Central Nervous System Effects of Cannabidiol

Ethan Russo, MD
Founder/CEO: CReDO Science
https://credo-science.com
ethanrusso@comcast.net
Conflict of Interest Statement

Ethan Russo, MD is Founder/CEO of CReDO Science
• https://credo-science.com
• Chief Medical Officer of Andira Pharmaceuticals
• Andira – Bringing Healing to Life
• Senior Medical Advisor of Canurta Pharmaceuticals
• Reversing Chronic Disease with Polyphenols | Canurta®
• Additionally, consultant to many companies and entities

None represent a conflict of interest to this presentation
Cannabidiol and the Endocannabinoid System (ECS)

Brain Sci. 2023, 13(9), 1305; https://doi.org/10.3390/brainsci13091305
11 Sep 2023

Figure 2
The mechanism of action of cannabidiol in the management of epilepsy. (a) Cannabinoid molecular mechanism of action in epilepsy. CBD performs an inhibitory role on FAAT resulting in activation of CB1, CB2, and TRPV1 receptors. Anandamide levels are also increased due to FAAH inhibition. (b) This image represents the type of cannabinoid receptors present in the human endocannabinoid system, i.e., CB1 and CB2, found in varying parts of body. It is a system having a lock and key mechanism with specific functions performed by both CB1 and CB2. CB1 has greater affinity for both THC and AEA as compared to CB2. Abbreviations: CBD: cannabinoid; AEA: anandamide; CB1: cannabinoid receptor1; D2: dopamine receptor 2; FAAH: fatty acid amide hydrolase. TRPV1: transient receptor potential vanilloid 1, THC: tetrahydrocannabinol.
Cannabidiol Neurotoxicity: A Short Story I

IV administration of CBD to rhesus monkeys produced an LD$_{50}$ of 212 mg/kg (Rosenkrantz 1981) [equivalent to 68.4 mg/kg in human], while 90-day oral treatment up to 300 mg/kg [equivalent to 4.8 grams/day in human] produced little change apart from increased hepatic and renal weights.

Intoxication signs in monkeys were only apparent at oral doses 20-50X the IV dose.
Cannabidiol produced no teratogenic effects in mice (Dalterio 1983).

Cannabidiol (in the 4th study of its kind) produced no chromosomal abnormalities in human cannabis smokers (Matsuyama 1981).

A 2018 CDER review of pure CBD to 250 mg/kg in Wistar rat produced minimal toxicity. 210365Orig1s000PharmR.pdf (fda.gov)
Misconceptions About Cannabidiol (Russo 2017)

A tiny amount is enough (actually more is better).

It is not psychoactive (actually anti-anxiety and anti-psychotic).

It is a sedative, disproven (Nicholson 2004): sedation may be operative with high doses, with drug-drug interactions or terpenoid effects, i.e., myrcene.

It turns into THC in the body (Merrick 2016; Russo 2017) (actually upregulates anandamide and the endocannabinoid system (ECS)).
Herkenham et al. (1990) used tritiated CP55,940 to map CB$_1$ receptor density in the brains of human, dog, monkey, rat, and guinea pig.

The CB$_1$ density in the cerebellum of dogs was much greater than that of humans.

Elucidated findings of static ataxia in dogs as bioassay for cannabis potency in early 20$^{th}$ century (Walton 1938).
CBD MOA: Receptors I

- CB receptors (homeostatic regulatory): $CB_1 K_b$ 79 nM as partial agonist; $CB_2 K_b$ 138 nM as partial agonist/inverse agonist?
- TRPV1 (heat/acid/ethanol/capsaicin): $EC_{50}$ 1 µM, $IC_{50}$ 600 nM as agonist
- Glycine receptors (inhibitory neurotransmitter): $\alpha_1 EC_{50}$ 12.3 µM; $\alpha_1\beta EC_{50}$ 18.1 µM as positive allosteric modulators (PAMs)
- GABA (inhibitory) receptors
- GPR55 receptor (putative cannabinoid receptor): $IC_{50}$ 350 nM as antagonist
- $5-HT_{1A}$ (anxiety et al.): 80% displacement at 16 µM as agonist
CBD MOA: Receptors II

- 5-HT$_{2A}$: weak partial agonist
- PPAR$_{\gamma}$ (nuclear receptor affecting gene transcription): IC$_{50}$ 5 µM as agonist
- Opioid receptors: µ receptor EC$_{50}$ 4.38 µM; δ receptor 4.10 µM as positive allosteric modulators (PAM)
- GPR18 receptor (cell migration): agonist 30 µM
- Abnormal-CBD receptor (vasomotor, proliferation): 1 µM as antagonist
Glycine Receptors

• Ionotropic inhibitory receptors working through chloride currents. Caffeine is a competitive antagonist (Duan 2009).
• Abundant in the lamina II of the spinal dorsal horn involved in integration of pain signals.
• CBD acts as a positive allosteric modulator (PAM) at the $\alpha_3$ glycine receptor ($EC_{50}$ 12.3 µM), boosting endogenous glycine with reduction of inflammatory and neuropathic pain (Xiong 2012).
GABA Receptors

- The chief inhibitory receptors of the CNS.
- $\text{GABA}_A$ is ionotropic (ligand-gated ion channels), whereas $\text{GABA}_B$ is a G-protein coupled receptor (GPCR, metabotropic).
- CBD acts as positive allosteric modulator at $\text{GABA}_A$ receptors (Bakas 2017), promoting CNS inhibition to produce anti-anxiety and anticonvulsant effects.
Serotonin-1A Receptor (5-HT$_{1A}$)

- A GPCR that mediates hyperpolarization reducing postsynaptic neuron firing affecting neuromodulation.
- In addition to direct agonism (16 µM) (Russo 2005), it may also be a PAM.
- Overall, effects include benefit on acute migraine (Peroutka 1992), neuroprotection (Pazos 2013), analgesia (Thapa 2019), antidepressant (Zanelati 2010, Linge 2016), anti-anxiety (Blessing 2015), anti-emetic/anti-nausea (Rock 2012).
- Anticonvulsant effects are suggested by reduction of 5-HT$_{1A}$ binding on positron emission tomography (PET) in human temporal lobe epilepsy (Savic 2004, Merlet 2004), and benefits in various animal models.
CBD displaced the agonist tritiated 8-Hydroxy-2-dipropylaminotetralin (8-OH-DPAT) from cloned human 5-HT$_{1A}$ receptor in a concentration-dependent manner (80% displacement at 16 µM).

CBD is an agonist at the receptor as evidenced by increasing $[^{35}\text{S}]\text{GTPgS}$ binding and negative coupling to cAMP production.
PPARγ (Peroxisome Proliferator-activated Receptors)

- Nuclear receptors involved in lipid storage, glucose/energy metabolism, cell differentiation and inflammation.
- PPAR agonists are utilized clinically for hypercholesterolemia, hypertriglyceridemia, insulin resistance, metabolic syndrome and Type II DM.
- CBD activation of PPARγ ($IC_{50}$ 5 µM) produces anti-cancer effects (Chearwae 2008, Ramer 2013), neuroprotection (Hind 2016), decreased AD amyloid plaque (Esposito 2011), decreased gut inflammation (DeFilippis 2011).
GPR55 Receptor

- Endogenous ligand = LPI (L-α-lysophosphatidylinositol), which is increased after seizures → binds to GPR55 → cycle of seizures.
- CBD blocks GPR55 receptor (antagonist) (Whalley et al. 2018), decreasing glutamate, which decreases neuronal excitability and increasing GABA, which promotes neuronal calming.
- GPR55 upregulated in osteoporosis (Idris, 2010).
Excitation of sensory neurons by agonists induces a refractory state wherein fibers do not respond to additional agonist challenge (e.g., acid).

Desensitization is a rapid loss of receptor activity in the presence of an agonist, attributable to a conformational change in TRPV1 (or even neuronal loss), although some attribute this to changes in expression of SP and CGRP (Kissin 2011).

Tachyphylaxis is a diminishing response after repeated administration, reflecting a transition from open (active, susceptible) to closed (resistant) state (Szallasi 1999).
TRPV1 Desensitization I

- TRPV1 agonists may be pungent (capsaicin) vs. non-pungent (CBD)

- An ideal therapeutic agent would be a ligand that:
  1) does not strongly activate TRPV1 acutely to cause pain, but leads to its rapid defunctionalization, and
  2) has a favorable desensitization/pungency ratio (Palazzo 2010)
CBD and TRPV1 Desensitization II

- CBD ($K_i=3 \, \mu\text{M}$) proved as potent as capsaicin ($K_i=2.6 \, \mu\text{M}$) in binding assays (Bisogno 2001).

- CBD (10 $\mu\text{M}$) also desensitized TRPV1 to capsaicin activation, thus “turning down the heat and pain.” (Russo 2016).
TRPV1 Anticonvulsant Effects

- TRPV1 is over-expressed in epilepsy, producing hyperexcitability (Shu 2013).
- CBD may be anticonvulsant through desensitization of TRPV1 via reduction of Ca$^{++}$
- EC$_{50}$ 1 µM; IC$_{50}$ 600 nM (Mecha 2017).
- CBD increases seizure threshold in maximal electroshock model in TRPV1 knockout mice (Gray 2020).
Adenosine Receptors

Involved in cardiac rhythm/circulation, renal blood flow, immune function, sleep regulation, inflammatory diseases, neurodegenerative disorders

- CBD, as a competitive inhibitor ($IC_{50}$ 120 nM) reduces adenosine re-uptake via equilibrative nucleoside transporter 1 (ENT1) (Carrier 2006).
- CBD has neuroprotective effects in mouse hypoxic-ischemic encephalopathy model (Castillo 2010).
- Adenosine concentration is inversely proportional with neuroexcitability (Williams-Karnesky 2013); Adenosine has anti-inflammatory and anticonvulsant effects, upregulated post-ictally, then down-regulated during epileptogenesis.

- CBD 5 mg/kg/d in rats attenuated heroin-seeking behavior reinstated by conditioned stimuli, even 24 h to 2 wks later.

- CBD reversed changes in AMPA GluR1 and CB₁R expression in NAc induced by heroin.

- Authors proposed CBD as treatment for heroin craving and relapse.

- Patients with damage in the insula (e.g., cerebrovascular accidents or trauma) were able to quit smoking tobacco without relapse or urges.

- The insula appears to be a critical neural center mediating nicotine addiction.

- Urge for drugs further localized to insula for cocaine, EtOH, heroin (Naqvi 2009, 2010).
Cannabidiol and Drug Abuse Liability

- 31 cannabis smokers were tested with CBD doses up to 800 mg with or without concomitant smoking (Babalonis 2017).

- CBD was placebo-like on all doses tested and produced no signals consistent with drug abuse liability (DAL).
CBD 600 mg po functionally deactivated the left insula (with a role in addiction) in human volunteers vs. placebo (p<0.01), without accompanying sedation or other psychoactive changes (Borgwardt 2008).
Cannabidiol and Schizophrenia I

- Cannabidiol 800 mg po per day vs. amisulpride in 42 patients for 4 weeks (Leweke 2012).
- Positive and Negative Syndrome Scores (PANSS) were improved in each (p=0.001), but negative symptoms were notably better on CBD (p=0.001) with fewer extrapyramidal AEs (p=0.006), less weight gain (p=0.01) and prolactin elevation (p=0.001).
- Increased AEA levels were associated with decreased psychotic symptoms with cannabidiol (p=0.0012), and with significantly fewer extrapyramidal symptoms (p=0.006), weight gain (p=0.010), and lower prolactin increase (p=0.001).
Cannabidiol and Schizophrenia II

- 45 controls on anti-psychotics vs. 43 on 1000 mg CBD divided BID over 6 weeks (McGuire 2018).
- Positive psychotic symptoms decreased on CBD ($p=0.019$).
- Clinician ratings favored CBD ($p=0.018$).
- Motor speed favored CBD ($p<0.05$).
- Neither patients nor examiners were able to distinguish verum from placebo.
- Positive psychotic symptoms were positively diminished from baseline post-treatment ($p=0.019$).
- Adverse events were actually greater in the placebo group (35 in 15 patients) than CBD (30 in 15 patients).

- RCT in 120 Dravet patients, Epidiolex 20 mg/kg/d vs placebo.
- Median monthly seizure frequency fell from 12.4->5.9 vs. 14.9->14.1 (p=0.01)
- 43% of CBD patients had 50% or more seizure reduction vs. 27% for placebo
- 5% CBD pts. became sz.-free vs. 0% for placebo
- Caregiver Global Impression of Change improved 1 category or better on CBD vs. placebo (p=0.02)
- Adverse events included diarrhea, vomiting, fatigue, pyrexia, somnolence, abnormal liver function tests.

- RCT of 171 patients with intractable seizures 2° LGS over 14 weeks utilizing adjunctive 20 mg/kg/d of Epidiolex (CBD extract) vs. placebo divided BID.
- Median percentage reduction in drop seizure frequency (primary outcome measure) was 43.9% on CBD vs. 21.8% on placebo (*p*=0.0135).
- For the 12-week maintenance period, after titration, the difference between groups was 17.21 seizures/month (*p*=0.0096).

- 44% of CBD patients had frequency reductions of 50% or more in drop seizures vs. 24% of placebo ($p=0.0043$)
- Significantly more CBD patients achieved benefits of 25% or more, or 75% or more seizure reduction.
- AEs were diarrhea, somnolence, pyrexia, decreased appetite and vomiting.
CBD Dose-Response: Pure vs. Extract

In animal studies of analgesia, pure CBD produces a biphasic dose-response curve such that smaller doses reduce pain responses until a peak is reached, after which further increases in dose are ineffective (Gallily 2014).

Interestingly, the application of a full spectrum cannabis extract with equivalent doses of CBD eliminates the biphasic response in favor of a linear dose-response curve such that the botanical extract is analgesic at any dose with no observed ceiling effect (Gallily 2014).
Cannabidiol as AED: Pure vs. Extract

Meta-analysis of 11 studies (N=670), 71% of patients improved with CBD-predominant cannabis extracts vs. 36% on purified CBD ($p<0.0001$) (Pamplona 2018).

50% improvement in seizure frequency was equal and 10% of both groups achieved seizure-free status.

Mean daily doses were 27.1 mg/kg/d for purified CBD vs. 6.1 mg/kg/d. for CBD-rich cannabis extracts, 22.5% of that for pure CBD.

AEs were demonstrably higher in purified CBD vs. high-CBD extract patients ($p<0.0001$).
Cannabidiol References I

Cannabidiol References II

- Dirikoc, S., S. A. Priola, M. Marella, N. Zsürger, and J. Chabry. 2007. 'Nonpsychoactive cannabidiol prevents prion accumulation and protects neurons against prion toxicity', *J Neurosci*, 27: 9537-44.
Cannabidiol References III

Cannabidiol References IV


Naqvi, N. H., D. Rudrauf, H. Damasio, and A. Bechara. 2007. 'Damage to the insula disrupts addiction to cigarette smoking', Science, 315: 531-4.


Cannabidiol References VI

Cannabidiol References VII

Acknowledgements

- Thanks to Bonni Goldstein, MD, and Hunter Land, PhD, for provision of review materials.
- Thanks to Nishi Whiteley and Julie Ermisch for technical assistance.