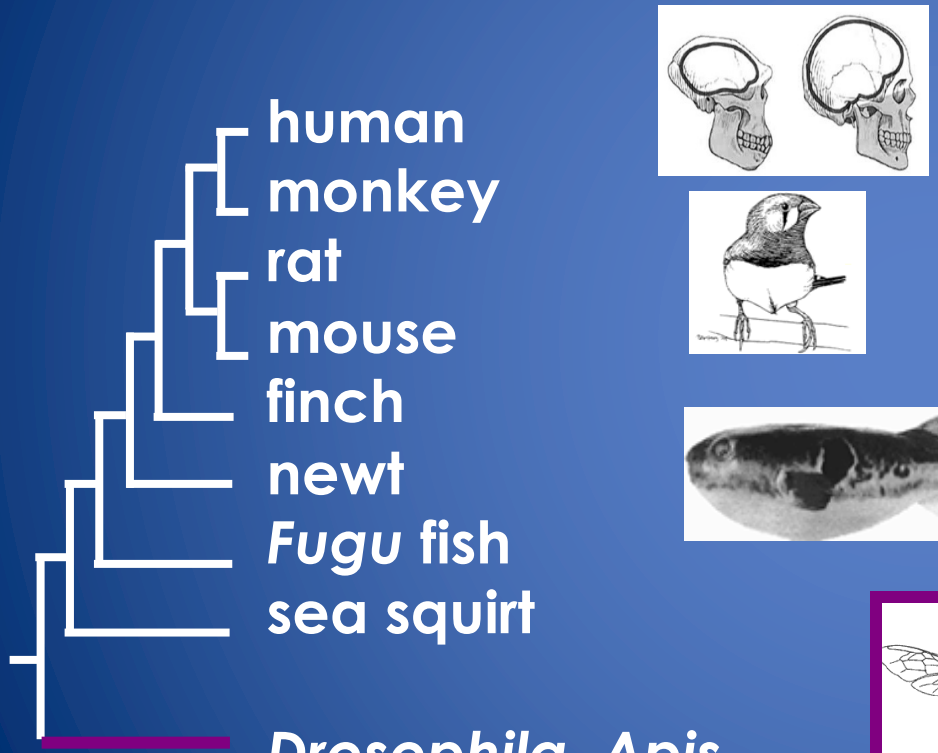
Terry et al. 2010

CB2 Receptor Distribution



Ahmad, 2013

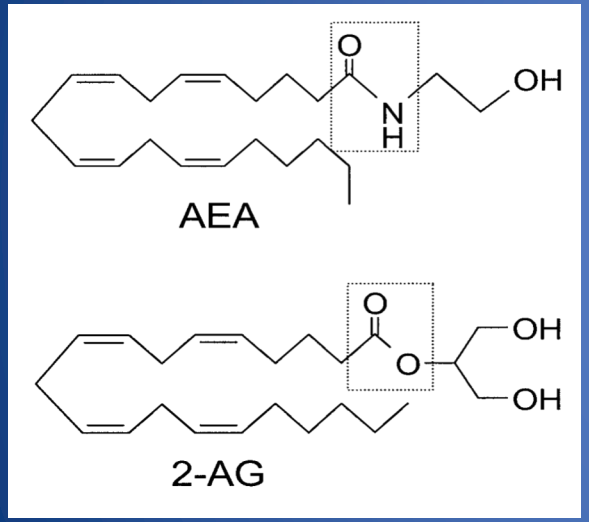
CB Receptors Evolved 600 Million Years Ago



McPartland, 2006

Endogenous Cannabinoids

Endogenous Cannabinoid Ligands: The Endocannabinoids



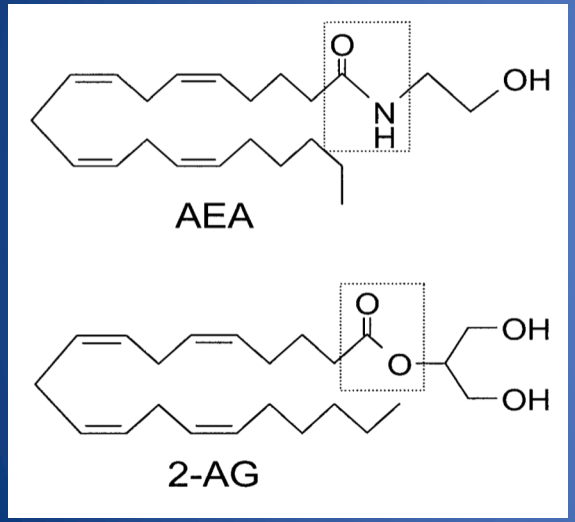
Anandamide (AEA)

Devane, Mechoulam *et al.*, 1992

2-arachidonoylglycerol (2-AG)

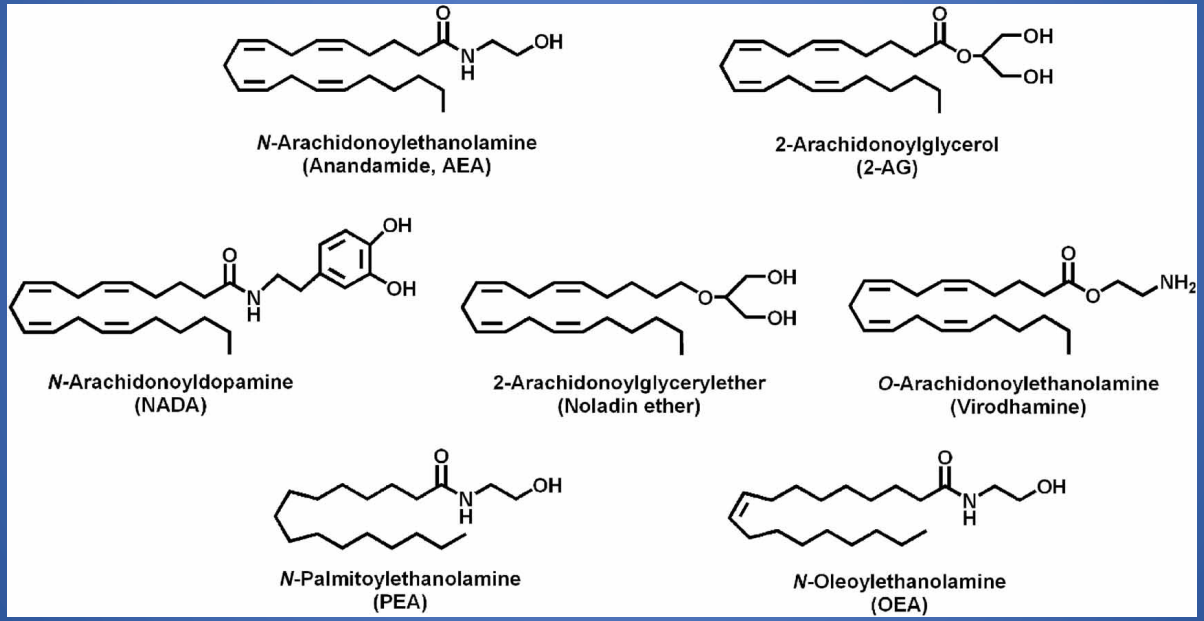
Mechoulam *et al.*, 1995
Sugiura *et al.*, 1995

Endogenous Cannabinoid Ligands: The Endocannabinoids



- Retrograde messengers in nervous system.
- Autocrine and paracrine mediators elsewhere.
- Endocrine effects of circulating eCBs
- Synthesized "on demand" from cell membrane precursors (arachidonic acid derivatives) and immediately released.
- Degraded by enzymatic hydrolysis
  - AEA: fatty acid amide hydrolase (FAAH)
  - 2-AG: monoacylglycerol lipase (MAGL)

Numerous Other Endogenous Cannabinoids



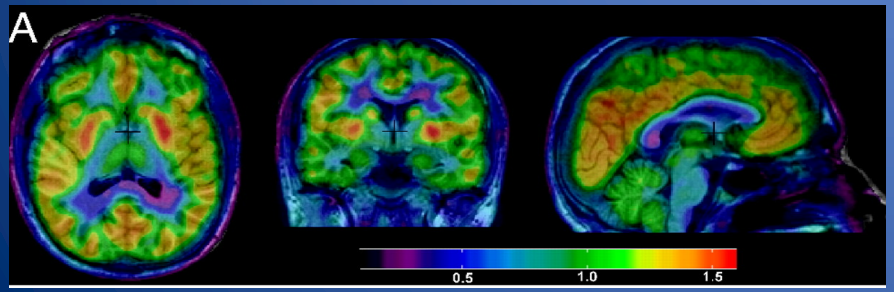
Battista et al., 2012

Other Endocannabinoid Targets

- GPR55 (Ryberg, 2007) (Staton, 2008)
- TRPV1 "capsaicin receptor" (Ross, 2003)
- PPARs: Peroxisome proliferator-activated receptors (O'sullivan, 2007)
- Voltage-gated ion channels
  - Ca2+, Na+, and various types of K+ channels
- Ligand-gated ion channels
  - 5-HT3 and nicotinic ACh receptors. (Oz, 2006)

CB1 Receptor Distribution in CNS

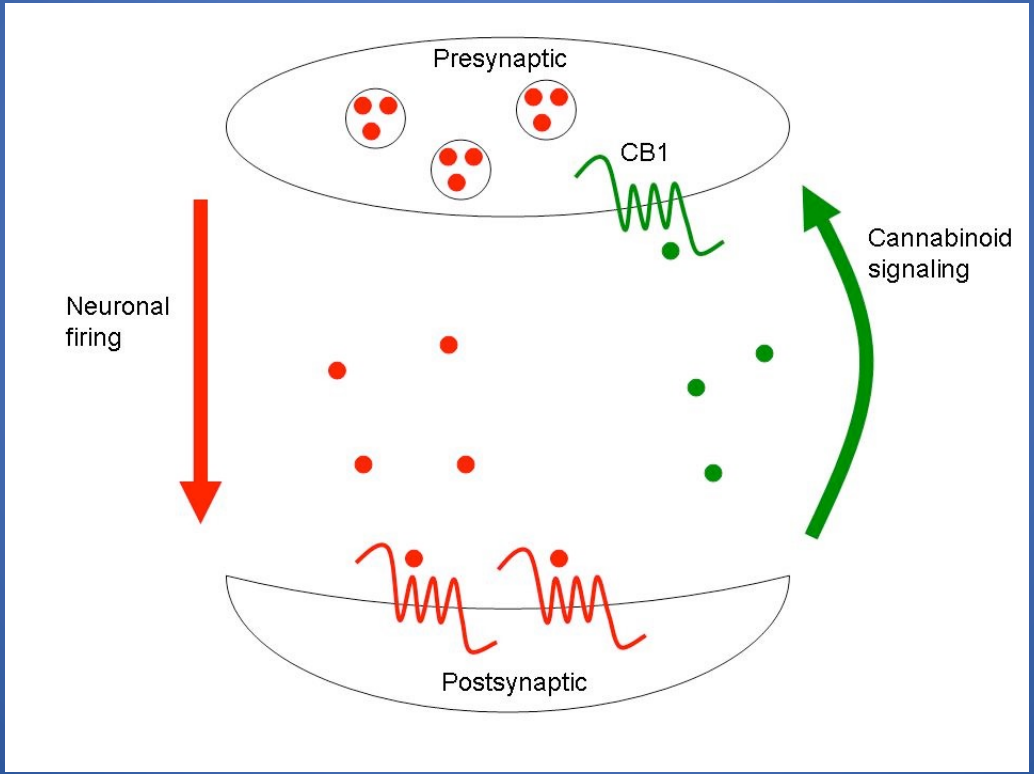
- One of the most common G protein coupled receptor in the brain
- Highest densities:
  - hippocampus
  - cerebral cortex
  - cerebellum
  - amygdaloid nucleus
  - basal ganglia



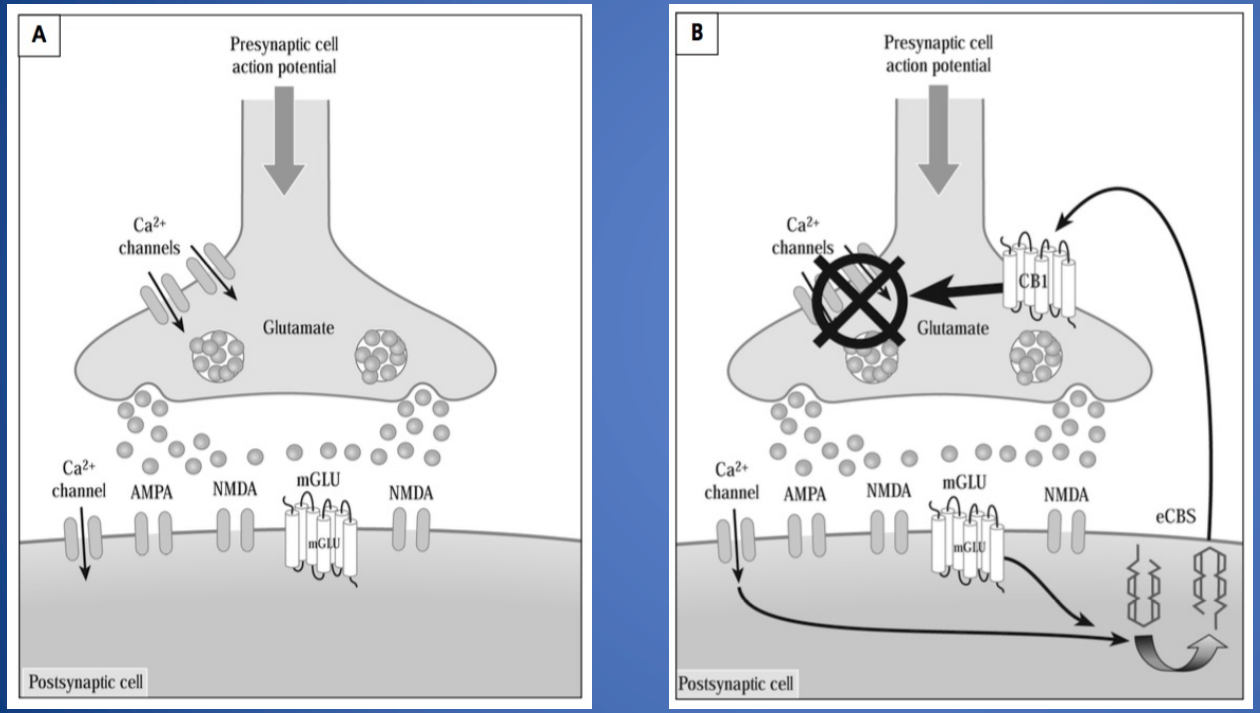
- Correlate with changes in:
  - short-term memory
  - cognition
  - mood and emotion
  - motor function
  - nociception
- Virtually absent in brainstem cardiorespiratory centers – no lethal overdose

Glass, 1997
Burns, 2007

Cannabinoid Activity in the Synapse: Retrograde Signaling



Retrograde Synaptic Transmission



Depolarization-induced suppression of excitation

Replace GABA for glutamate = depolarization-induced suppression of inhibition

McPartland, John M. "The endocannabinoid system: an osteopathic perspective." *The Journal of the American Osteopathic Association* 108.10 (2008): 586-600.

Mechanisms By Which Cannabinoids Modulate Neural Plasticity

- Neurogenesis
  - pCREB: phosphorylated cAMP response element-binding protein
  - BDNF: brain-derived neurotrophic factor
- Depolarization-induced suppression of excitation (DSE)
- Depolarization-induced suppression of inhibition (DSI)
- Long-term potentiation (LTP)
- Long-term depression (LTD)

Fishbein, 2012
Lovinger, 2008

Neural Protection

- AEA and 2-AG are endogenous neuroprotective agents produced by the nervous system upon both chemical and mechanical trauma. (Mechoulam, 2002)
- Δ9-THC, CBD, AEA, 2-AG, and HU-210 all decrease glutamate excitotoxicity. (Baker, 2003)
  - Reduce seizure activity
  - Limit infarct size post-stroke
- Cannabinoids effective at reducing and preventing perinatal brain injury (reviewed in Fernández-López et al., 2013)

Autonomic Tone

- Sympathetic Nervous System: CB1
  - Inhibits norepinephrine release
  - Dampens sympathetically mediated pain
  - Modulates hypothalamic–pituitary–adrenal (HPA) axis and hypothalamic-locus coeruleus-norepinephrine (HLN) axis

- Parasympathetic Nervous System: CB1
  - Reduces elevated activity, providing the antiemetic effects of cannabinoids.

Pertwee, 2005

Autonomic Tone – Vascular and Cardiac

- Myocardial CB1 activation: vagally mediated biphasic effects in heart rate and cardiac contractility
- Vascular tissue CB1 activation: vasodilation
- Antihypertensive effects in humans
- Protective role in myocardial ischemia has been suggested in rodent studies.

(Pacher, 2006)

Endocannabinoid System and Pain

Pre-clinical models show ECS activation causes antinociceptive effects in

- Acute Pain
- Persistent Inflammatory Pain
- Neuropathic Pain

Guindon, 2009

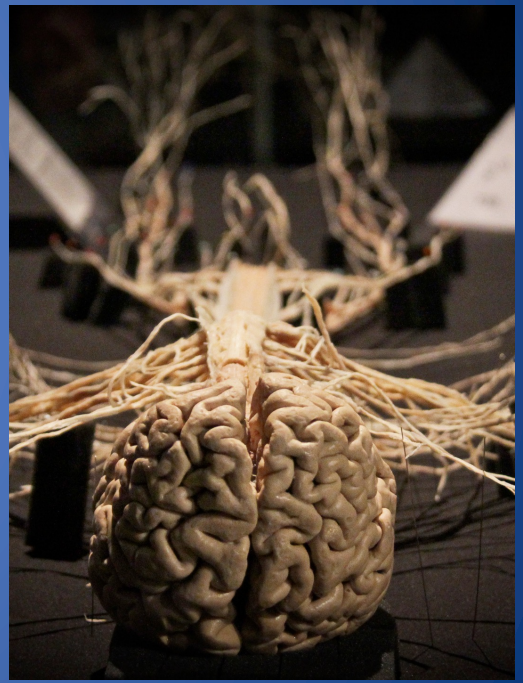
Cannabinoid tetrad test:

- Hypomotility
- Catalepsy
- Hypothermia
- **Analgesia**

Martin, 1991

Antinociceptive Effects Of Cannabinoids Involve Many Mechanisms

- Descending pain inhibitory pathway
- Peripheral terminals of nociceptors
- Dorsal horn
- Supratentorial sites



Reviewed in McPartland, 2008; Guindon, 2009

Image: Bodyworlds.com

Cannabinoid-Opioid Synergy

- Opioid and cannabinoid receptors are both present in pain signaling regions of the brain and spinal cord.
- Opioid and cannabinoid signaling pathways interact with each other.
- Administering cannabinoids with opioids results in a greater than additive antinociceptive (anti-pain) effect.

reviewed in Cichewicz, 2004

Cannabinoid-Opioid Synergy

Opioid-sparing Effect of Cannabinoids: A Systematic Review and Meta-analysis

- 17 of 19 pre-clinical studies demonstrated synergistic effects from opioid-cannabinoid co-administration.
- The ED_{50} of morphine administered in combination with THC is 3.6 times lower than the ED_{50} of morphine alone (95% CI 1.95, 6.76; n = 6).
- The ED_{50} for codeine administered in combination with THC was 9.5 times lower than the ED_{50} of codeine alone. (95% CI 1.6, 57.5, n = 2)

Nielsen et al., 2017

Endocannabinoid Neurophysiology Summary

- Retrograde synaptic transmission
- Neuroprotection
- Neuroplasticity
- Autonomic regulation
- Antinociception
- Synergy with opioid system

Endocannabinoids in Embryology

- CB1 detected in mouse embryos as early as second day of gestation.
- Blastocyst implantation into the endometrium requires suitable levels of AEA.
- Proliferation and differentiation of neural stem cells are shaped by extracellular cues provided by endocannabinoids.

Park, 2004

6 day old human embryo implanting itself onto the wall of the womb

Endocannabinoid Activity in Bone

- Osteoblasts and Osteoclasts
  - produce AEA and 2-AG
  - express CB2 receptor:
    - ↓ osteoclast activity
    - ↑ osteoblast activity

- CB1 receptors are present in sympathetic nerve terminals in close proximity to osteoblasts.
  - retrograde CB1 signaling inhibits norepinephrine release and alleviates the tonic sympathetic restrain of bone formation

Bab, 2008

ECS Modulates Immune Cells

- T- and B-lymphocyte proliferation
- T- and B-lymphocyte apoptosis
- Macrophage-mediated killing of sensitized cells
- Inflammatory cytokine production
- Immune cell activation by inflammatory stimuli
- Chemotaxis
- Inflammatory cell migration

Endocannabinoid Immuno*modulation*

- ↓ Th1 cytokines: IL-2, IFNγ, TNFα
- ↓ Metalloproteinases
- ↑ Th2 cytokines: IL-4, IL-5, IL-10
- ↑ subsets of B, T, & NK cells

reviewed in McPartland, 2008

Endocannabinoids in the Digestive System

CB1 receptor modulates

- Enteric nervous system
- Gastric acid secretion
- Lower esophageal sphincter tone
- Intestinal motility, visceral pain, and inflammation

Reviewed in Galli, 2011; Izzo, 2008

Endocannabinoids in the Digestive System

CB2 receptors

- Lamina propria, plasma cells, activated macrophages
- Myenteric and submucosal plexus ganglia in human ileum
- Involved in the inhibition of inflammation, visceral pain, and intestinal motility in the inflamed gut

Reviewed in Galli, 2011; Izzo, 2008

ECS in Hunger and Metabolism

- Human breast milk contains endocannabinoids
- Newborn mice given CB1 antagonist stop suckling and die.
- The endocannabinoid system modulates cell metabolism via ghrelin, leptin, orexin, and adiponectin signaling pathways.
- Obesity leads to excessive production of endocannabinoids by adipocytes, which drives CB1 into a feed-forward dysfunction, contributing to metabolic syndrome.

Fride, 2004
Matias, 2007

Summary

- The ECS is widely distributed throughout the body.
- The primary function of the ECS is cellular homeostasis.
- Our understanding of the ECS is incomplete, emerging, and suggests significant complexity.
- Manipulation of the ECS may provide effective treatment for a wide variety of diseases.

"...modulating endocannabinoid system activity may have therapeutic potential

in almost all diseases affecting humans,

including obesity/metabolic syndrome; diabetes and diabetic complications; pain; neurodegenerative, inflammatory, cardiovascular, liver, gastrointestinal and skin diseases; psychiatric disorders; cachexia; cancer; and chemotherapy-induced nausea and vomiting, amongst many others."

Pacher, Pál, and George Kunos. "Modulating the endocannabinoid system in human health and disease–successes and failures." *FEBS Journal* 280.9 (2013): 1918-1943.

ECS Dysfunction?

Cannabinoid Receptor Polymorphisms

Associated with:

- Schizophrenia Subtypes (Ujike, 2002)
- Alcohol Dependence (Schmidt, 2002)
- Body Mass Index (Gazzerro, 2006)
- Central Obesity (Jaeger, 2008)
- ADHD and PTSD (Lu, 2008)
- Happiness (Matsunaga, 2014)
- Serum lipid profiles (Luis et al., 2016)
- Headache w/ nausea during life stress (Juhasz et al., 2016)
- Response to a Mediterranean hypocaloric diet (de Luis et al., 2016)
- Risk of cyclic vomiting syndrome (Wasilewski et al., 2017)
- Marijuana demand (Aston et al., 2017)

Cannabis and Cannabinoid Research
Volume 1.1, 2016
DOI: 10.1089/can.2016.0009

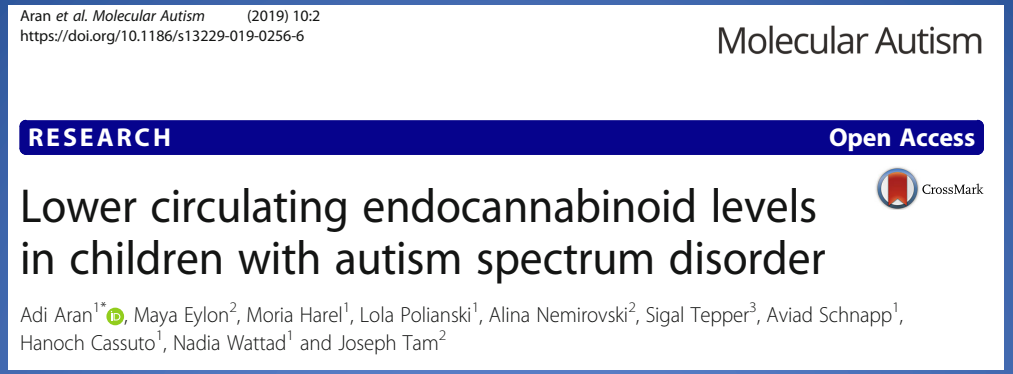
Cannabis and Cannabinoid Research

Mary Ann Liebert, Inc. publishers

REVIEW Open Access

Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes

Ethan B. Russo*



Aran *et al. Molecular Autism* (2019) 10:2
https://doi.org/10.1186/s13229-019-0256-6

Molecular Autism

RESEARCH Open Access

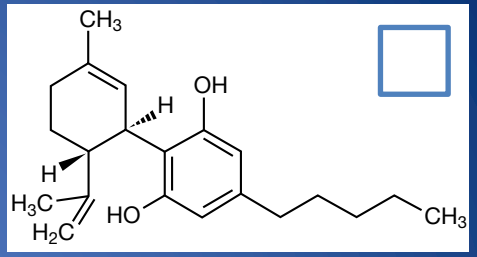
Lower circulating endocannabinoid levels in children with autism spectrum disorder

Adi Aran[1*], Maya Eylon[2], Moria Harel[1], Lola Polianski[1], Alina Nemirovski[2], Sigal Tepper[3], Aviad Schnapp[1], Hanoch Cassuto[1], Nadia Wattad[1] and Joseph Tam[2]

- 93 children w/ ASD matched to 93 neurotypical controls
- Children with ASD had lower levels of AEA, OEA, & PEA

Cannabinoid Pharmacology

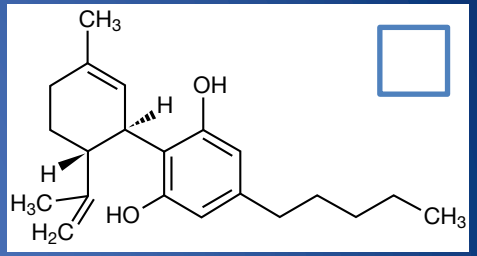
Δ9-THC



- THC mimics AEA and 2- AG by acting as an partial agonist at CB1 and CB2.
- Analgesic, antipruritic, antispasmodic, antioxidant, bronchodilatory, neuroprotective, anti-inflammatory, antiemetic, psychoactive

Reviewed in Pertwee, 2008

Δ9-THC: Non-CB Targets



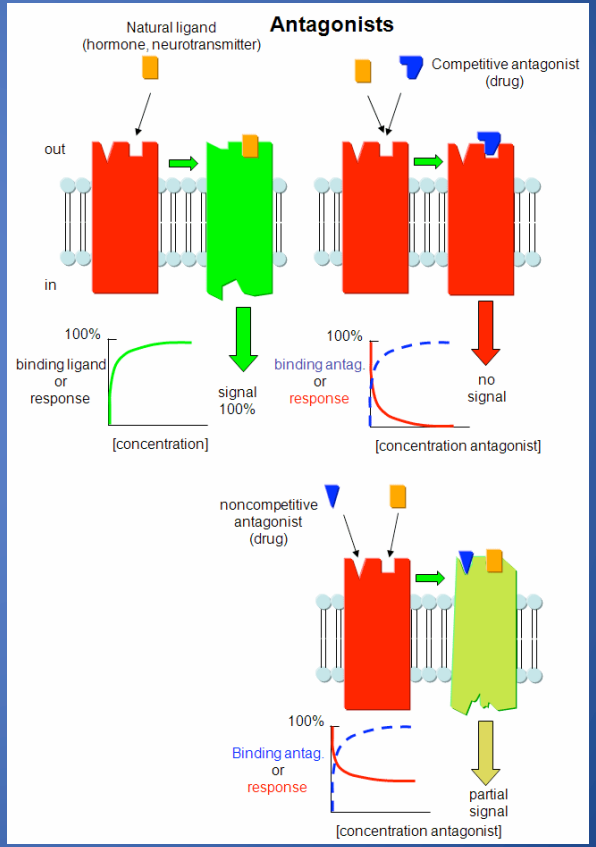
- Activates
  - GPR18
  - GPR55
  - PPARγ nuclear receptor
  - TRPA1,TRPV2, TRPV3, TRPV4
- Inhibits
  - 5-HT3A
  - TRPM8
  - GPR55

Reviewed in Pertwee, Roger G., ed. *Handbook of cannabis*. Oxford University Press, USA, 2014.

CBD Mechanism of Action

- Very low affinity for CB1 and CB2 receptors
- Allosteric antagonism of CB1 & CB2 agonists
- Non-competitive inverse agonist

Zhornitsky & Potvin, 2012; Laprairie etal., 2015; Morales et al., 2016;



http://biowiki.ucdavis.edu/Biochemistry/Transport_and_Kinetics/Enzyme_Inhibition/Agonist_and_Antagonist_of_Ligand_Binding

CBD: Other Mechanisms of Action

- Activates
  - 5-HT_{1A} serotonergic
  - TRPV1-4
  - PPARγ nuclear receptor
  - GPR18
  - α3 glycine
- Antagonizes
  - GPR55
  - α-adrenergic
  - μ-opioid receptors
  - Adenosine receptors
  - GPR18

- Inhibits uptake
  - noradrenaline
  - dopamine
  - serotonin
  - GABA
  - anandamide

- Inhibits activity of fatty amide hydrolase (FAAH) and numerous other enzymes
- Acts on mitochondria Ca^2 stores via VDAC1
- And more…

reviewed in Zhornitsky, 2012; Pertwee, 2014

Cannabidiol's Effects on the Brain

- Anxiolytic
- Antipsychotic
- Antidepressive
- Antiseizure
- Antispasticity
- Anti-inflammatory

Rong, et al. 2017

THC & CBD Synergism

Cannabidiol (CBD)

- Antagonizes undesirable effects of THC such as intoxication, sedation and tachycardia
- Enhances the analgesic, anti-emetic, and anti-carcinogenic properties of THC.

Russo & Guy, 2006

Neuropsychopharmacology (2010) 35, 1879–1885
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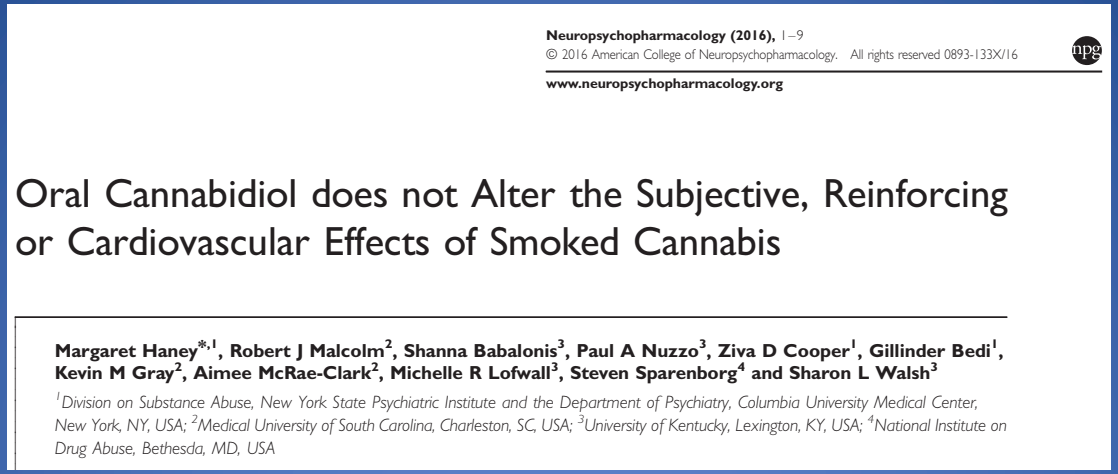
www.neuropsychopharmacology.org

Cannabidiol Attenuates the Appetitive Effects of Δ_9-Tetrahydrocannabinol in Humans Smoking Their Chosen Cannabis

Celia JA Morgan*[,1], Tom P Freeman[1], Gráinne L Schafer[1] and H Valerie Curran[1]

[1]Clinical Psychopharmacology Unit, Research Department of Clinical, Health and Educational Psychology, University College London, London, UK



Neuropsychopharmacology (2016), 1–9
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www.neuropsychopharmacology.org

Oral Cannabidiol does not Alter the Subjective, Reinforcing or Cardiovascular Effects of Smoked Cannabis

Margaret Haney*[,1], Robert J Malcolm[2], Shanna Babalonis[3], Paul A Nuzzo[3], Ziva D Cooper[1], Gillinder Bedi[1], Kevin M Gray[2], Aimee McRae-Clark[2], Michelle R Lofwall[3], Steven Sparenborg[4] and Sharon L Walsh[3]

[1]Division on Substance Abuse, New York State Psychiatric Institute and the Department of Psychiatry, Columbia University Medical Center, New York, NY, USA; [2]Medical University of South Carolina, Charleston, SC, USA; [3]University of Kentucky, Lexington, KY, USA; [4]National Institute on Drug Abuse, Bethesda, MD, USA

- Assessed the influence of oral CBD (0, 200, 400, 800mg) on smoked cannabis (0.01% & 5.3–5.8% THC).
- Non-treatment-seeking, healthy cannabis smokers (n = 31)
- CBD was administered 90 min prior to cannabis administration.

- Conclusion: oral CBD does not reduce the reinforcing, physiological, or positive subjective effects of smoked cannabis

Contents lists available at ScienceDirect

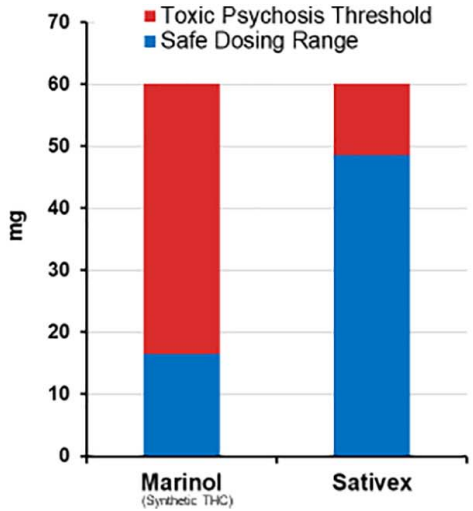
European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Review Article

Practical considerations in medical cannabis administration and dosing

Caroline A. MacCallum[a,*], Ethan B. Russo[b]



Results imply a markedly better therapeutic index and safety margin for nabiximols (THC/CBD extracts) over pure THC

Other Active Phytoconstituents

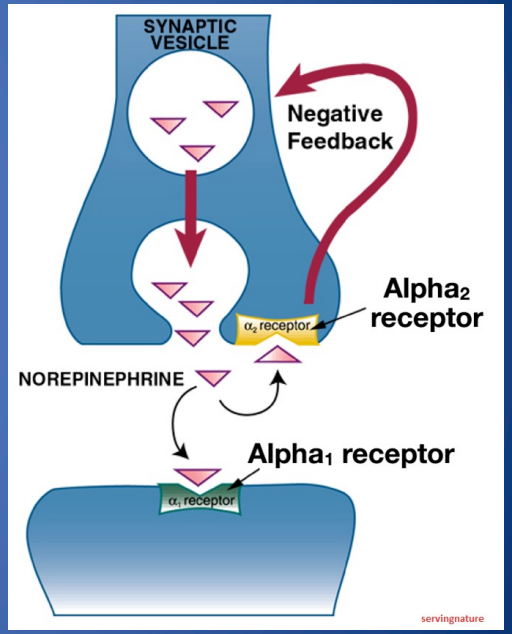
- 150+ cannabinoids including THC, CBN, CBD, CBC, CBG, THCV and other minor cannabinoids.
- Terpenoids and flavonoids also have therapeutic properties.
- Acidic (raw) cannabinoids (e.g. THCA, CBDA) have different properties and mechanisms of action.
- Antioxidant and antimicrobial properties

CBG: Mechanisms of Action

- CBG readily crosses the blood-brain-barrier in rodents
- CB1 & CB2:
  - CBG is more like THC, but with a lower affinity (by a factor of between 5-fold and 27-fold)
- Ion Channels
  - CBD and CBG are comparable at six transient receptor potential cation channels (TRPA1, TRPV1, TRPV2. TRPV3, TRPV4, and TRPM8)

CBG: α-2 Adrenoceptor

- Agonism results in decreased sympathetic nervous system activity
  - CBG had higher affinity than clonidine (computational model)
  - CBG's receptor sub-type selectivity awaits further elucidation
- Implications for blood pressure, pain, ADD/ADHD, opiate withdrawal, tic disorders, PTSD, dementia, etc.



CBG: Therapeutic Potential

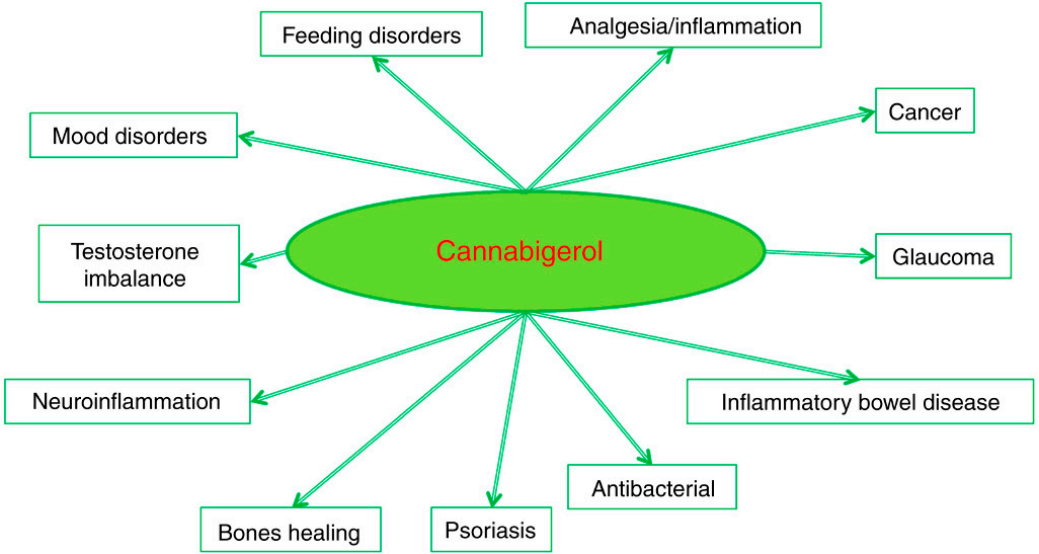
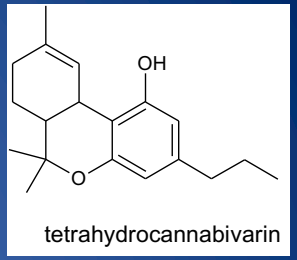


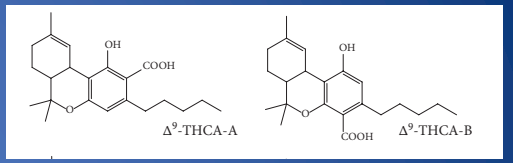
FIGURE 99.2 **Possible therapeutic applications of cannabigerol.** Cannabigerol has been suggested as a possible therapeutic agent for several conditions. To date, for most of these the exact mechanism of action awaits elucidation.

Tetrahydrocannabivarin (THCV)



- CB1 antagonist at low doses (Thomas et al. 2005)
- CB1 agonist at higher doses (Pertwee 2007)
- Produces weight loss, decreased body fat and serum leptin concentrations with increased energy expenditure in obese mice (Cawthorne 2007; Riedel 2009)
- Anticonvulsant (Hill 2010)
- Decreased edema & hyperalgesia (Bolognini 2010)
- Lacks AE liabilities of inverse agonists (McPartland 2015)

Tetrahydrocannabinolic Acid (THCA)



- Pharmacologically distinct from THC
  - Little to no activity at CB1 and CB2 (McPartland et al., 2017)
- No psychoactivity observed (Grunfeld & Edery, 1969)
  - rhesus monkeys (≤ 5 mg/kg), mice (≤ 20 mg/kg), dogs (≤ 7 mg/kg)
- Immunomodulatory, anti-inflammatory, neuroprotective, and antineoplastic effects
  - Suppress TNF-a release, independent of CB1 or CB2 in vitro (Verhoeckx et al., 2006).
  - Scavenges free radicals, inhibits breast and prostate carcinoma cell lines (Moreno-Sanz, 2016)

THCA - continued

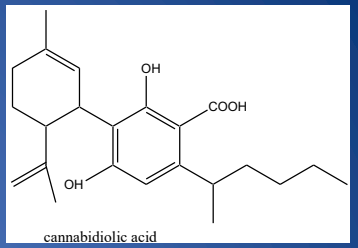
- Anti-inflammatory and anti-fibrotic effects in animal models of chemically- and obseity-induced injury (Carmona-Hidalgo et al., 2020)
- Reduces adiposity and prevents metabolic disease via PPARγ (Palomares et al., 2020)
- CB1 positive allosteric modulator? (Palomares et al., 2020)
- In vitro and ex vivo models of inflammatory bowel disease demonstrated anti-inflammatory effects of THCA without the biphasic pro-inflammatory effects seen with CBD. (Nallathambi et al., 2017)

THC Confounder?

Ultra-low Dose THC 0.002 mg/kg

- Cardioprotection in mice (Waldman et al, 2013)
- Liver protection in ischemia/reperfusion injury in mice (Hochhauser et al., 2015)
- Long-lasting activation of protective signaling molecules in the brain (Fishbein et al., 2008)

CBDA



- Shares the ability of CBD to activate 5-HT1A, but much stronger
- Does not act upon CB1 or CB2
- Activates GPR55, TRPA1, TRPV1, and TRPM8
- Cox-2 inhibition

Reviewed in Russo and Marcu, 2017

CBDA: Superior Bioavailability and Efficacy

- CBD demonstrated antiemetic effects at 5 mg/kg; CBDA was effective at 0.0005 mg/kg.
  - Dose–response curve for the antiemetic effect of CBDA was not biphasic, as has been reported for CBD, with potentiation of vomiting at 20–40 mg/kg.

– Rock et al., 2013

- Orally administered CBD was effective at preventing hyperalgesia at 10 mg/kg, while oral CBDA was effective at 0.1 mg/kg.

– Rock et al., 2018

- In a rodent model of the seizure disorder Dravet syndrome, CBD reduced seizures at 100 mg/kg, while CBDA was effective at 10 mg/kg.

– Anderson et al., 2019

Thank you!

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