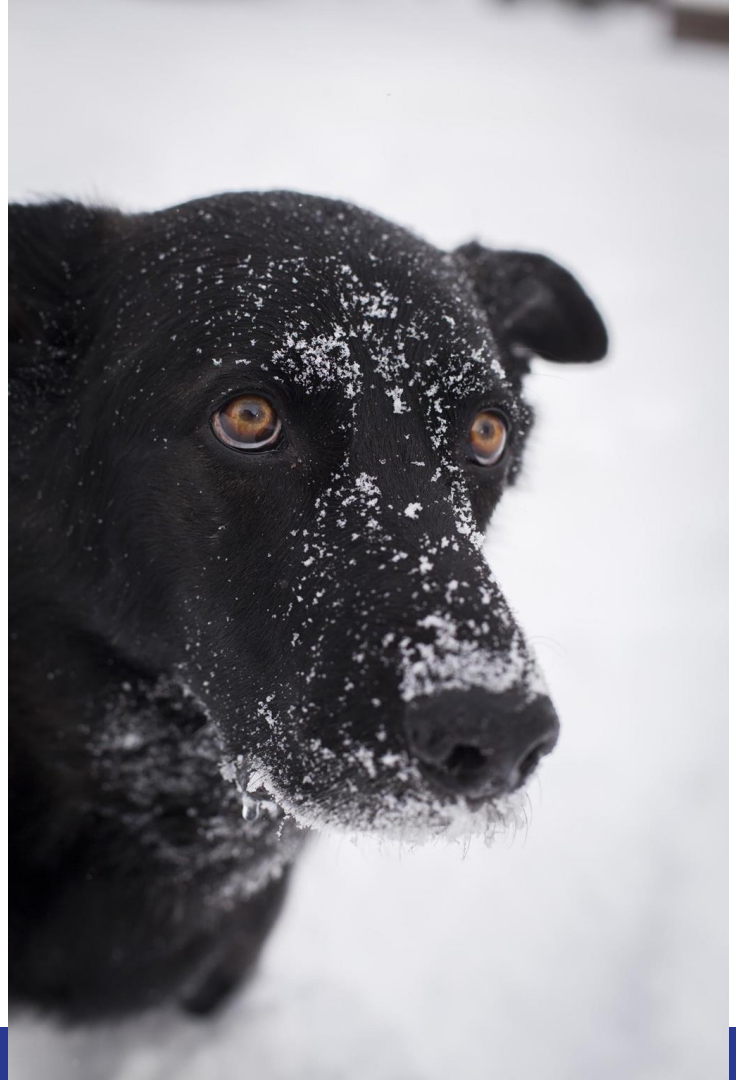
Epilepsy & CBD

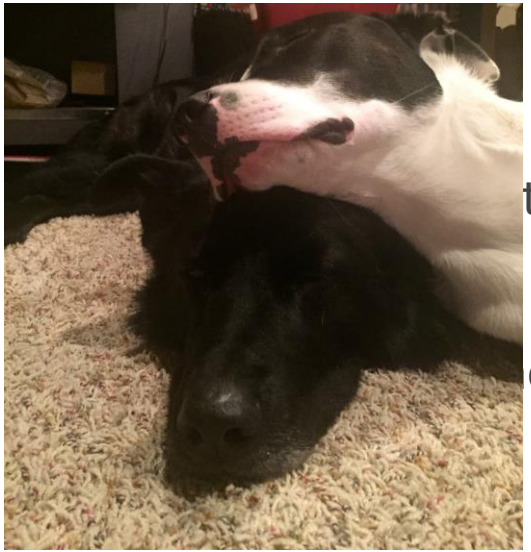
The Chain Ganglion:
Andre H, Danna O, Emma W



Meet Bubba!

Bubba is a 7 year old German Shepherd mix.

He loves long walks,



dinner time,

ticks,

d also...

...he is epileptic!

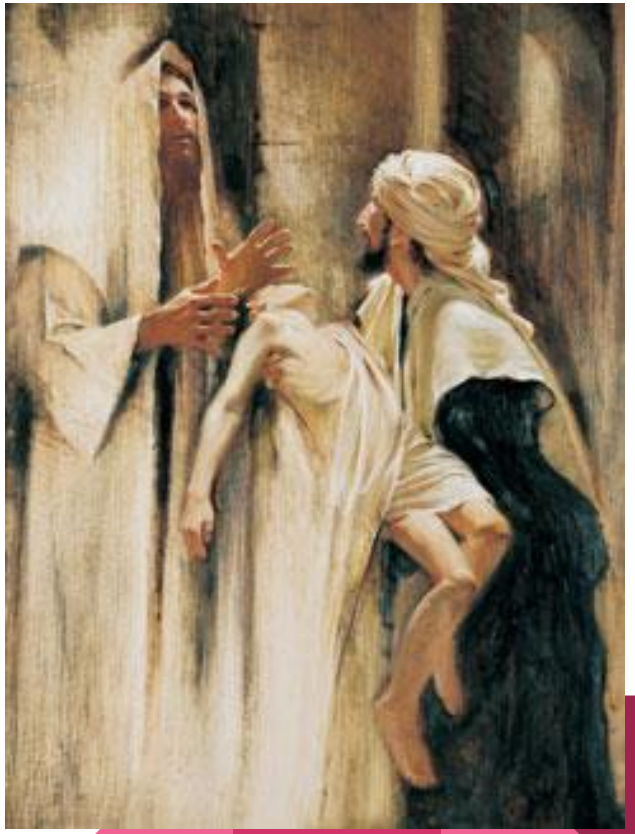
- Idiopathic epilepsy
  - ~60% of epilepsy is idiopathic
- On a regimen of KBr and Phenobarbital
- When he was first adopted he had seizures approximately every 2 weeks, which was much more frequent than we had been told to expect.

After a few months of the frequent seizures, we decided to start him on CBD and he improved almost immediately.

- His seizures became much less frequent (every 14-16 weeks)
- Shorter in duration with faster recovery
- Able to significantly lower the dose of other medications
    - Huge benefit because traditional epilepsy medications are hard on the liver

Ancient Outlook

- Historical perspective on seizures varies by culture
  - The Hammurabi Code (1780 BC) limited the rights of epileptics (marriage, oaths, as slaves); the hand of sin
  - Christian perspective of possession; infection through breath
- Stigma led to isolation furthering stereotypes
- Stigma present today in US laws
  - People with epilepsy were forbidden to marry in 17 states, until 1956
  - Last state repealed in 1980

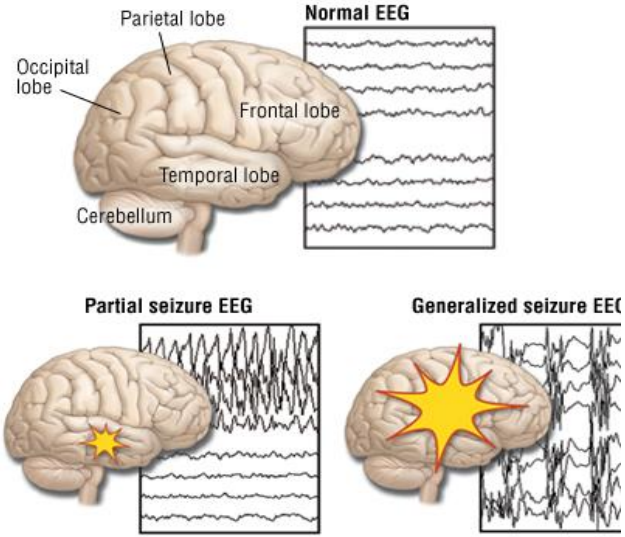


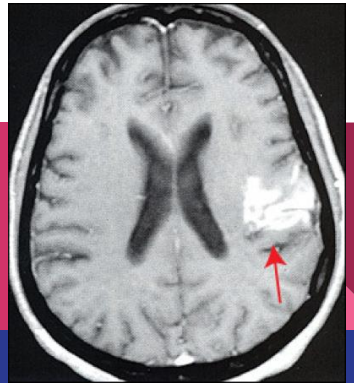
What is epilepsy?

- Epilepsy is defined as a clinical syndrome with recurrent and unpredictable seizures. These seizures can take place without identifiable cause. A cause can only be found in about 1 in 100 people
- Seen mostly in people who are over the age and 60 and young children
- Seizures are moments moments of vigorous shaking and there is no guarantee how long one may last, this can sometimes lead broken bones and other physical injuries

Diagnosis of Epilepsy

- **Electroencephalogram (EEG)**
  - Used to record electrical activity on skull with 21 electrodes
  - Under normal conditions EEG activity in the brain will be low, but depending on the severity of the seizure the activity gets much bigger and more frequent
- **Imaging studies**
  - MRI and CT may be used to find location of a scar or damaged brain tissue.
  - PET scans may be used to examine blood flow





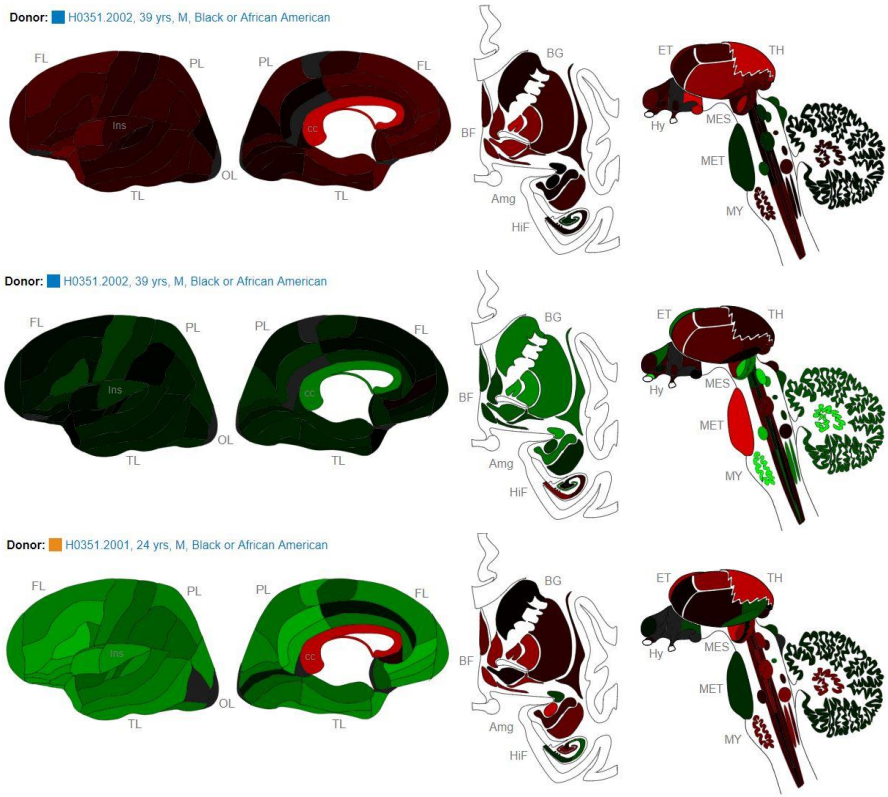
Causes of Epilepsy

The majority of epilepsy is *de novo* and idiopathic. Acquired epilepsy often has an identifiable cause.

- Genetics
- Structural abnormality
- Trauma
- Stroke
- Tumors
- Infectious disease
- Unknown causes

Glutamate and GABA

- GABA plays an inhibitory role
  - Allows Cl^- into the cell and K^+ out of the cell causing hyperpolarization
  - $GABA_a$ ligand gated ion channel and $GABA_b$ a GPCR
- Glu plays an excitatory role
  - Increase membrane permeability for Ca, Na, K
  - AMPA receptors, NMDA receptors, and metabotropic glutamate receptors
- Decrease in GABA and increase in Glu change inhibitory/excitatory balance



Top: $GABA_a$ receptors in brain
Middle: AMPA receptors in brain
Bottom: NMDA receptors in brain

Emma

Types of Seizures

- **Focal seizure:** abnormal electrical activity in only one area of the brain. Can spread and become a generalized seizure.
  - Simple focal
  - Complex focal
- **Generalized seizures:** discharge of neurons in both hemispheres. Most common type of epilepsy, starting in one area and spreading across the entire brain.
  - Tonic-clonic (grand mal)
  - Absence (petit mal)
  - Myoclonic
  - Atonic
- **Status epilepticus:** frequent and long seizures without regaining consciousness. Seizures >5 minutes, and results in 42,000 deaths per year in the US.

Epileptic Triggers

- Fever
- Substance withdrawal (alcohol/benzodiazepines)
- Flashing lights or sounds
- Low blood sugar
- Stress
- Lack of sleep
- Hormones

While triggers may induce seizure, they do NOT cause epilepsy

Genetic Markers of Epilepsy

MANY genetic markers of epilepsy exist, often indicating dysfunction of channels (channelopathies). General themes include:

- **Overactive Na^+ or Ca^{2+} channels**
- **Inactive or underactive K^+ channels**

A number of these genes are **implicated in other disorders**, and are related to other genes involving channel subunits.

Different mutations can cause different types of epilepsy.

Danna

TABLE 1 Known Mutations in Ion Channels and Receptors in Epilepsy

Gene	Protein	Inheritance	Type of seizure	Presumed mode of action
SCN1A	Nav1.1 Na^+ channel, alpha subunit	>150 De novo mutations	Febrile, generalized tonic–clonic, Dravet syndrome	Slow inactivation, broadening of the action potential, persistent current
SCN2A	Nav1.2 Na^+ channel alpha subunit	Autosomal dominant	Benign familiar epilepsy syndrome	Slow inactivation, broadening of the action potential, persistent current
KCNA1	Kv1.1 Shaker related K^+ channel	Autosomal dominant	Focal epilepsy	Slowed repolarization of the action potential noninactivating currents that normally raise the threshold for excitability, loss of function increases excitability
KCNQ2	Kv7.2, M-current cation current	Autosomal dominant	Benign familiar epilepsy syndrome with tonic–clonic seizures	
KCNQ3	Kv7.3, M-current, cation current	Autosomal dominant	Benign familiar epilepsy syndrome	Noninactivating currents that normally raise the threshold for excitability, loss of function increases excitability
HCN1	Hyperpolarization-activated K^+ channel	De novo mutations	Temporal lobe epilepsy	Shortened refractory period, enhanced excitability
KCNMA1	KCa1.1, MaxiK Ca^{2+}-activated K^+ channel	De novo mutations	Generalized epilepsy	Contributes to repolarization, stabilize resting membrane potential, loss of function causes hyperexcitability
KCNT1	KCa4.1, Ca^{2+}-activated K^+ channel	De novo mutations	Generalized epilepsy, nonconvulsing malignant migrating partial seizures of infancy is a rare epileptic encephalopathy	Stabilize resting membrane potential, loss of function causes hyperexcitability
CACNA1A	P/Q type Ca^{2+} channel	Autosomal dominant	Absence seizure	Required for neurotransmitter release, which, if mutated, is altered
CACNA1H	T-type Ca^{2+} channels	Autosomal dominant	Childhood absence seizure	Pacemaker, enhances pyramidal cell bursting
CHRNA4	nACH receptor alpha-4 subunit	Autosomal dominant	Autosomal dominant nocturnal frontal lobe epilepsy	Regulates excitability
CHRNB2	nACH receptor beta-2 subunit	Autosomal dominant	Autosomal dominant nocturnal frontal lobe epilepsy	Regulates excitability
CHRNA2	nACH receptor, alpha-2 subunit	De novo mutations	Autosomal dominant nocturnal frontal lobe epilepsy	Regulates excitability
GABRG2	GABA-A receptor, gamma-2 subunit	De novo mutations	Febrile seizure, absence seizure	Decreases tonic inhibition

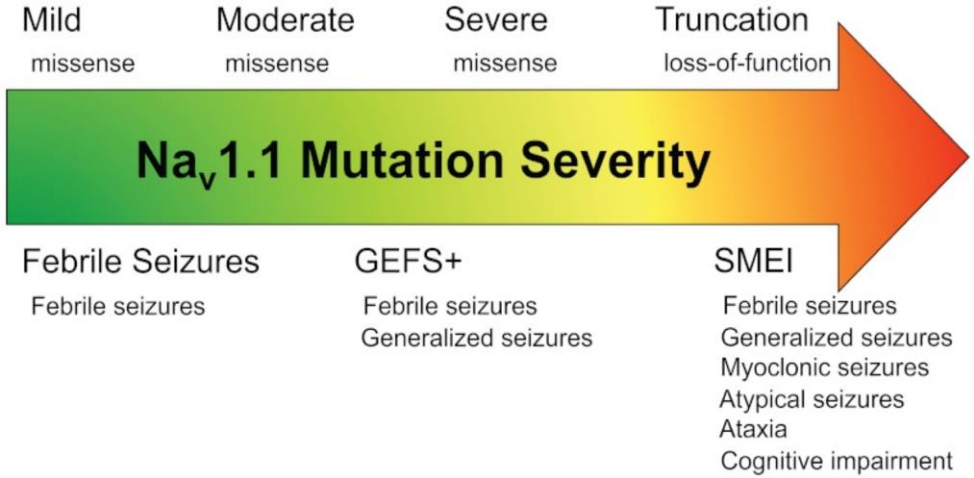
Table established based on data provided in: Lerche et al. J Physiol. *2013; 591.4: 753–764, & Jasper's Basic Mechanisms of the Epilepsies (Internet). 4th ed.*

SCN1A

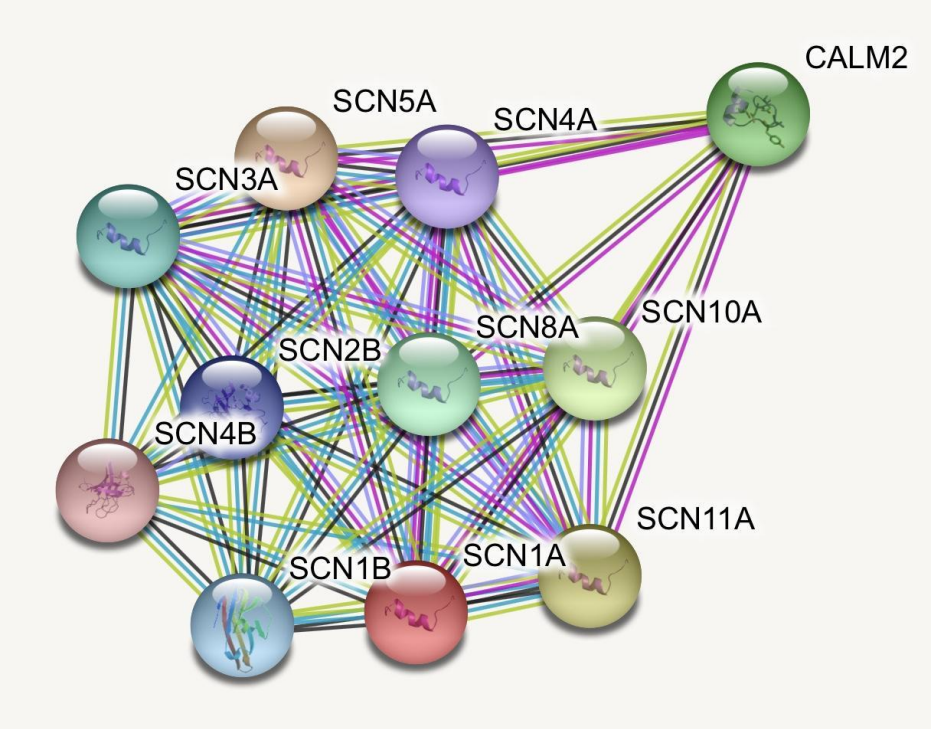
Involved in the formation of Nav1.1 **sodium channel** (alpha subunit)

Implicated in febrile seizures, Dravet syndrome, and generalized tonic-clonic seizures

The type of mutation can determine the severity, ranging from febrile seizures to Dravet syndrome (Severe Myoclonic Epilepsy of Infancy)

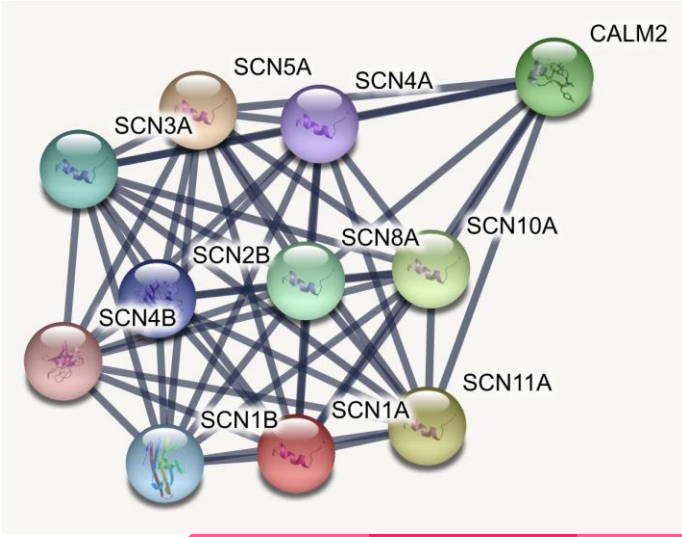


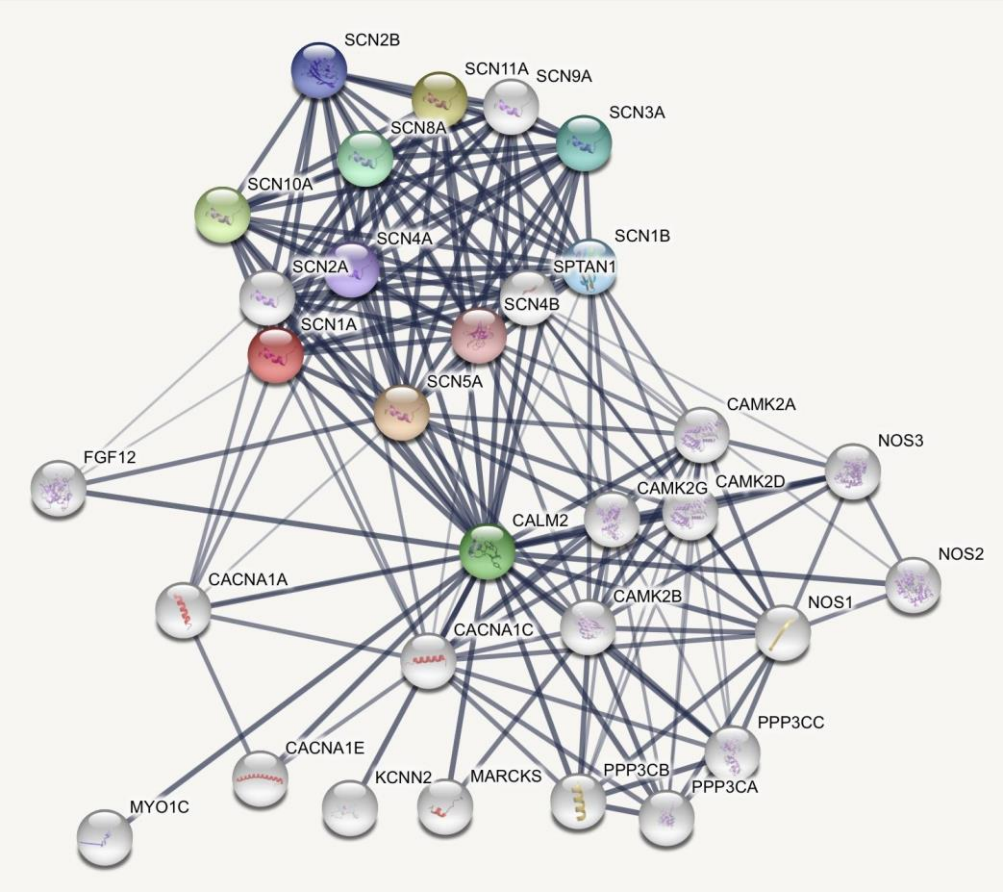
SCN1A



(CALM2 is Calmodulin 2, which mediates a large number of enzymes, ion channels, aquaporins and other proteins by Ca^{2+})

SCN1A is very highly connected to many other genes which also code different protein subunits of sodium channels. Clearly, these **linkages are well established in a variety of methods.**





It's **related with high confidence** to a number of genes apart from sodium channels, including other markers of epilepsy like **KCNN2** and **nitric oxide synthases** (which play a controversial role, seeming that overexpression of NOS is common in patients with epileptic history)

Epilepsy Comorbidity

- Migraine
- Bipolar Depression
- Anxiety
- Autism
- Alzheimer’s Disease
- (and more!)

Former and Current Treatments

- Former Treatments
  - Herbs
  - Surgery
    - Very **invasive**
    - Split brain surgery, temporal lobe surgery (patient HM), hemispherectomy
    - Large and variable side effects
- Current Treatments
  - Anticonvulsants
    - Work to **increase GABA action, as Na+ channel blockers, and/or Ca2+ channel blockers**
    - **Going off medication can make seizures worse**
  - Keto Diet
  - Biofeedback
  - Counterstimulation
  - Cannabidiol

Intro to CBD

- CBD is an abbreviation for cannabinoid
- CBD acts as an anti inflammatory, anticonvulsant, and antioxidant agent
- CBD is being explored in its use to aid treatment of neuroinflammation, epilepsy, oxidative injury, vomiting, and more.

Epilepsy occurs when a flood of excitation creates incessant and abnormal firing of neurons. CBDs modulates the amount of neurotransmitter released, this keeps the brain stable by keeping neurotransmitter levels balanced.

Uses for CBD

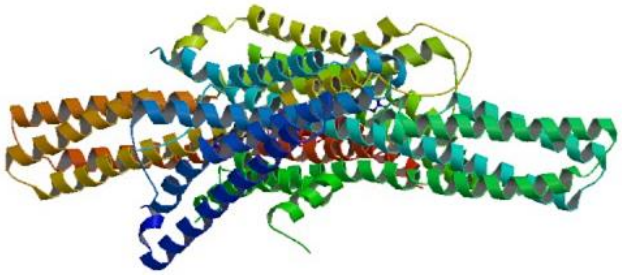
- Relieves pain and inflammation
- Has antipsychotic effects
- Reduces anxiety
- May help fight cancer
- Relieves nausea, a useful antiemetic
- May treat seizures or other neurological disorders
- Lowers incidence of diabetes

Benefits of CBD for Epilepsy

CBD may affect epilepsy through a variety of mechanisms. Some of the pathways may be more direct effects of CBD on receptors and signaling, while others may be indirect mechanisms. Potential mechanisms include:

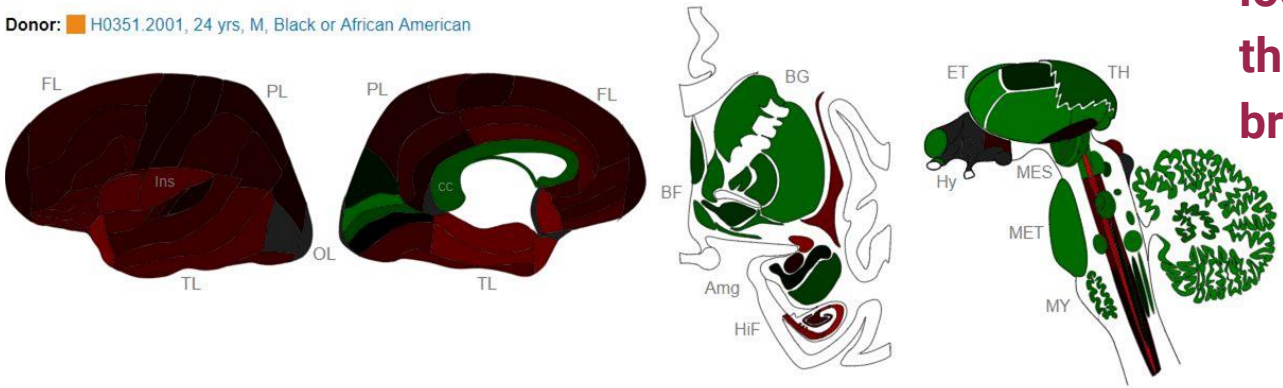
- Direct inhibition of CBD on the hippocampus
  - Via 5HT1A serotonergic autoreceptors?
- Indirect activation of the endocannabinoid system
  - Attenuates synaptic transmission
  - Induction of long term depression
- Modulation of epileptic triggers
  - Anxiolytic properties
  - Improved sleep
  - Hormonal repression
- Alleviation of comorbid symptoms
  - Anxiety, depression, migraine, bipolar, Alzheimer's

Where CBD acts



- CBDs has a **high affinity at $5HT_{1A}$ receptors**
  - $5HT_{1A}$ receptors are GPCRs
- CBD has **low affinity at cannabinoid receptors**.
  - CB1 receptors are located mostly throughout the brain
  - CB2 receptors are located in the spleen and in other immune cells

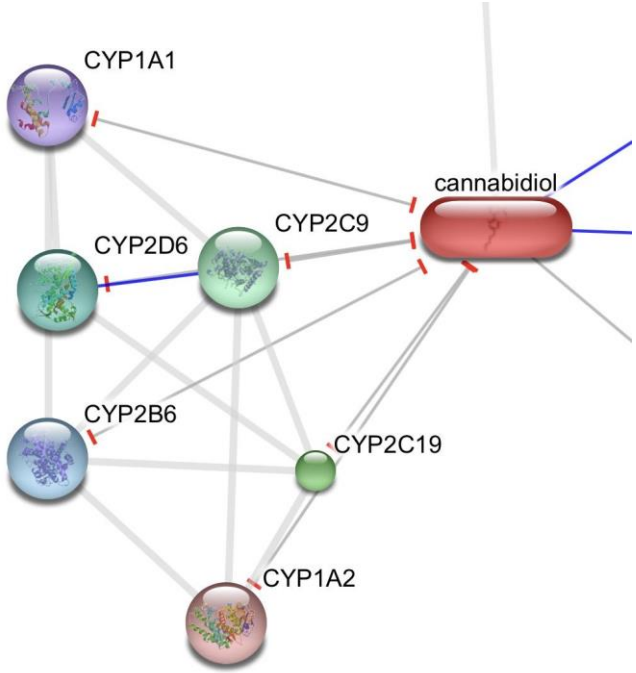
$5HT_{1A}$ receptor (above) and its locations throughout the brain (left)



Where CBD Acts cont.

Cannabidiol also **exerts an inhibitory effect on a variety of cytochrome p450 enzymes.** This is an important consideration in thinking about the effect of CBD in tandem with other medications as it may change drug metabolism.

- Does CBD actually control epilepsy extremely well?
- Does CBD just inhibit the breakdown of other medications, making lower doses more effective?



Indirect Activation of the Endocannabinoid System

CBD is a weak antagonist or negative allosteric modulator at CB1 and a weak agonist at CB2, however it also **inhibits the reuptake and breakdown of anandamide**, an endogenous cannabinoid which does activate CB receptors. CB1 receptors are prevalent in the CNS, and the relevant effects of their activation may include:

- Reducing activity at voltage gated calcium channels
- Attenuation of neurotransmitter release
- Induction of synaptic depression via TRPV1
- Modulation of hyper-corticosteroid secretion (HPA axis)
- Inhibition of excessive arousal in anxiety pathways
- Analgesia
- Increase in amount and quality of sleep

CB1 Distribution

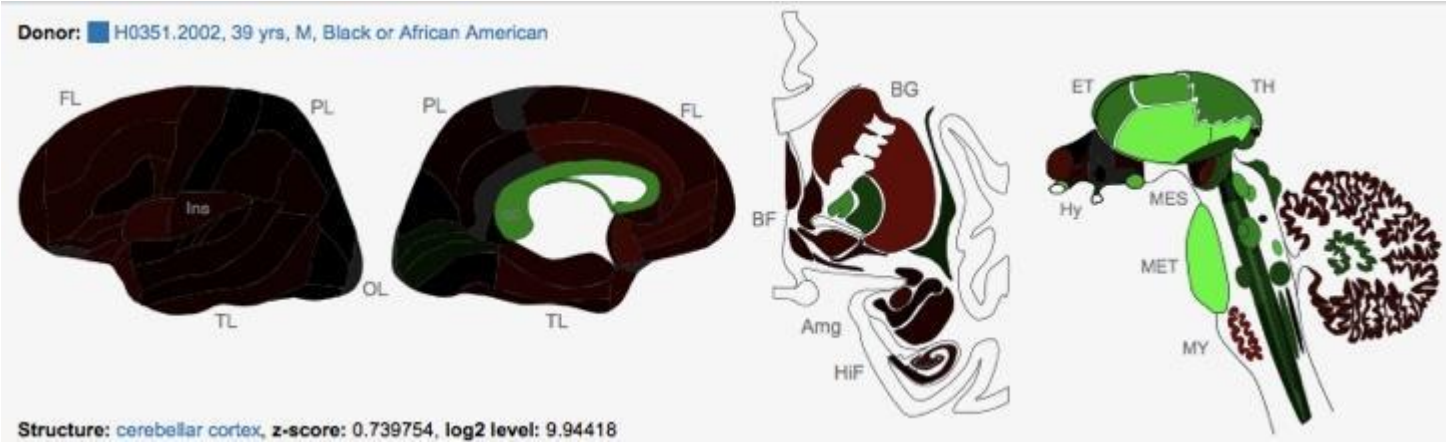
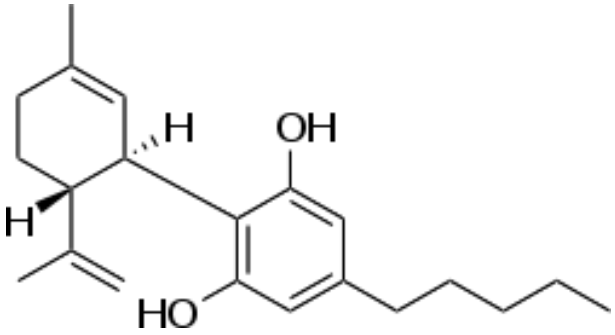


Image credit: Allen Institute.

- Expressed many places (most of the black represents mean amounts, not ‘no data’)
- Fairly similar expression to 5HT1A, but less in brainstem structures.

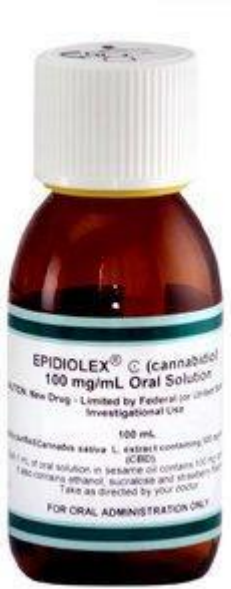
Epidiolex (cannabidiol)



- Patent No: US 9,474,726 B2
- Likely to be the **first ever marijuana-derived medication ever approved** by the FDA
- Federal health advisors panel **unanimously in favor** of the treatment at the meeting on April 19th, 2018
- FDA regulators due to make their decision in late June of this year
- GW Pharmaceuticals
  - Conducted three studies
  - **Positive results from all three**

Epidiolex

- Not meant to replace other CBD on the market, but rather to offer a **purified and regulated source**
- Clinicaltrials.gov has **six active trials** for Epidiolex and four more completed or unavailable trials, however none of them have any results posted here.
- Multiple news sources **report positive results** as described at the committee hearing
- Drugbank does not yet recognize the brand name, but does have some information on cannabidiol
    - A negative allosteric modulator of the CB1 receptor, the most abundant GPCR in the body
    - Activation of 5HT1A serotonergic receptors
    - Antagonizes alpha adrenergic receptors and mu opioid receptors



Epidiolex

From the GW Pharmaceuticals website:

*"**the exact MOA by which CBD produces its anticonvulsant effects is unknown**. Cannabidiol is a structurally novel anti-convulsant. Cannabidiol does not exert its anti-convulsant effects through CB1 receptors, nor through voltage-gated sodium channels. **CBD may exert a cumulative anti-convulsant effect, modulating a number of endogenous systems** including, but not limited to **neuronal inhibition** (synaptic and extrasynaptic GABA channels), **modulation of intracellular calcium** (TRPV, VDAC, GPR55), and possible **anti-inflammatory effects** (adenosine). CBD does not directly bind to, nor activate, CB1 and CB2 receptors at concentrations pharmacologically relevant to its anticonvulsant effect."*

The label use is for epileptic conditions which are severe and treatment resistant, although the introduction of this product in to the market introduces the possibility for off-label prescriptions and increased interest in CBD products.

Studies on CBDs

GW Pharmaceuticals conducted a study to determine if cannabis had any effect on people with epilepsy.

Epidiolex was used during this study. (99% CBD)

❏ **Results:**

- 12 week long study with 214 people ranging in age from 2 to 26.
- All had epilepsy and did not respond well to other forms of treatment
- During this study they found that seizures decreased by 54%

When does 1+1 = 3?

Through the Entourage Effect!

Refers to the potentiating effects of endocannabinoid metabolic byproducts on endocannabinoid function at CB1Rs and CB2Rs

- The sum is greater than the parts
  - The **combined** effects of compounds found in phytocannabinoids is greater than each compounds effect individually
  - CBD combined with THC, tetrahydrocannabivarin, cannabigerol, cannabichromene, and terpenes

Entourage Effect

- CB receptors, THC, and CBD
  - CBD has a low affinity at CB receptors while THC has a much higher affinity
  - The use of dual pathways may contribute to the mechanism of the entourage effect
- Terpenes
  - Considered safe by FDA
  - B-caryophyllene found in pepper, cinnamon, and other spices
    - Selectively binds to CB2 receptor acting as an agonist
      - Similar to THC, the combined effect of terpenes and CBD could result in greater efficacy

Hormonal Implications in Epilepsy

It has been documented that **increases in estrogen can induce seizures in epileptic patients**.

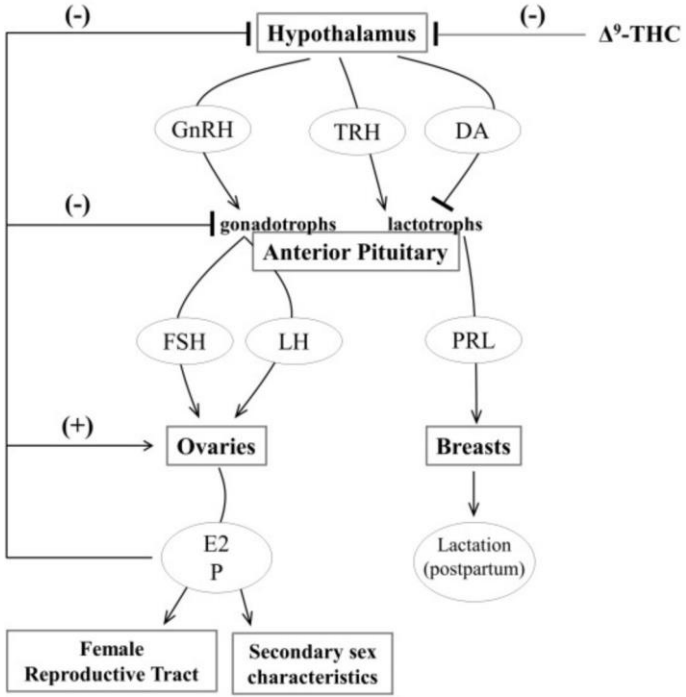
- This may be because higher levels of estrogen lead to higher levels of BDNF
- Increased BDNF in the hippocampus has been shown sufficient to trigger seizure
- Additionally, these same hormonal changes can trigger migraine, a disorder in which BDNF is also abnormally elevated.

CBD shown to reduce estrogen levels

- Evidence suggests this is due to the disruption of hypothalamic GnRH release and pituitary release of Luteinizing Hormone (LH)
    - Impacts both estrogen and progesterone
- Perhaps one way which CBD may help to manage epilepsy
- A reason why cannabis is being explored in the treatment of breast cancer

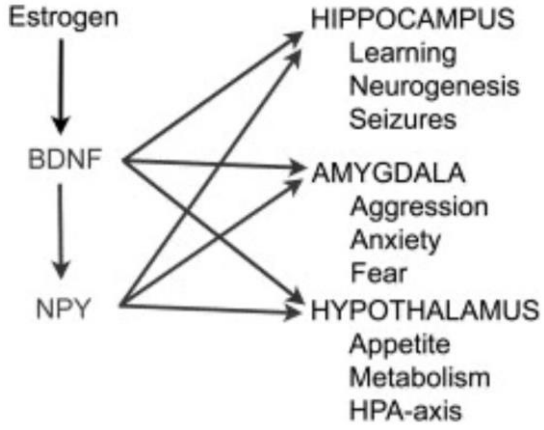
A theory: CBD may indirectly repress BDNF, thereby decreasing hormonally-triggered seizure?

Hormones cont.



Brentz, 2016

- Left diagram shows the (female) HPG axis Depicts only THC effects on the system
- **CBD exerts inhibitory effects on both the hypothalamus and anterior pituitary**
- Right diagram shows estrogen's role in a variety of neural processes



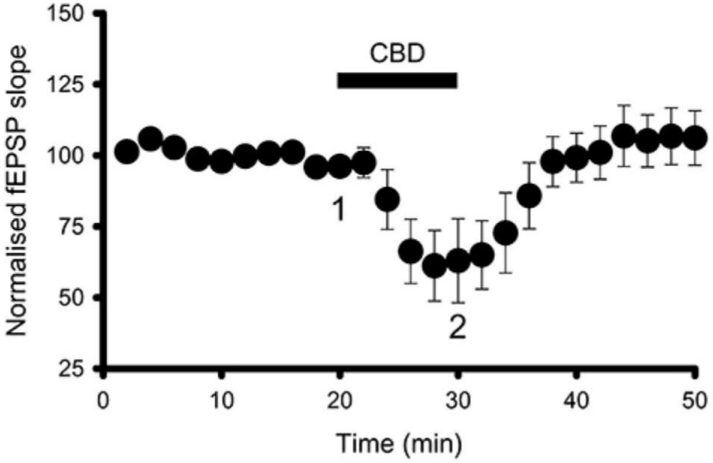
Scharfman and MacLusky, 2006

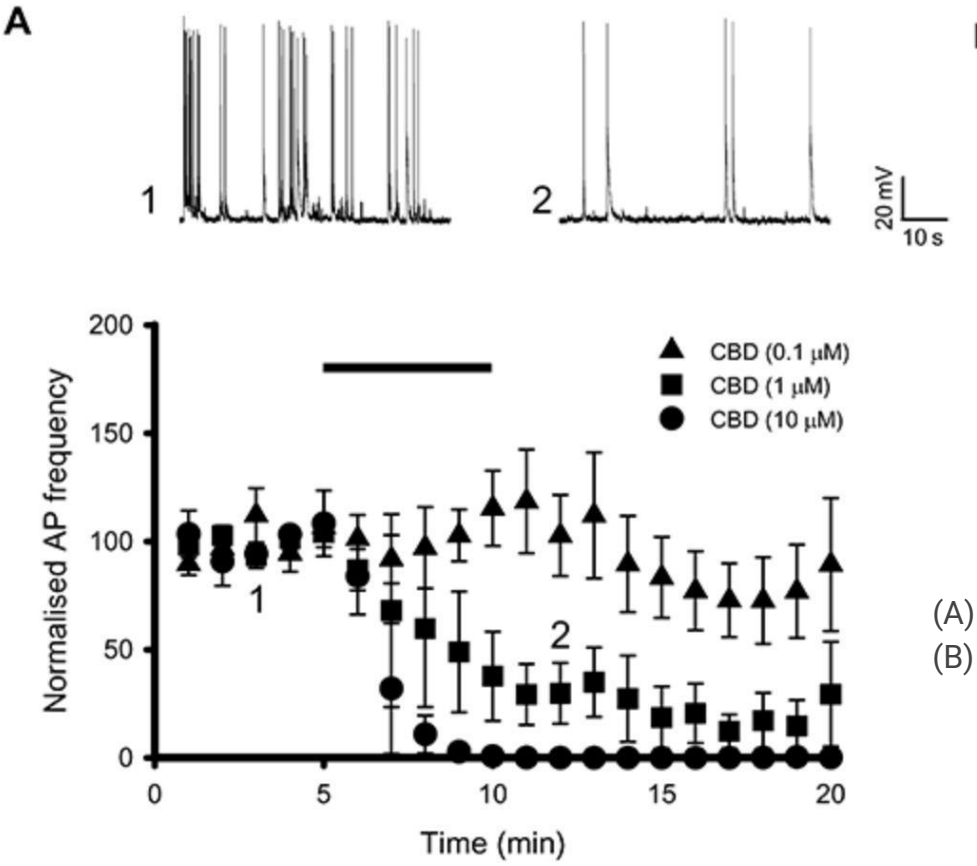
Inhibition - Ledgerwood et al., 2010

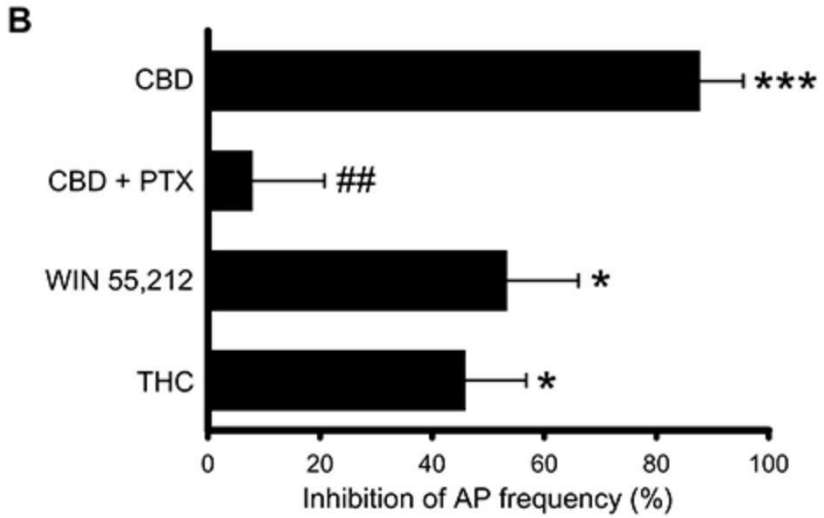
- **CBD is shown to inhibit synaptic transmission in hippocampal slices**
  - In many forms of epilepsy, seizures originate in the medial temporal lobe, an area that includes the hippocampus. General seizures continue to spread across the entire brain
- **Experiment suggests CBD reduces synaptic transmission in hippocampal in vitro through $5HT_{1A}$ activation and indirect CB1 activation**
  - Agonist at $5HT_{1A}$
    - Inhibits Ca_v3 subfamily of calcium channels
    - Modulates intracellular calcium levels
  - Weak antagonist at CB1
  - Weak inverse agonist at CB2

Inhibition cont.

- **Cannabidiol reduces spontaneous action potential frequency in cultured hippocampal neurons**
  - CBD was without effect on the resting membrane potential at all concentrations tested
  - Effects through Gαi GPCRs
  - Direct activation of $5HT_{1A}$ receptors + indirect activation of CB1 receptors (via anandamide)
  - $5HT_{1A}$ receptor antagonism shown to block anxiolytic effects of CBD



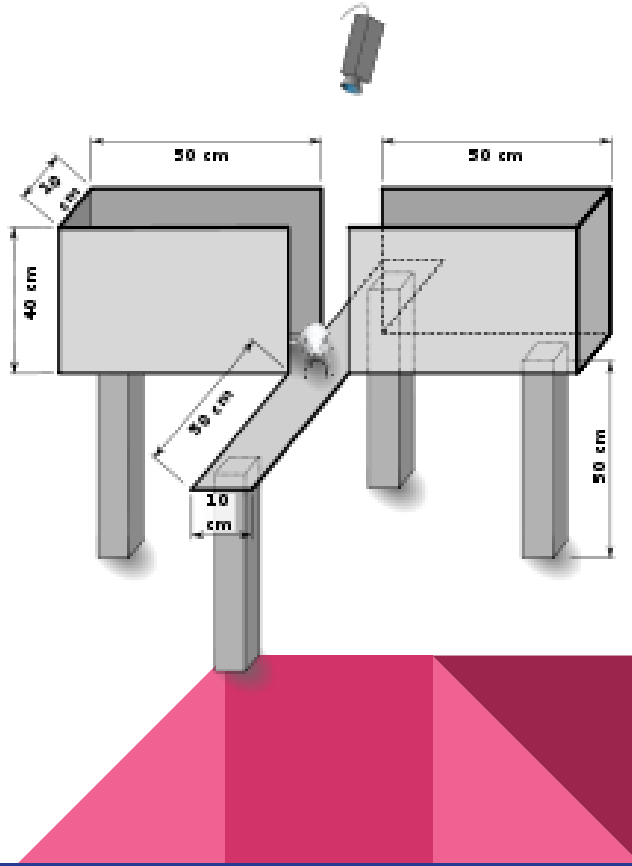




(A) CBD reduces firing frequency in dose-dependent manner
(B) CBD inhibited AP frequency more than CB receptor agonists, and effect was diminished by Pertussis toxin, which is a Gαi protein uncoupler.

Anxiolytic Properties

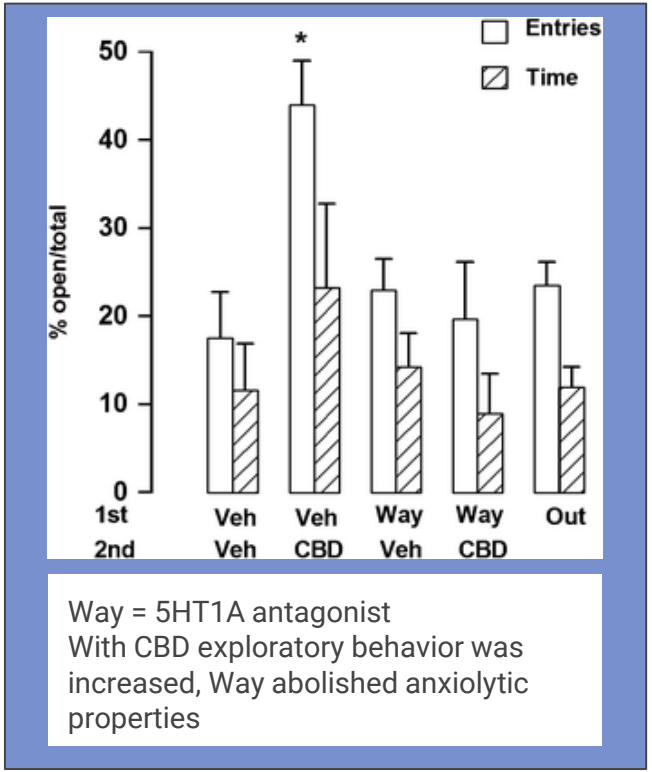
- **Stress and lack of sleep are triggers of epileptic seizures**
- In rats the elevated plus-maze model is used to trigger anxiety
  - Treatment with **CBD doses of 2.5, 5.0 and 10.0 mg/kg significantly increased the entry ratio** (open/total number of entries)
  - This increase is seen as **CBD working as an anxiolytic**
  - CBD at a dose of 20.0 mg/kg was no longer effective
  - None of the doses of CBD used changed total number of entries instead the raito to open arms
    - **Change in entries would indicate change in exploratory effect**



Anxiolytic Properties cont.

Campos and Guimarães, 2008

- $5HT_{1A}$ is a serotonin autoreceptor located on the cell bodies of serotonergic neurons. Its activation attenuates neural firing.
  - CBD is an agonist at $5HT_{1A}$
    - Suggested mechanism by which it mediates anxiolytic properties
  - Cannula aimed at dlPAG with CBD solution in elevated plus maze
  - $5HT_{1A}$ receptor antagonism blocks anxiolytic effects of CBD
  - CB1 antagonism produced no effect on anxiety



Way = 5HT1A antagonist
With CBD exploratory behavior was increased, Way abolished anxiolytic properties

Exploration of CBD in Other Disorders

- TBI
- Migraine
- Bipolar Depression
- Anxiety
- Multiple Sclerosis
- Cancer
- Chronic pain/inflammation
- Diabetes

A number of these **disorders being treated with CBD share genetic markers in common with epilepsy!** For example: SCN1A, ATP1A2, CACNA1A: epilepsy, migraine, bipolar

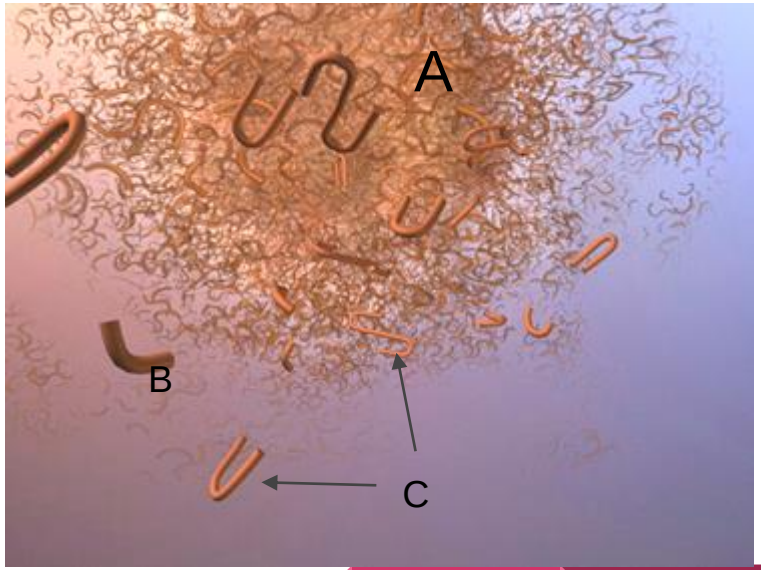
As time passes, CBD will probably be more thoroughly explored in a number of other disorders with related mechanisms.

On the other hand, cannabis use (though not CBD specifically) has been implicated in schizophrenia and psychotic disorders in at-risk individuals

- appears more likely that THC is responsible for those effects

Cannabidiol and Amyloid β Plaques

- Alzheimer's is often accompanied by seizures
- β amyloid derived from the fatty membrane surrounding nerve cells
  - **Clump together to form plaques**
  - Block cell signaling and result in immune response
- Positive correlation to these plaques and Alzheimer's
- The smaller **oligomers** are theorized to be **more harmful** due to their ability to move throughout the brain to cause **more damage**

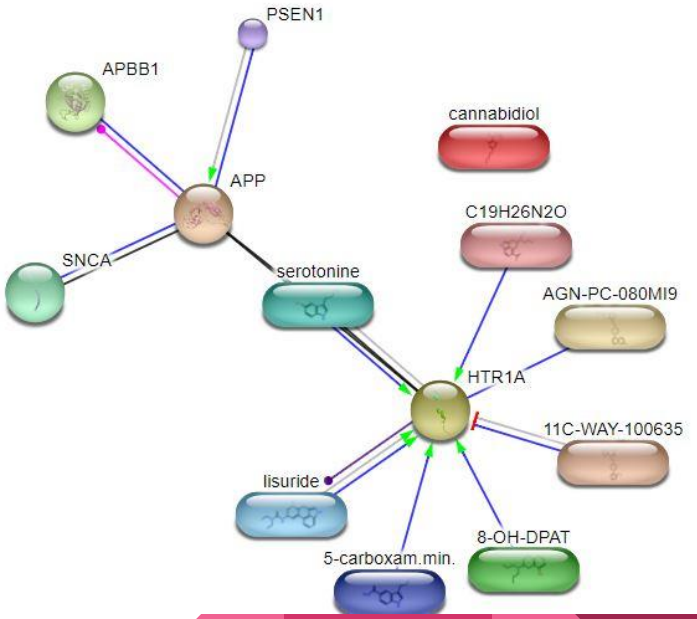


A) β amyloid
B) β amyloid plaques
C) oligomers

Cannabidiol and Amyloid β Plaques

- CBD has a high affinity for $5HT_{1A}$ receptors
- These receptors interact through serotonin to **inhibit Amyloid precursor protein**

- **Cannabidiol reduced neuroinflammation in mice injected with Aβ.** iNOS and IL-1β expression and release were inhibited
  - Limited conclusions can be made due to the small amount of research done



Interactions between 5Ht1a and Amyloid precursor protein

Drawbacks to CBD

- **Appropriate dosage** is still poorly understood
  - Many different factors to consider (strains, ratios, etc)
- Many **untrustworthy retailers** of the product
  - Especially in states where marijuana is still criminalized
  - 3rd party testing is important
- Possible **drug interactions**
  - Liver enzyme inhibitor, changes the appropriate dose of other drugs
- **Widespread** effects
  - CBD seems to act on many different areas of the brain and body
  - Potential unintended consequences such as decreased fertility
- Accessibility related to the **legality** of cannabis in general

In Summary…

- Current epilepsy medications have many **poor side effects** and don't always adequately manage epilepsy.
- CBD has **little affinity at CB1 and CB2** receptors, an **agonist** at **5HT1A** receptors, and helps **prevent the metabolism and reuptake** of endogenous cannabinoids
- The **exact mechanisms** by which CBD produces anticonvulsive effects are **unknown**
    - Could be **many different mechanisms**: reducing effects of epileptic triggers and/or changing neuronal excitability
- Epilepsy has **overlap with many other disorders**, and preliminary results have suggested efficacy of CBD in many of them
- CBD seems like **novel and effective antiepileptic drug** (AED), especially for poorly controlled, severe, and treatment resistant forms of epilepsy

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Thanks :)