Cannabis

PSYC 475 Thursday March 22, 2018 & Thursday March 29, 2018
Guest Lecturer-Haley Vecchiarelli

Lecture Outcomes

Lecture 1-Thursday, March 22, 2018

- Distinguish between endogenous cannabinoids, phytocannabinoids and synthetic cannabinoids
- Describe the effects of cannabinoids interacting with cannabinoid receptors
- Describe how cannabinoids are metabolized
- Analyze the effects of cannabinoids on behaviour and physiology
- Evaluate the efficacy of using *cannabis* (and cannabinoids) for medical treatment

Lecture 2-Thursday, March 29, 2018

- Summarize the history of *cannabis*
    - Outline racialized factors affecting legalization in Canada and US
- Analyze the factors affecting rate of *cannabis* use
- Summarize adverse effects of cannabis use
- Describe the consequences of cannabis use disorder
- Compare pros and cons of *cannabis* legalization in Canada

Cannabinoids—Phytocannabinoids, Endocannabinoids and Synthetic cannabinoids

Content Warning

Racialized language

The next slide contains discussion of racialized language and terms related to *cannabis*.

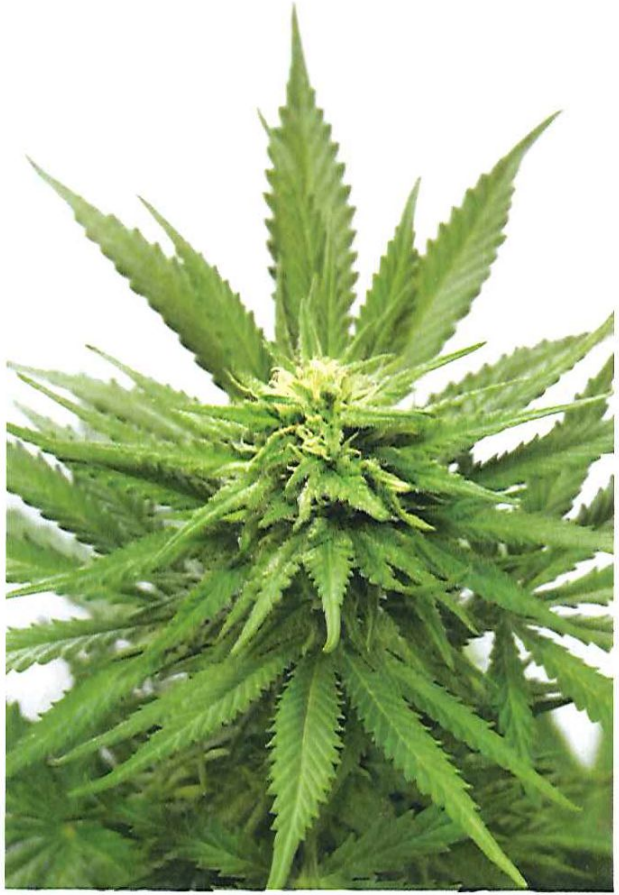
Terminology—*Cannabis* versus Marijuana

- Marijuana is not inherently racist
  - Term brought by Mexican immigrants to USA to describe *cannabis*
- However, term has become racialized
  - In early 20th century, term was weaponized by Harry Anslinger to stir up xenophobia, stigmatization and a racial panic over *cannabis* so it could outlawed in US
- *Cannabis* is a broader, more accurate term to refer to anything related to the plant

Cannabis plants

- Cannabinoids are derived from the *Cannabis* (hemp) plants
  - *Cannabis indica* and ***sativa***
- Male and female plants
  - Male plants are taller and have thicker stems and fewer leaves
  - Female plants are shorter and have more extensive branching and leaf structure
    - Flowers contain high density of the glands that produce cannabinoids
- Produces hundreds of phytocannabinoids

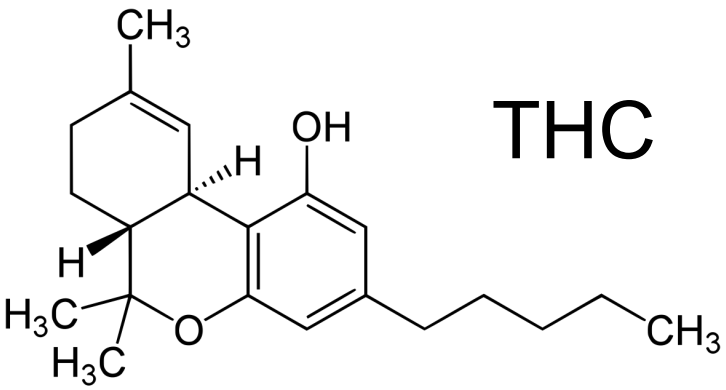
Figure 14-1 A female cannabis plant in flower.



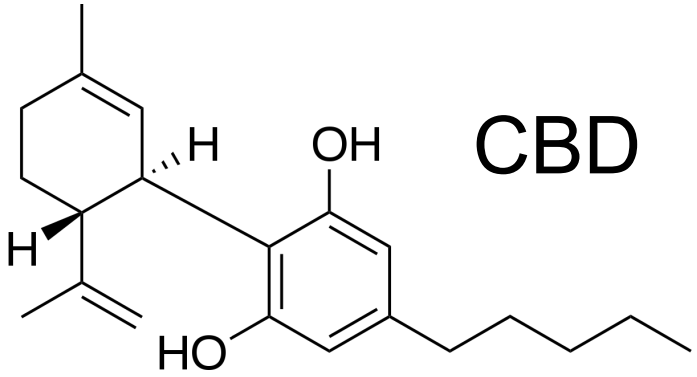
Fotolia

Phytocannabinoids

- Hundreds of phytocannabinoids produced by the *Cannabis* plants
- Structurally similar, lipid molecules
- Two main, most abundant
  - Delta-9-tetrahydrocannabinol (THC)
    - Psychoactive
    - Identified in 1964
  - Cannabidiol (CBD)
    - Non-psychoactive



THC



CBD

Cannabinoid Preparations

- *Cannabis*
  - Smoked, baked or vaped
- Bhang
  - Dried plant material (minus resin), consumed orally, low potency
  - Used in social and religious festivals
- Ganja/Sinsemilla/Skunk
  - Made with buds of female plants with resin, usually smoked
- Hashish/Charas/Resin
  - Dried resin from the top of female plants by hand rubbing or sifting
- Hash Oil
  - Prepared by boiling plant material or resin in alcohol

Cannabis Potencies

- Average THC content in *Cannabis*
  - 1960's—1.5 % THC
  - 1980's—3-4 % THC
  - 1990's—5 % THC
  - 2008—8-9 % THC
  - 2013—12.6 % THC
  - Currently in Colorado average is 18.7 % and in Netherlands is 15-16 %
- *Cannabis* is potentially capable of producing plants with up to 54 % THC
- Potent strains have always existed, but selective breeding and cultivation have yielded THC with rising levels

Cannabis Potencies

- Sinsemilla preps have average THC content of 15 %
  - But can be increased by cross-breeding and hydroponics
- Resin preps have approximately 30 % THC content
- Hash oil has seen largest increase in potency, averages 50 % THC content, but can be up to 80 %

Cannabis Potencies

- CBD content averages 0.4 %
  - Has been relatively stable over time
- *Indica* plants tend to have higher CBD content than *sativa* plants

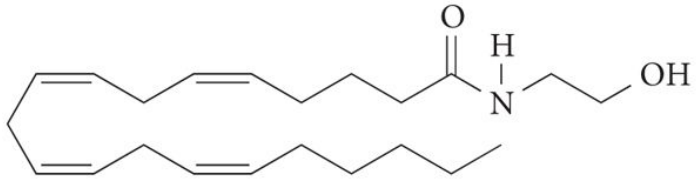
Overall trend in potencies to increase THC and increase THC/CBD ratio

Extracted Cannabinoids

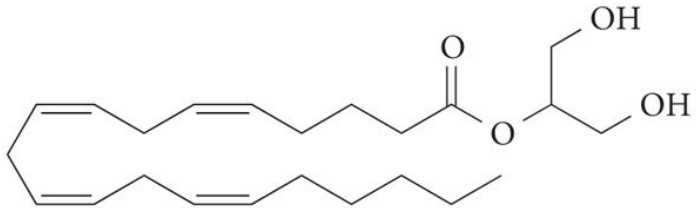
- Sativex (nabiximols)
  - Oral spray
  - 1:1 THC and CBD + other phytocannabinoids
  - Used to treat pain symptoms
  - Side effects include dizziness, headaches, fatigue, drowsiness, nausea and diarrhea
  - Currently approved for use in UK, Spain, Sweden, Denmark, Germany, Canada and New Zealand

Endocannabinoids

- Two arachidonic acid derived lipid signalling molecules
  - N-arachidonoyl ethanolamide; anandamide (AEA) (1992)
  - 2-arachidonoyl glycerol (2-AG) (1995)
- Almost all cell types have ability to synthesize endocannabinoids



Arachidonoyl ethanolamide

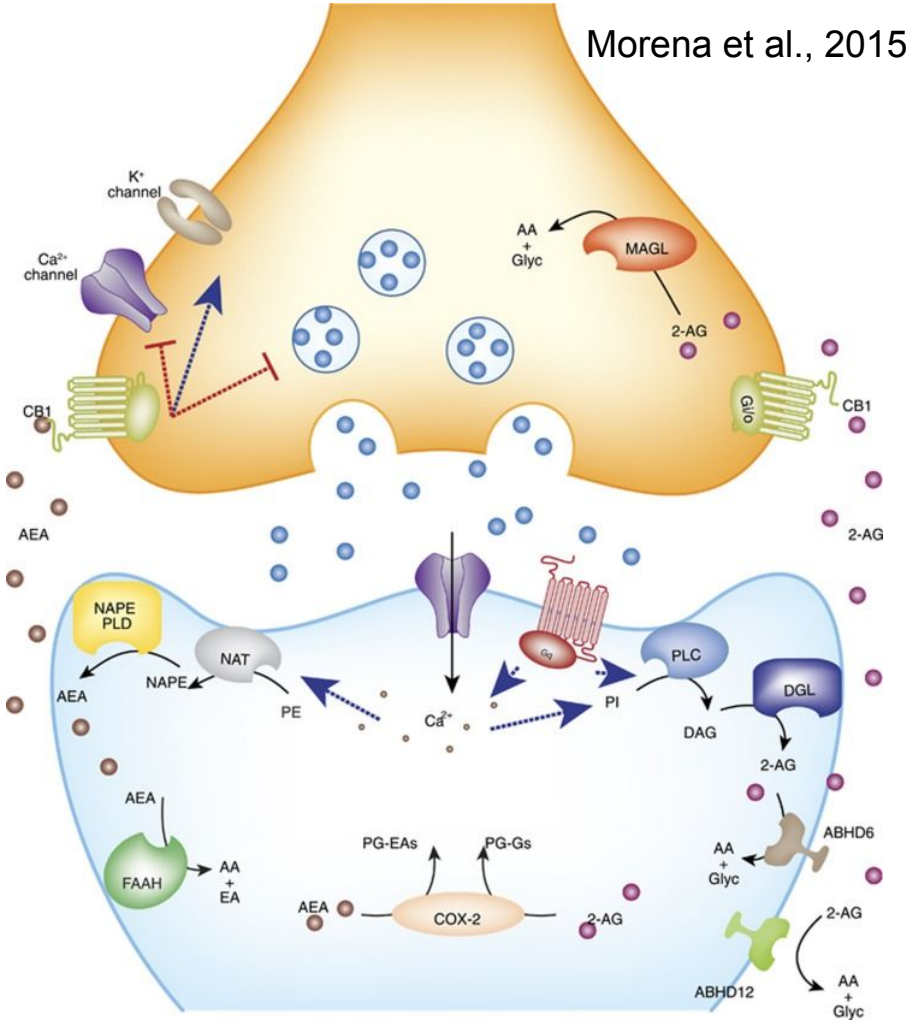


2-Arachidonoyl glycerol

Nature Reviews | Neuroscience

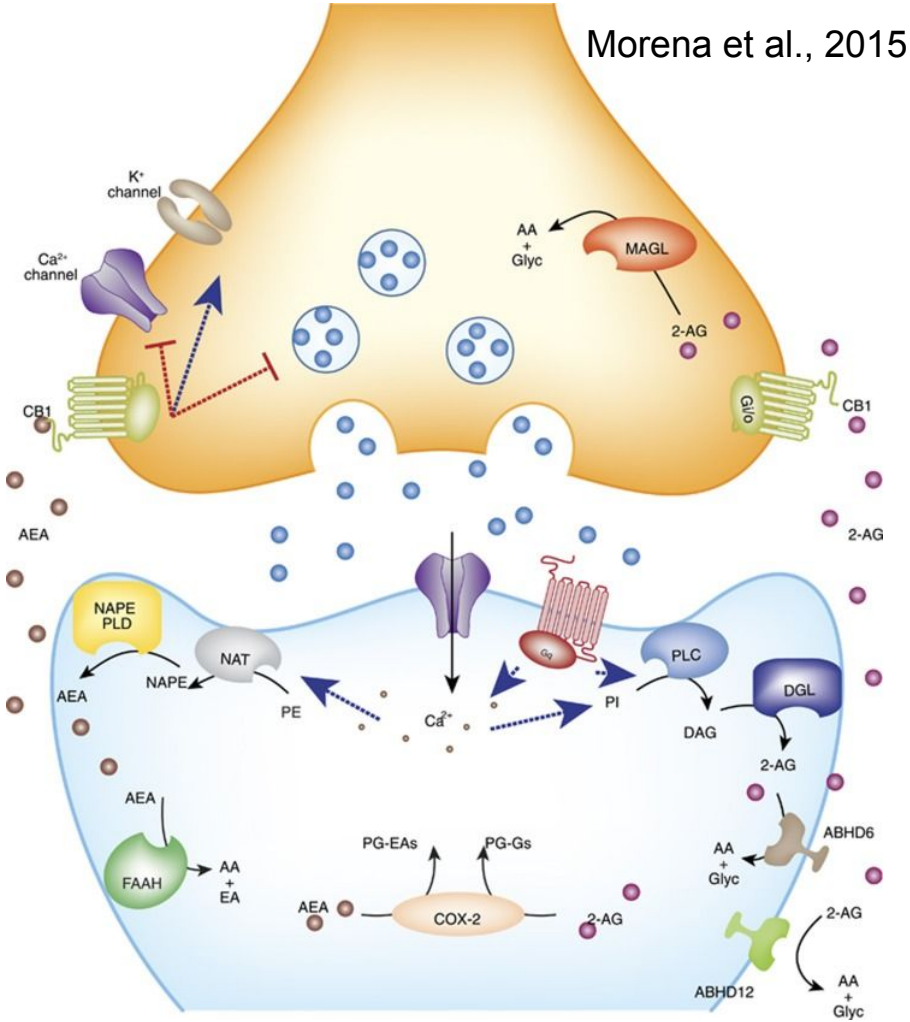
Endocannabinoid System

- AEA
  - Synthesized by NAT/NAPE-PLD from phosphatidyl-ethanolamine (PE)
  - Metabolized by FAAH (fatty acid amide hydrolase) into arachidonic acid and ethanolamide and COX-2 into prostaglandin-ethanolamides



Endocannabinoid System

- 2-AG
  - Synthesized by PLC/DAGL from phosphoinositide (PI)
  - Metabolized by MAGL, ABHD6/12 to arachidonic acid and glycerol and COX-2 to form prostaglandin-glycerols



Synthetic Cannabinoids—Medicinal/Research

- Nabilone (Cesamet) and dronabinol (Marinol)
  - Fully synthetic THC isomers
  - Used in treatment of AIDS-related anorexia and wasting and to ease chemotherapy-induced nausea and vomiting
  - Side effects include alterations in mood
- Cannabinoid receptor agonists
  - Often structurally different than phytocannabinoids, but act on same receptors
  - Potent, high affinity
- Cannabinoid receptor antagonists (Rimonabant)
  - Weight loss tool
  - Pulled off market because of increased suicidality

Synthetic Cannabinoids—Recreational

- Original ones were K2, Spice, Kronic (now 150+)
- Mirror chemical composition of synthetic agonists
  - Many not tested, so behavioural, psychological, pharmacokinetic and toxicological profiles are not known
- Although called synthetic *cannabis*, most contain no *cannabis* material
  - Instead synthetic compounds are sprayed over other plants (some of which have psychotropic properties)
- Problems
  - Amount and variety of synthetic cannabinoids varies (including on the plant products)
  - Laced with other compounds (including PCP or rat poison)

Summary

Phytocannabinoids, Endocannabinoids and Synthetic Cannabinoids

Phytocannabinoids are derived from the *Cannabis* plants (two main, THC and CBD).

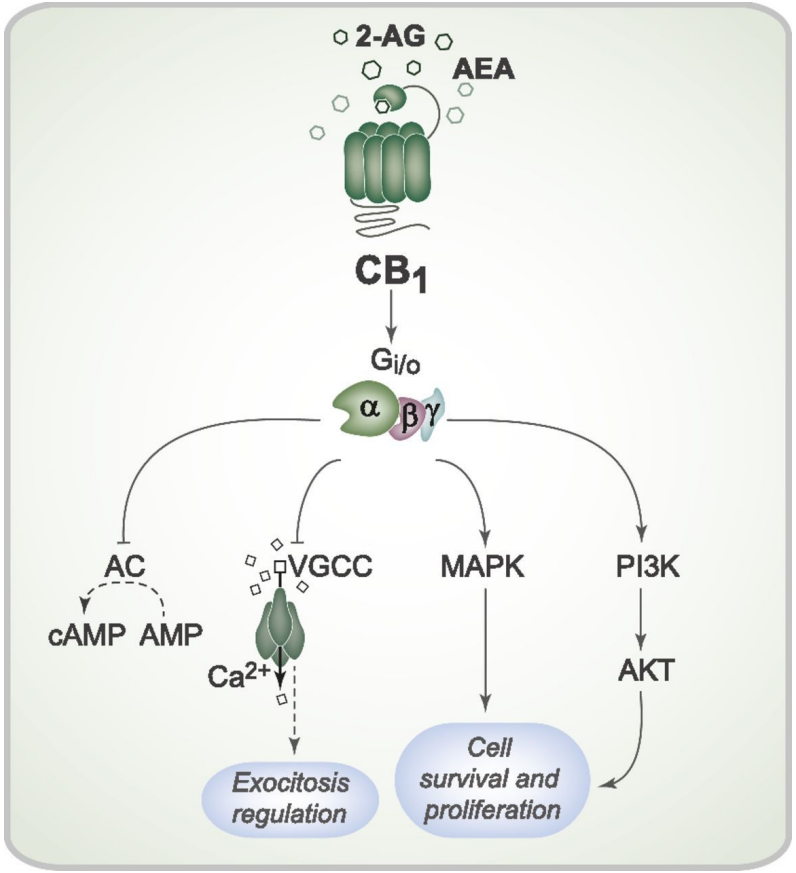
Endocannabinoids are produced by the body (two main, AEA and 2-AG).

Synthetic cannabinoids are human made, and resemble phytocannabinoids, endocannabinoids or are synthetic agonists of the cannabinoid receptor.

Cannabinoid Receptors

Cannabinoid Receptors

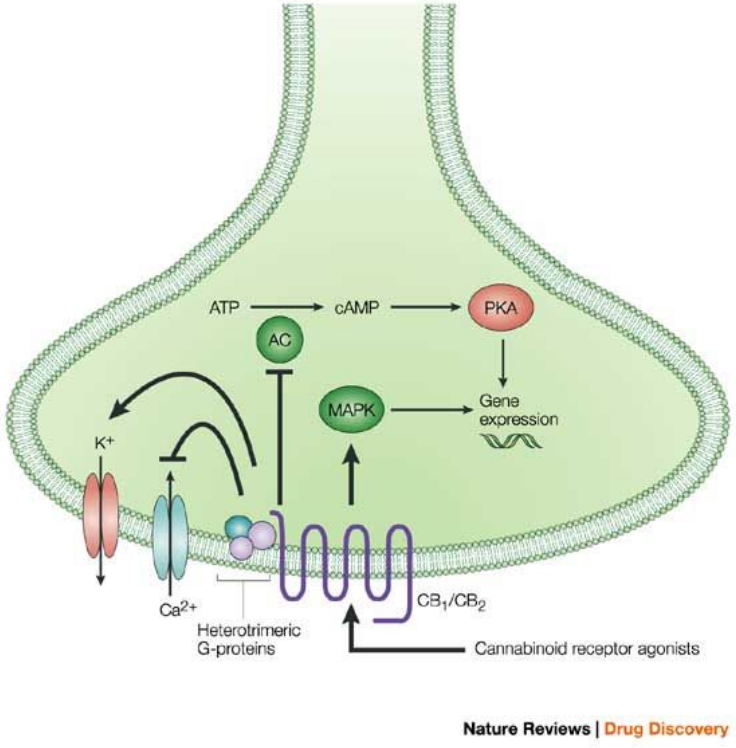
- CB1/2 Receptor
  - G-protein coupled receptor
    - $G_{i/o}$
  - Upon activation
    - Decreases intracellular adenylate cyclase (AC) and cAMP
    - Increases MAP kinase
    - Activate K^+ channels
    - Inhibit voltage-gated Ca^{2+} channels



Olmo et al., 2016

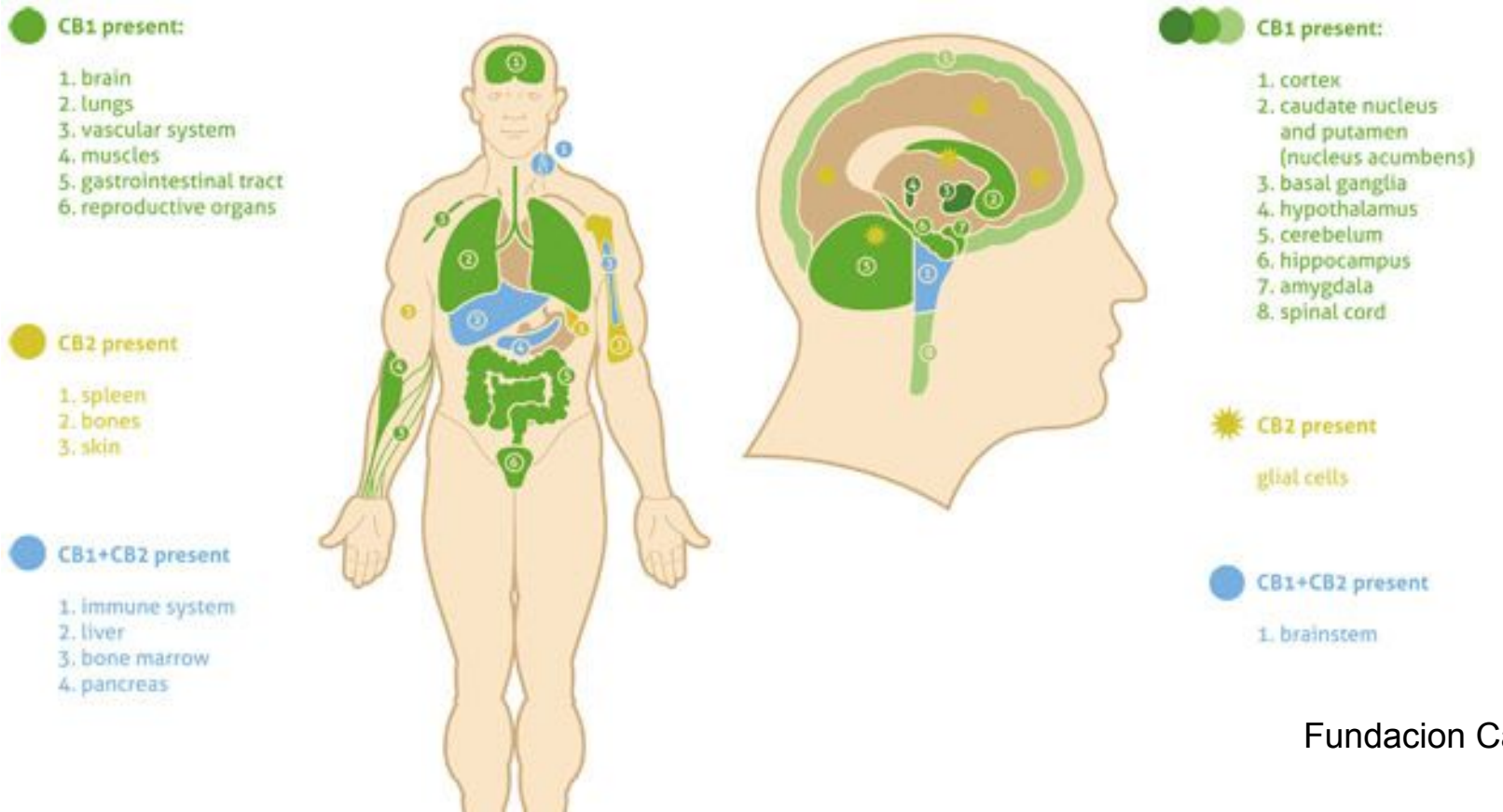
Cannabinoid Receptor Type 2

- CB2 Receptor
  - G-protein coupled receptor
    - $G_{i/o}$
  - Upon activation
    - Decreases intracellular adenylate cyclase (AC) and cAMP
    - Increases MAP kinase
    - Activate K^+ channels
    - Inhibit voltage-gated Ca^{2+} channels



Di Marzo et al., 2004

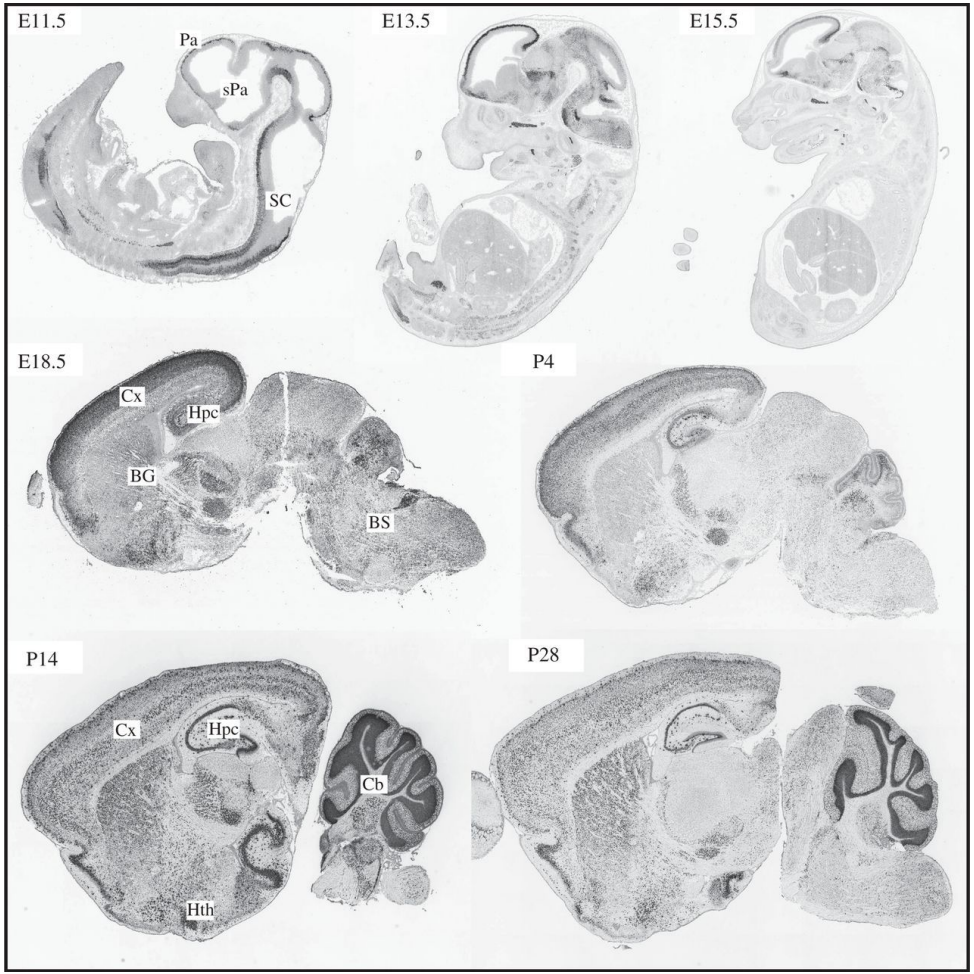
Cannabinoid Receptor Distribution



Fundacion Canna

CB1 Brain Expression

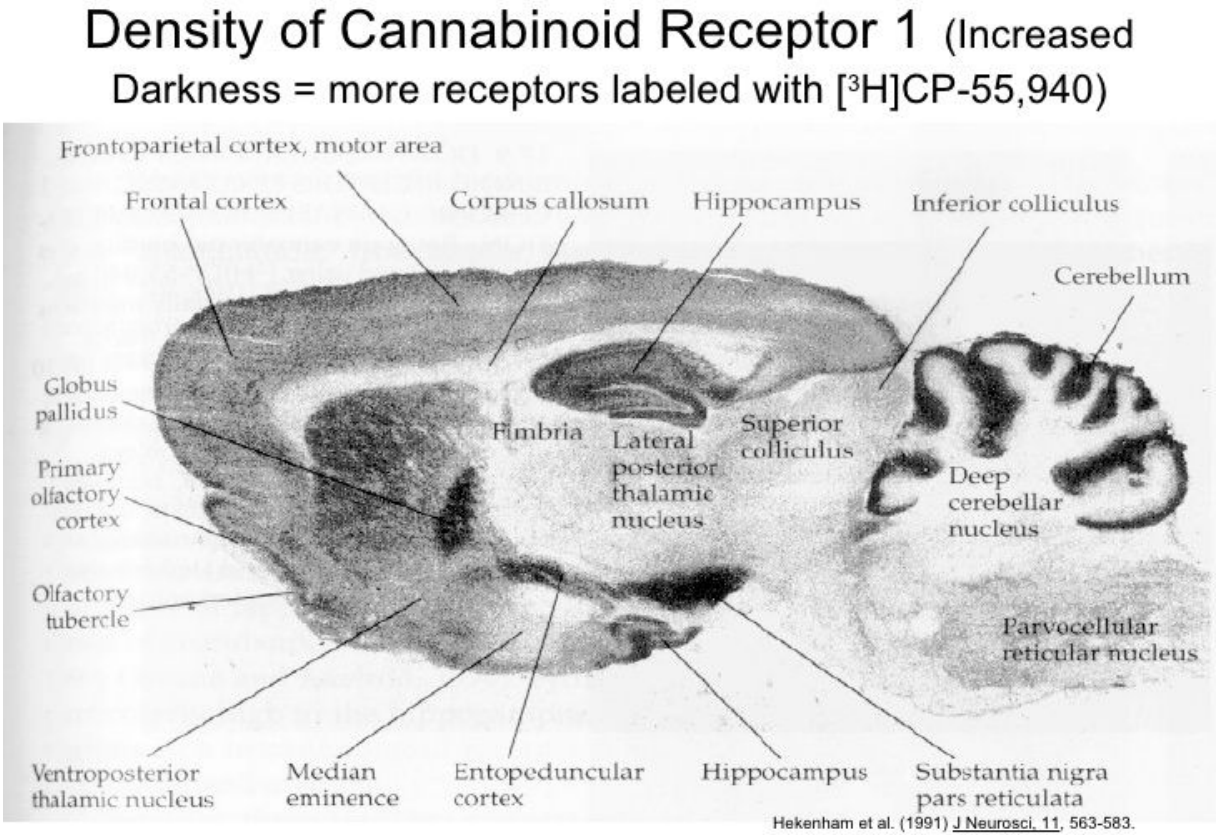
- Changes with development



Allen Brain Atlas

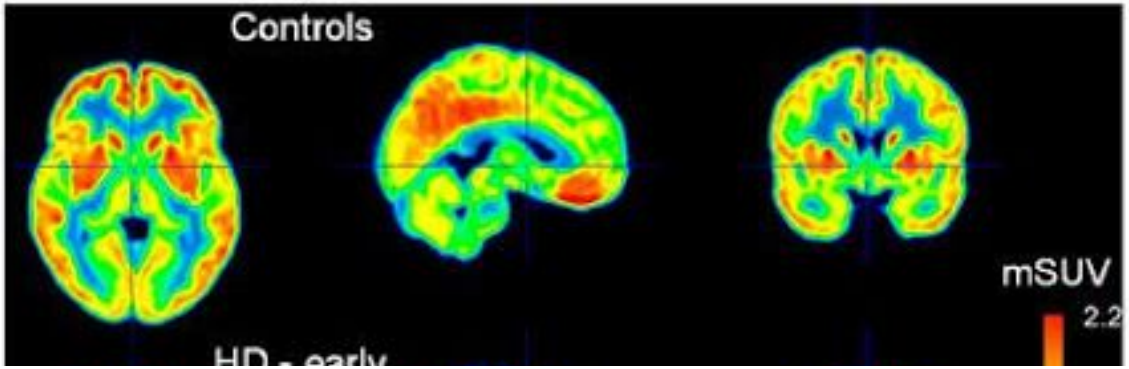
CB1 Brain Expression

- Changes with development
- In adult mice, high expression in cerebellum, hippocampus, cortex but not thalamus



CB1 Brain Expression

- Human PET imaging studies now allow researchers to image the density of CB1 receptors
- Similar densities as found in rodents and primates



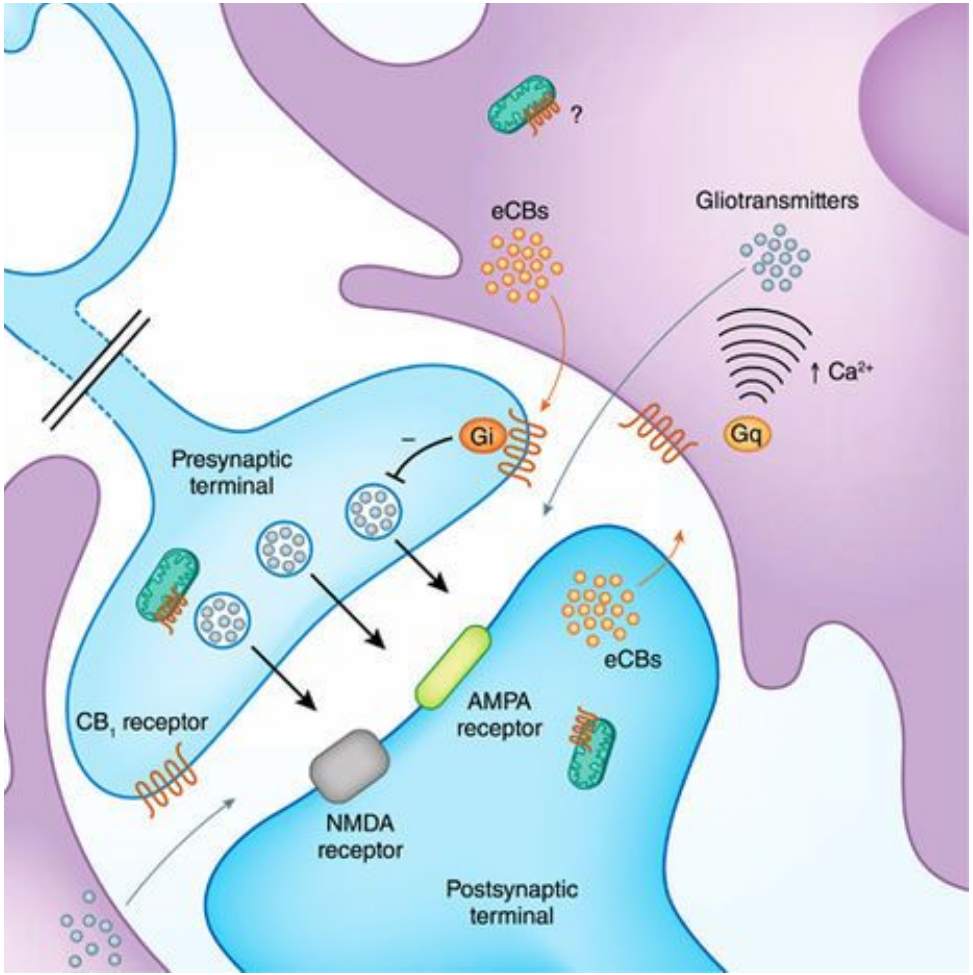
Van Laere et al., 2010

CB2 Brain Expression

- Controversial if found in the brain
- Not expressed on neurons during steady state conditions (except in brainstem)
- Somewhat expressed on glia, changes with conditions

CB1 and Neurons

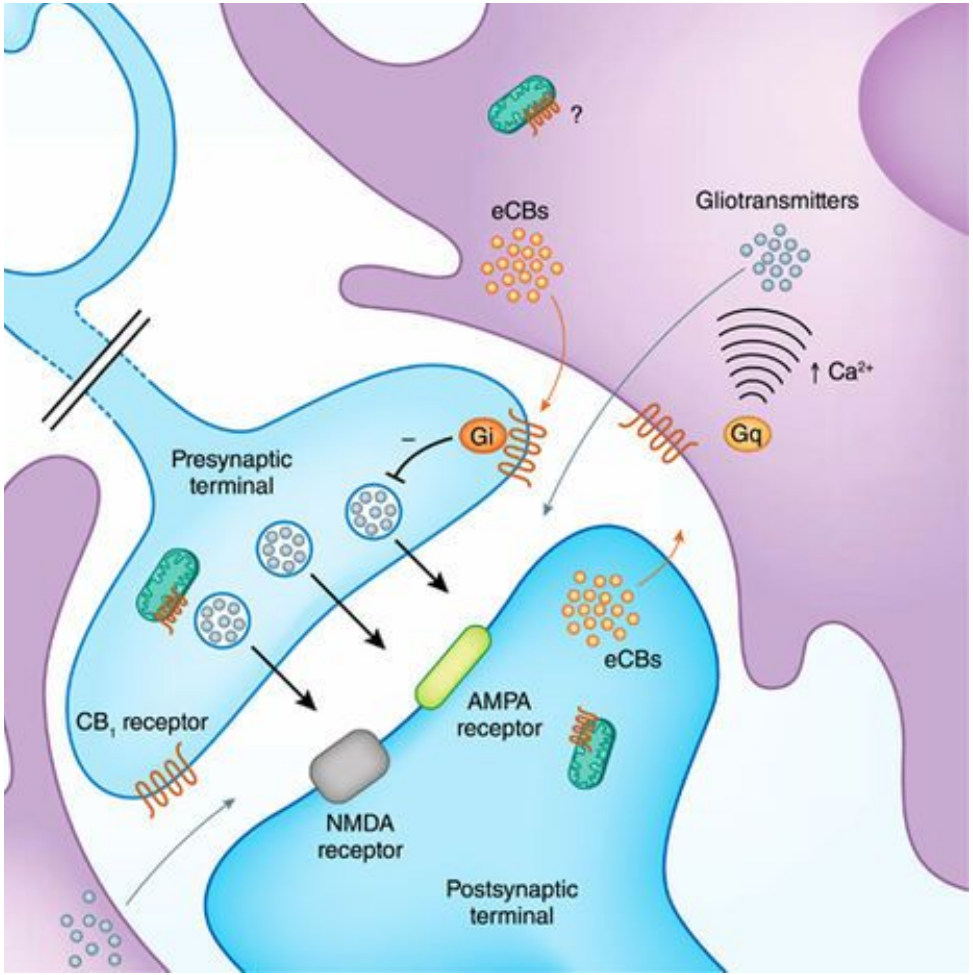
- Endocannabinoids are produced in postsynaptic cells in response to neural activation
- Activate CB1 receptors on presynaptic cells
- Inhibit further neurotransmission



Busquets-Garcia et al., 2017

CB1 and Neurons

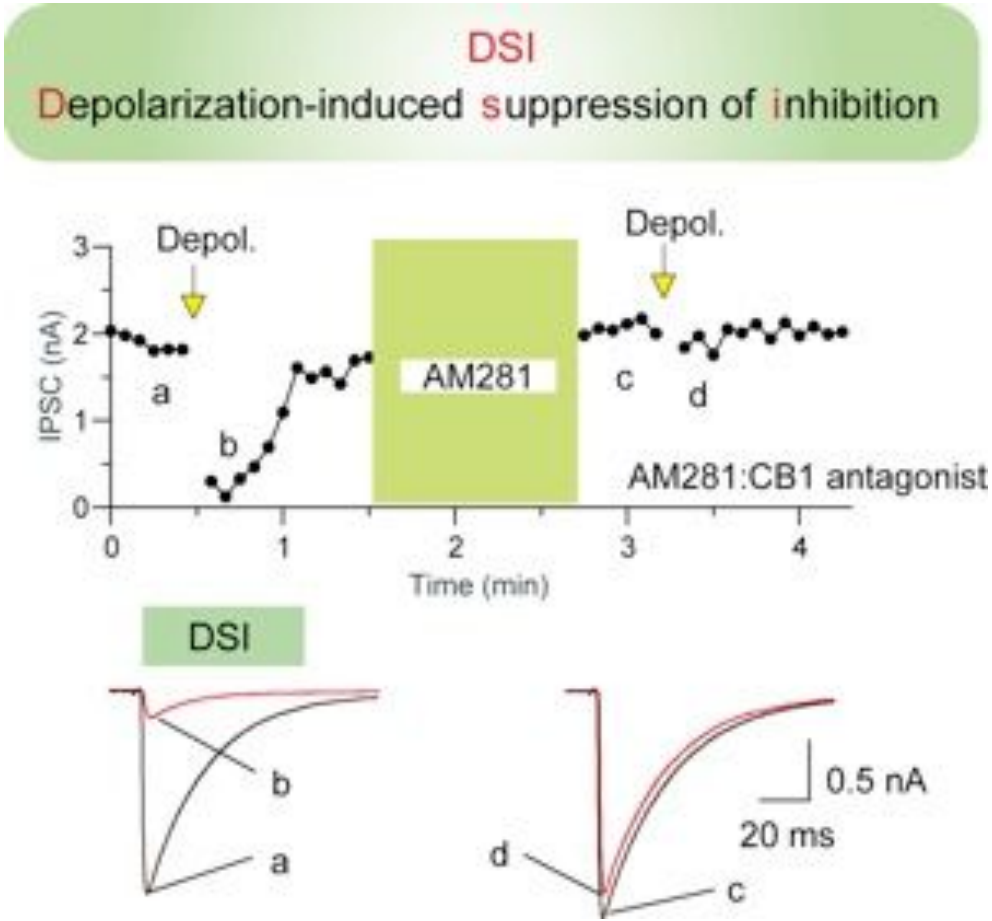
- Expressed on most neuronal cell types, including glutamatergic, GABAergic, dopaminergic, norepinephrinergic, serotoninergic etc…
  - Most highly expressed on GABAergic cells



Busquets-Garcia et al., 2017

DSE and DSI

- Depolarization-induced suppression of excitation and inhibition
- Mediated by CB1 receptors



Kano Lab

Cannabinoid Affinities for Receptors

- AEA
  - GPR55
  - CB1 partial agonist
  - CB2 partial agonist
  - TRPV1
  - PPARα, PPARγ
- 2-AG
  - CB1 agonist
  - CB2 agonist
- THC
  - CB1 (partial) agonist
  - GPR55
  - CB2 (partial) agonist
- CBD
  - CB1 negative allosteric modulator, low affinity
  - CB2 negative allosteric modulator, low affinity
  - GPR55 antagonist

Cannabinoid Affinities for Receptors

- CB1
  - THC
  - 2-AG
  - AEA (partial)
- CB2
  - THC
  - 2-AG
  - AEA (partial)
- TRPV1
  - AEA
- GPR55
  - THC
  - AEA
- PPARα
  - AEA
- PPARγ
  - THC
  - AEA

Summary

Cannabinoid Receptors

There are two cannabinoid receptors (CB1 and CB2), which are $G_{i/o}$ coupled. They inhibit cAMP and induce MAP kinase.

Cannabinoid receptor are present throughout the body, but CB1 are enriched in brain, particularly in cortical and limbic brain regions.

Summary

Cannabinoid Receptors

In neurons, endocannabinoids are synthesized on demand and act on presynaptic CB1 receptors to inhibit neurotransmission.

Responsible for DSE and DSI.

Summary

Cannabinoid Receptors

Cannabinoids have different affinities for receptors.

- THC and 2-AG are full agonists at CB1 and CB2
- AEA is a partial agonist at CB1 and CB2
- CBD is a negative allosteric modulator of CB1 and CB2

Let’s Compare

THC

CBD

2-AG

AEA

2-AG

AEA

THC

CBD

2-AG

AEA

THC

CBD

2-AG

AEA

THC

CBD

2-AG

AEA

THC

CBD

2-AG

AEA

THC

CBD

2-AG

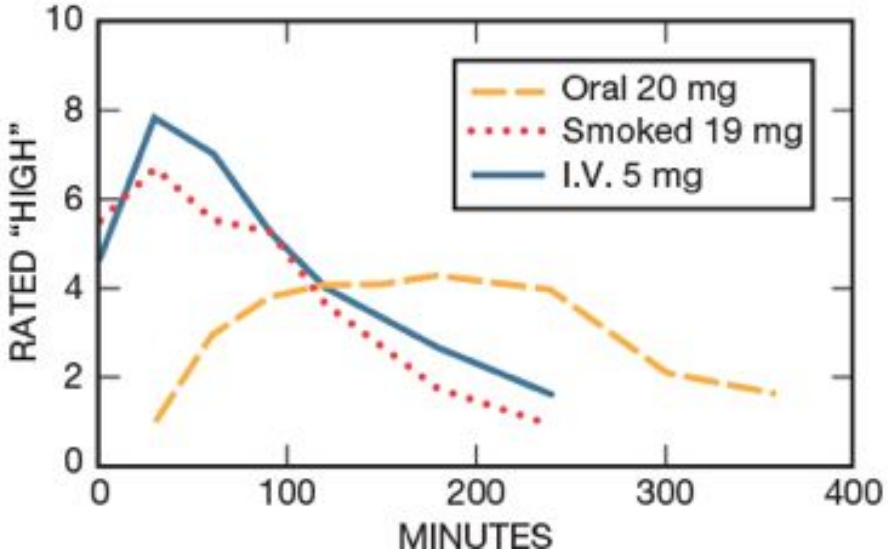
AEA

Cannabinoid Metabolism

Routes of Administration

- THC is a weak acid (pKA 10.6)
- Lipid molecules
- Routes
  - Oral
  - Inhalation
  - Pharmaceutical routes
    - Buccal
    - Suppositories
    - Transdermal patch
    - IV

Figure 14-2 Time course of subjective "high" following the administration of THC in varying doses and via different routes. (Adapted from Agurell et al., 1986.)



Oral Administration

- Low bioavailability (THC = 5-20 %; CBD 6-19 %)
  - Erratic metabolism in the gut
  - First-pass metabolism in the liver = high enzymatic breakdown
  - Absorption may be increased by adding oil to the plant material
- Timeline
  - Onset: 30-90 min after intake
  - Peak: 1-4 hours after intake
  - Duration: 4-12 hours after intake (but reported up to 24 hours)

Inhalation—Smoking

- Cannabinoids are readily and rapidly absorbed into systemic circulation from the respiratory tract
- Heating *cannabis* plant material converts the parent compound of THC into its active form and volatilizes it so that it can be inhaled
- Timeline
  - Onset: few minutes after intake
  - Peak: 6-10 minutes after intake
  - Duration: 2-4 hours after intake

Inhalation—Smoking

- Lungs are highly effective in delivering cannabinoids to the bloodstream, burning cannabis and inhaling the smoke is not a very efficient means to deliver to lungs
  - Before inhalation
    - Apx. 70 % of THC content is destroyed by burning or remains in the plant
    - Additional losses occur through smoke that escapes between puffs
  - During inhalation
    - 50 % of smoke is exhaled
    - Some contents are metabolized in lungs before reaching bloodstream
  - Therefore, only 10-27 % of THC content reaches bloodstream

Inhalation—Smoking

- Experienced smokers tend to take deep draws and hold smoke for longer period of time before exhaling, therefore greater THC bioavailability compared in inexperienced smokers
- However, holding smoke does not contribute much to the absorption of THC
    - Instead depth of inhalation and frequency of puffs are a much greater determinants of THC absorption

Inhalation—Vaping

- Cannabinoids are highly volatile and will vaporize at temperatures lower than those attained during combustion of plant material
  - When heated, cannabinoids can aerosolized and can be inhaled
  - Some reduction in exposure to noxious chemicals present in smoke
- Similar to smoking, still an inefficient means of delivering cannabinoids to lungs
- Bioavailability is 30-55 %

Other Routes of Administration

- Sativex
  - Buccal spray
  - Similar bioavailability to oral administration, not as quick absorption as smoking
- Inhaler
  - Peak absorption at 3 min through lungs
- Suppositories
  - Greater availability to oral administration, no first-pass metabolism
- Transdermal patch
  - Cannabinoids would accumulate in skin due to high lipophilicity
- IV
  - Need oil-based solvent, which is irritating
  - Timeline
    - Similar to inhalation

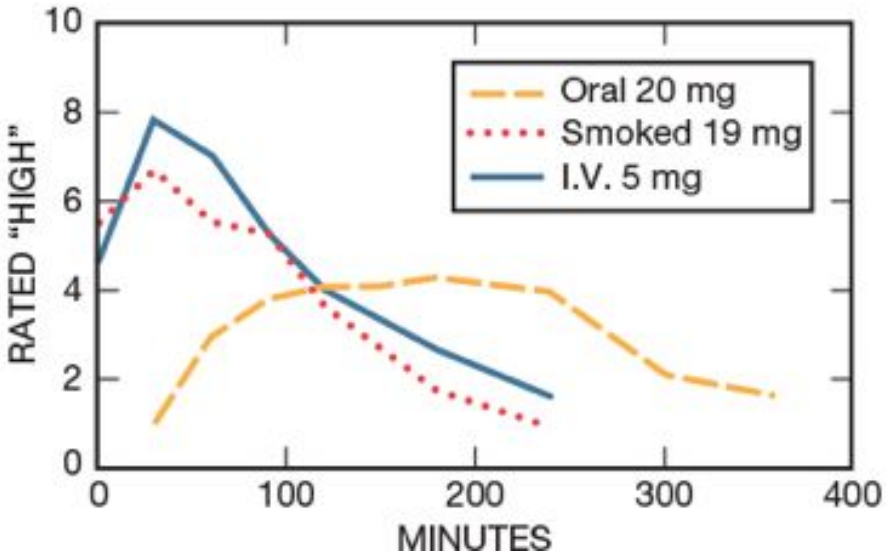
Distribution—*Cannabis*

- After smoking, cannabinoids are quickly removed from the blood and distributed throughout the entire body
  - Cannabinoids are lipophilic, so their distribution depends on the rate of blood flow to tissues and organs
    - Concentrated in regions that are most highly perfused, such as the lungs, kidneys, heart, and liver
    - Cannabinoids also accumulate in body fat
      - Long-term storage site
    - Despite the high rate of blood flow to the brain, THC tends not to concentrate there
      - Approximately 1 %

Administration, Distribution and Subjective “High”

- Route of administration affects distribution timeline
  - Smoked and IV lead to quicker blood levels compared to oral
- Low amount that reaches the brain (1 %) may be related to how long subjective high takes

Figure 14-2 Time course of subjective “high” following the administration of THC in varying doses and via different routes. (Adapted from Agurell et al., 1986.)



Distribution—Recreational Synthetic Cannabinoids

- Not well understood
- Rapid biotransformation and storage
- Shorter duration of subjective high compared to smoked *cannabis*

Elimination—THC

- Some metabolism in lungs, but largely in liver
- CYP450s, expressed throughout body
- Primary metabolite
  - 11-hydroxy-THC
    - Also a CB1/CB2 agonist
    - Crosses BBB
- Secondary metabolites
  - 100’s with a variety of functions and affinities
  - Less lipid soluble, therefore easier to excrete
- Conjugated to glucuronic acid, essential for removal from body
- Half-life is 30 hours to 4 days (slow release from lipid stores)
- Largely excreted in feces (65 %) and urine (20 %)

Elimination—CBD

- Some metabolism in lungs, but largely in liver
- CYP450s, expressed throughout body
- Primary metabolite
  - 7-hydroxy-CBD
- Secondary metabolites
- Half-life is 9 to 32 hours

Elimination—Synthetics

- Shorter duration compared to phytocannabinoids
- Undergo primary metabolism by CYP450s in lungs, liver and brain

Summary

Cannabinoid Metabolism

Multiple routes of cannabinoid administration; route of administration can affect timeline of effects and subjective high.

Oral administration has low bioavailability and leads to slower peak subjective high.

Although lungs do a great job of delivering cannabinoids to blood, smoking is inefficient to deliver to lungs.

Summary

Cannabinoid Metabolism

Cannabinoids are quickly removed from blood and distributed to tissues with high blood perfusion.

Except the brain, 1 % THC

Cannabinoids are primarily metabolized in lungs/liver by CYP450s. Metabolites may have additional effects.

Cannabinoids Effects on Behaviour and Physiology

Content Warning

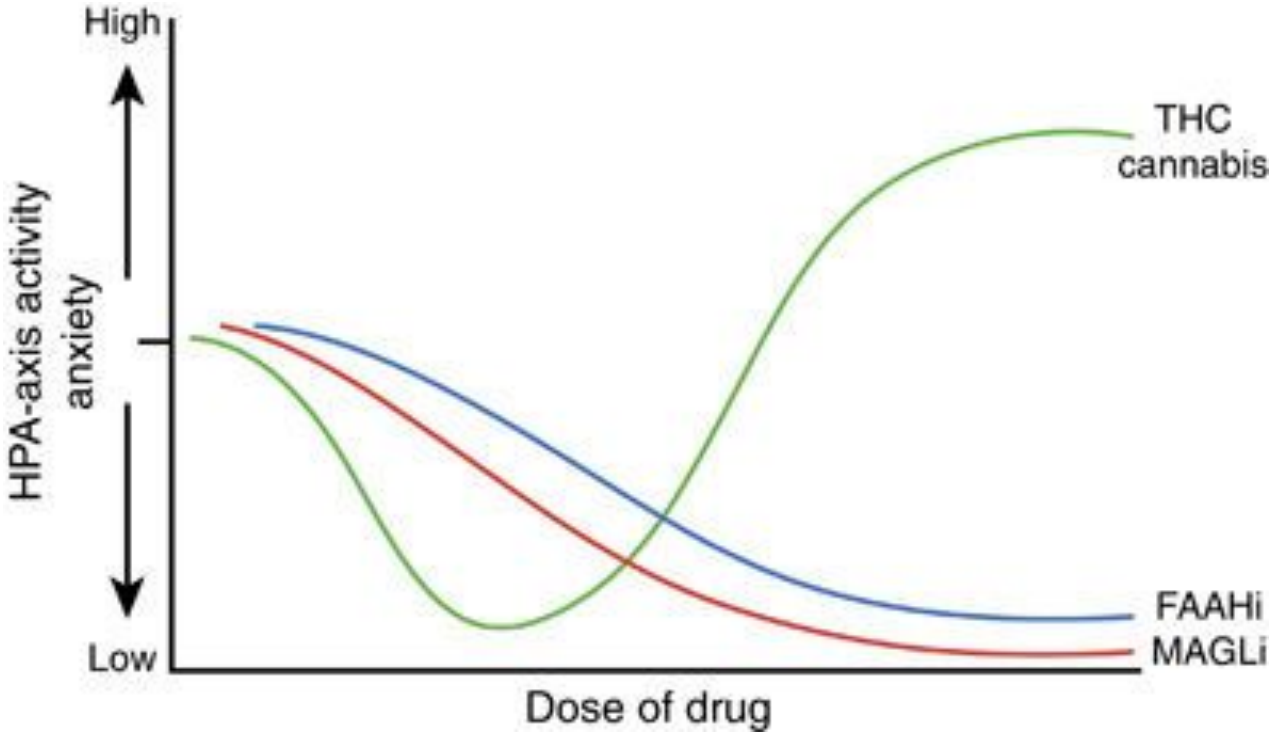
Use of animals in research.

The next few slides discuss the use of animals in scientific experiments.

Cannabinoid Effects on Animal Behaviour

- Discrimination Behaviour
  - Rodents can discriminate THC from placebo
    - Generalizes to delta-8-THC, nabilone, 11-OH-THC, AEA but not CBD
- Unconditioned Behaviour
  - Taming behaviour (reduction of aggressive behaviour)
  - Reduction of anxiety*
  - Reduction in food intake
  - Alteration in food preference

Cannabinoid Effects—
Unconditioned Behaviour, Anxiety

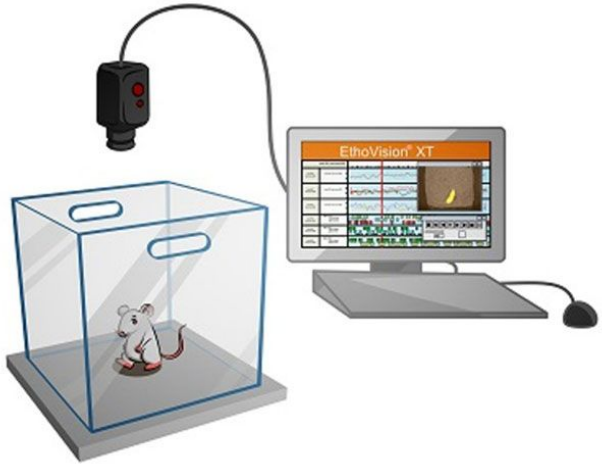


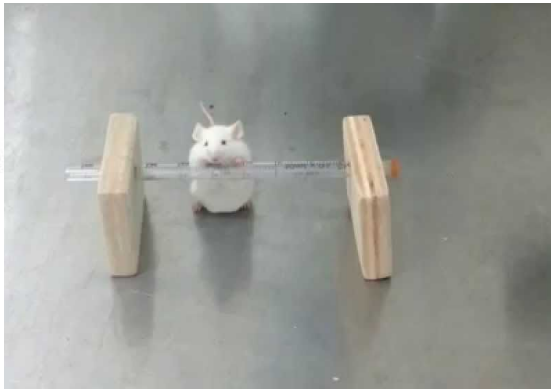
Hill et al., 2017

Unconditioned Behaviour—Tetrad

Rodents will respond to THC and cannabinoids with a tetrad of behaviours

- Spontaneous activity
- Catalepsy
- Hypothermia
- Analgesia





Conditioned Behaviour—Animals

- Interferes with short-term memory tasks
  - Chronic exposure during adolescence can impair adult short-term memory
- Influence on long-term memory is unclear
  - Inability to transfer learning from drugged and non-drugged states
  - May improve drug associated cues
  - CPP or CPA*
  - In primates, chronic exposure during adolescence can impair spatial memory

Self-Administration—Animals

- Classically, no reliable self-administration protocols in animals
- Recent studies have established THC self-administration
  - IV self-administration in squirrel monkeys (Tanda et al., 2016)
  - Rats learn to self-administer THC directly into VTA or NAc (Zangen, 2006)
  - Pre-exposure to a THC:CBD (10:1) vapor facilitates self-administration (Melis et al., 2017)
- Caveats (Wenzel and Cheer, 2017)
  - Discrepancies in route of administration
  - Chemical constituents of drug
  - Cannabinoids produce locomotor and working memory side effects at higher doses which may could confound task performance
- Rodents and squirrel monkeys will self-administer AEA and 2-AG

Summary

Effects of Cannabinoids on Animal Behaviour

Rodents can discriminate THC from placebo.

Rodents will exhibit a tetrad of behaviours (spontaneous activity, catalepsy, hypothermia, analgesia) in response to cannabinoids.

THC induces a dose-dependent effect on anxiety.

There are mixed results on development of animal self-administration protocols.

Cannabinoid Effects on Human Body

- Dilation of small blood vessels, dry mouth, compulsion to drink, munchies, increased heart rate, increased muscle relaxation, fluctuation in body temperature, drop in blood pressure, nausea, dizziness, vomiting
  - Appetite effect plateaus with chronic use
    - Synthetic compounds better at constantly stimulating appetite
- Dose-dependent
  - Increased doses lead to increase cortisol, increased anxiety, decreased beta-wave activity, increases blood pressure
    - Often opposing effects based on dose
      - “Inverted U”
- Synthetic cannabinoids have similar effects, but often a greater magnitude

Cannabinoid Effects on Sleep

- At low doses *cannabis* is sedating, causes fatigue and drowsiness and decreased alertness
- Effects on sleep (acute, lower doses)
  - Decreases latency to sleep onset, increases total sleep time, reducing REM time, increases slow-wave sleep
- Effects on sleep (high doses)
  - Insomnia, restlessness, increases time to fall asleep, decreases REM and SWS
- Effects on sleep (chronic)
  - Reduction in SWS
- Sativex and other cannabinoid pharmaceuticals
  - Help people with chronic pain sleep

Cannabinoid Effects on Perception

- Effects varied and may be an intensification or distortion of sensory experiences
- Dose dependent effects on users' ratings of perceptual alteration, mild synesthesia and hallucinations
- Distortion of rating of passage of time, slowing in subjective rate

Cannabinoid Effects on Mood

- Typical exposure is swings of mood from euphoric gaiety (social) to placid dreaminess (individual)
    - Often with high doses there is anxiety, foreboding, panic and dysphoria
- Research definition is “ feeling of intoxication, with decreased anxiety, alertness, depression, and tension and increased sociability”
- Subjective effects of *cannabis* differ based on individuals, route of administration, strain, synthetic vs. phytocannabinoids
    - CBD can mitigate some effects of THC

Cannabinoid Effects on Creativity

- Users report that *cannabis* improves one's appreciation of music and art, and enhances creativity
- Testing for creativity
  - Divergent thinking occurs when people search for a variety of solutions to a loosely defined problem
  - Convergent thinking, which takes place when individuals search for a single, ideal solution to a very well-defined problem
- Personality traits and history of *cannabis* use can modify the effects on creativity

Cannabinoid Effects on Violence

- Numerous longitudinal and cross-sectional studies have failed to find an association between even heavy or chronic cannabis use in adolescents and adults and an increased likelihood of committing a violent act
- We will discuss historical findings and framings regarding *cannabis* and violence next lecture

Cannabinoid Effects on Memory

- *Cannabis* affects verbal and episodic short-term memory (working memory) but not long-term memory
  - Dose-dependent
  - Tolerance to effects, heavy users less affected
  - Mixed results on whether this persists past period of intoxication
- Memory performance of *cannabis* users may be on par with that of non-users on certain tasks, the level of activation in brain regions associated with the task is increased in *cannabis* users

Cannabinoid Effects on Dissociation

- Similar to rodents, when users acquired information in one state, they had difficulty transferring it to the other state
  - May be asymmetrical
    - Can remember information acquired during non-intoxicated state while intoxicated, but not the other way

Cannabinoid Effects on Motor Performance

- Due to complexity of tasks, difficult to summarize
- Generally, complex tasks that incorporate sensory, motor and decision-making capacities are those that are most impaired by *cannabis*
- Tolerance to effects, heavy users less affected

Cannabinoid Effects on Driving

- *Cannabis* intoxication is associated with increased risk of motor vehicle collision and likelihood for being responsible for causing a crash increases proportionally with *cannabis* dose
- Intoxicated drivers report being aware of their impairment and increased effort to drive, and thus try to compensate by driving slower and taking fewer risks
- Tolerance to effects, heavy users less affected
- Difficult to test
    - Disconnect between pharmacokinetic and psychoactive profiles make it difficult to develop a reliable test of impairment

Cannabinoid Effects on Drug Discrimination

- Experienced smokers can easily distinguish between joints that contain THC and those that do not; also able to discriminate orally administered THC
    - There is a lower limit of detection

Cannabinoid Effects on Self-Administration

- Self-administration of *cannabis* by humans in experimental settings has been demonstrated many times
- Curiously, a highly consistent finding across studies is a difficulty in establishing a dose effect relationship between cannabis potency and the rate of self-administration or subjective ratings of "high"
    - The relationship between "strength," "good effect," "liking," and "take again" ratings after smoking or oral *cannabis* found no THC-dose dependent effects
- Act of smoking, appearance of the marijuana joint, taste, and smell of marijuana all contribute to users' expectancies and consequent subjective effects
- Users may be ability to titrate dose by altering their smoking behavior

Cannabinoid Effects

- Subjective versus objective measures, change in subjective measure, but little to no change in objective measures
  - Perception
  - Mood
  - Creativity

Summary

Cannabinoid Effects on Human Behaviour

There is an “inverted U” response to *cannabis*/THC on many outcomes (e.g. anxiety, nausea, blood pressure, sleep).

Tolerance with chronic use to some outcomes (e.g. memory and motor performances).

Difference in subjective versus objective measures of outcomes (e.g. perception, mood and creativity).

Cannabis—Lecture 2

Lecture 1-Thursday, March 22, 2018

- Distinguish between endogenous cannabinoids, phytocannabinoids and synthetic cannabinoids
- Describe the effects of cannabinoids interacting with cannabinoid receptors
- Describe how cannabinoids are metabolized
- Analyze the effects of cannabinoids on behaviour and physiology
- Evaluate the efficacy of using *cannabis* (and cannabinoids) for medical treatment

Lecture 2-Tuesday, March 27, 2018

- Summarize the history of *cannabis*
    - Outline racialized factors affecting legalization in Canada and US
- Analyze the factors affecting rate of *cannabis* use
- Summarize adverse effects of cannabis use
- Describe the consequences of cannabis use disorder
- Compare pros and cons of *cannabis* legalization in Canada

Let’s Review

List the 4 Major Cannabinoids

List the 4 Major Cannabinoids

What receptor(s) do they act on?

- Phytocannabinoids
  - THC
  - CBD
- Endocannabinoids
  - 2-AG
  - AEA

How High?

Rank the subjective “high” reported by users with the various methods of administration.

- Oral
- Smoked
- IV

How High?

Rank the subjective “high” reported by users with the various methods of administration.

1. Smoked
2. IV
3. Oral

Cannabinoids and Rodents

How do they react?
4 behaviours: what are they collectively and specifically?

Cannabinoids and Rodents

How do they react?
4 behaviours: what are they collectively and specifically?

Tetrad

- Spontaneous activity
- Catalepsy
- Hypothermia
- Analgesia

Cannabinoids and Humans

Different doses produce what kind of shape on human behaviours?

Cannabinoids and Humans

Different doses produce what kind of shape on human behaviours?

An “inverted U”

- Lower doses of THC
  - Reduced anxiety, nausea
  - Increase in sleep
- Higher doses
  - Increased anxiety
  - Decreased sleep

Tolerance to many behaviours (esp. self-reported ones) with chronic use

Cannabis History: Cultivation, Medicine, Usage Rates & Legalization

Content Warning

Racialized Language & Images

The following slides contains racialized language and images that contain racialized images.

Early History

- Difficult to trace back where *cannabis* first originated, as it was cultivated and spread prior to recorded history
  - Likely originated in central Asia
  - Thought to be oldest non-food cultivated plant
- Stone Age findings of hemp rope in Taiwan
- Spread to Europe, Mediterranean, Middle East, Central Asia and China by Scythians
- African slave trade brought *cannabis* to South and North America
  - No evidence that it was used by peoples indigenous to Turtle Island prior
- Became important colonial crop in 1600’s
  - Hemp rope

Early Medical History

- Important to note that the history of medicine predates Enlightenment
- Oldest known written reports in Egypt of using *cannabis* medicinally
  - “A treatment for the eyes”
    - Glaucoma? Inflammation?
- Reports in China from 2800 BCE
  - “Protracted taking may make one fat, strong and never senile”
- Reports in India from 1600 BCE
  - “Ability to release user from anxiety”
- Reports in Africa from 2000 years ago
  - Used to treat headache and for obstetrical practice

“Modern” Medical History (1800’s)

- William O’Shaughnessy, British physician & chemist teaching in India
  - *Cannabis* was an effective anticonvulsant, antispasmodic, and appetite stimulant and for treatment of tetanus, neuralgia, dysmenorrhea, asthma, gonorrhea, cholera, rabies, migraine, and delirium tremens
  - Sent tinctures to England, and these began to be used in Europe and North America
- John Clendinning, British physician
  - First to use *cannabis* tinctures in England (for migraine treatment)
- J.J. Moreau de Tours, French psychiatrist
  - Treatment of melancholia, hypomania, and other forms of mental illness
  - Induce “model psychosis”

“Modern” Medical History (early 1900’s)

- *Cannabis* was used in medicine in Europe and North America in the late 1800’s and early 1900’s as a sedative, hypnotic, analgesic, and anticonvulsant agent
- By 1930s and 1940s usage largely waned
    - Varied plant material composition
    - Opioids and other compounds better at producing analgesic and sedative effects
    - Increased criminalization

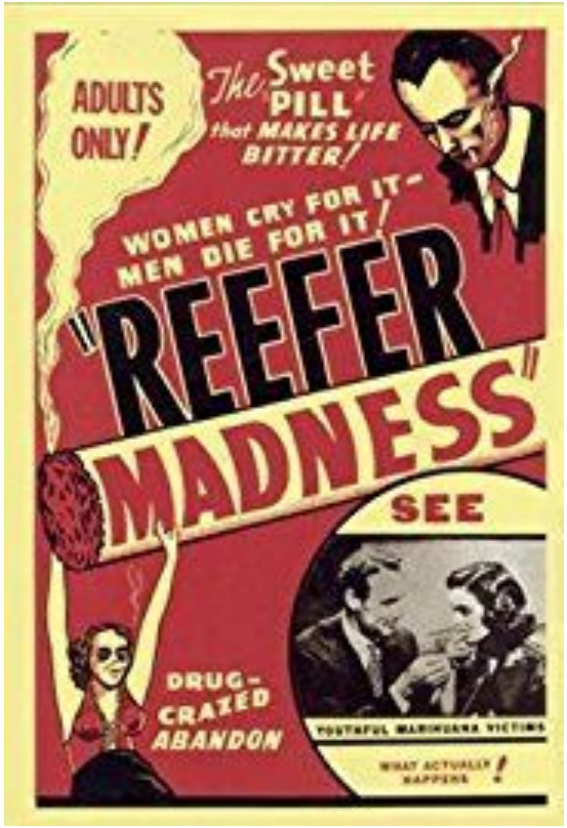
Cannabis Criminalization (mid-1900's)

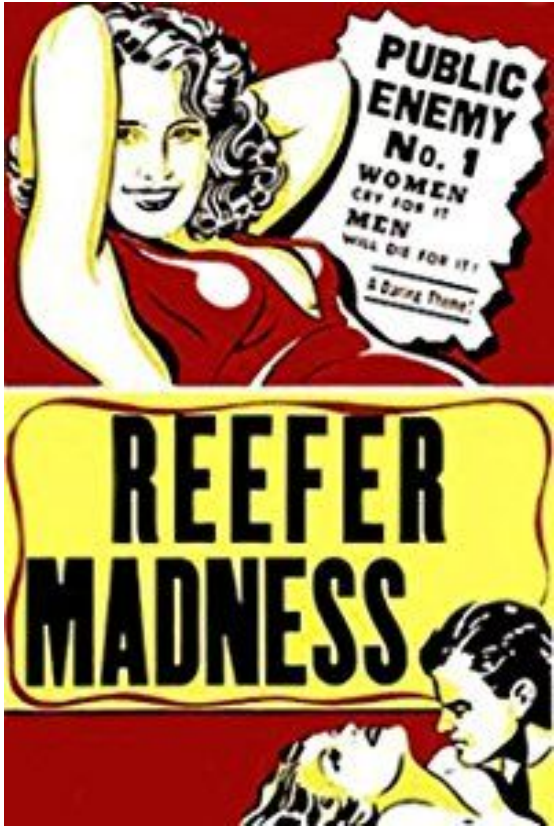
- United States
    - Use of marijuana (smoked *cannabis*) by Mexican labourers, Black musicians and racial minorities promoted moral panic
        - Rooted in racism and xenophobia
            - Thought to increased violence, illegal behaviour other moral failings
        - *Cannabis* tinctures still used by white, wealthy people
            - Sedative and hypnotic
                - Especially for women
    - 1913 California law was first; 1936 all 48 states had laws against it
    - 1937 "Marijuana Tax Act" levied heavy fines

Cannabis Criminalization (mid-1900's)

- Canada
  - Labeled as a narcotic in 1923 (Narcotic Control Act) along with opioids
    - Could still be prescribed
- 1925 International Opium Conference
  - Egyptian officials argued that *cannabis* posed as dangerous threat to society as opium; promoted banning of hashish (outside of medicine/science)
    - Other countries objected (esp. India)
  - Compromise: no exportation to countries that banned it, importation only to countries using it for medical/scientific reasons
- 1928 Dangerous Drug Act (UK)
  - Criminalized *cannabis* possession

“Reefer Madness”





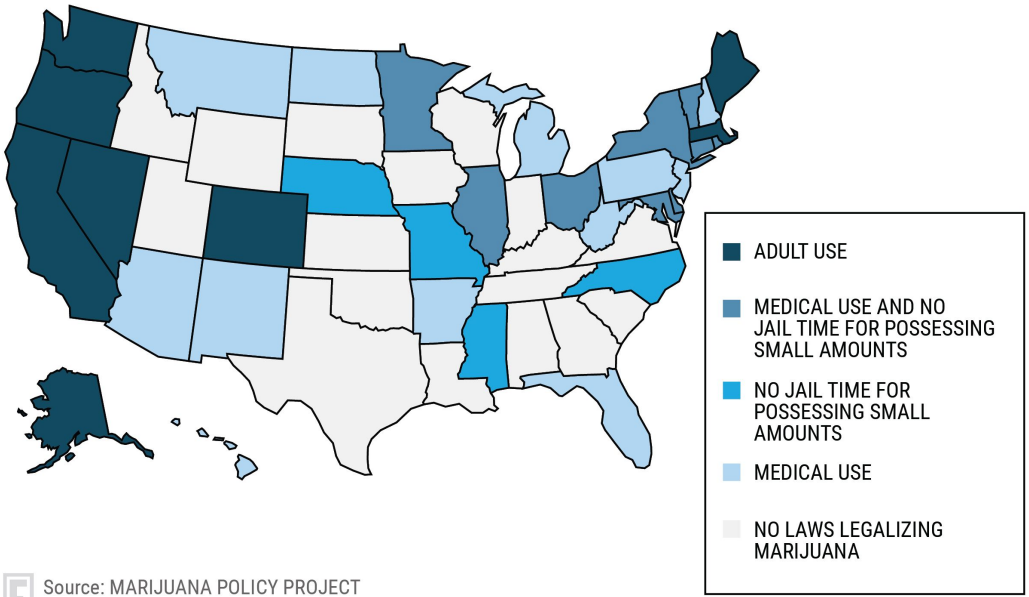
US *Cannabis* Criminalization

- 1970's
  - Increase in *cannabis* popularity and usage (peak recreational usage)
  - Renewed interested in medical usage but concern over dangers of use
    - Polarization of lay and scientific opinions
      - Difficult to study
- Controlled Substances Act (1970)
  - Ruled cannabis has no potential medical benefit and high abuse liability
  - Schedule 1 Drug
- 1980's Just Say No, heavy drug enforcement
- In the States, still Schedule 1 drug and illegal federally

US *Cannabis* Legalization

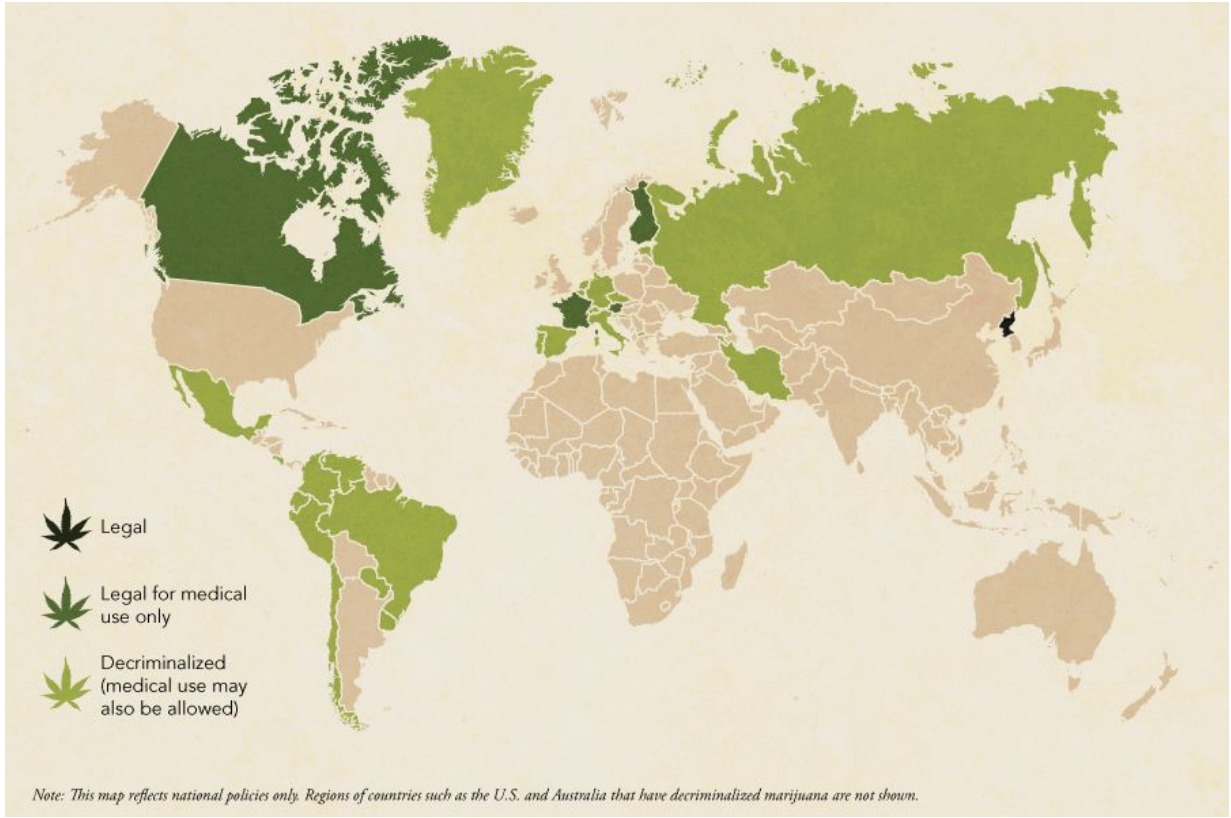
STATE CANNABIS LAWS

- Although marijuana remains illegal under federal law, more states are choosing to put legalization on the ballot. Nearly a quarter of Americans live in places where adult use of cannabis is legal.



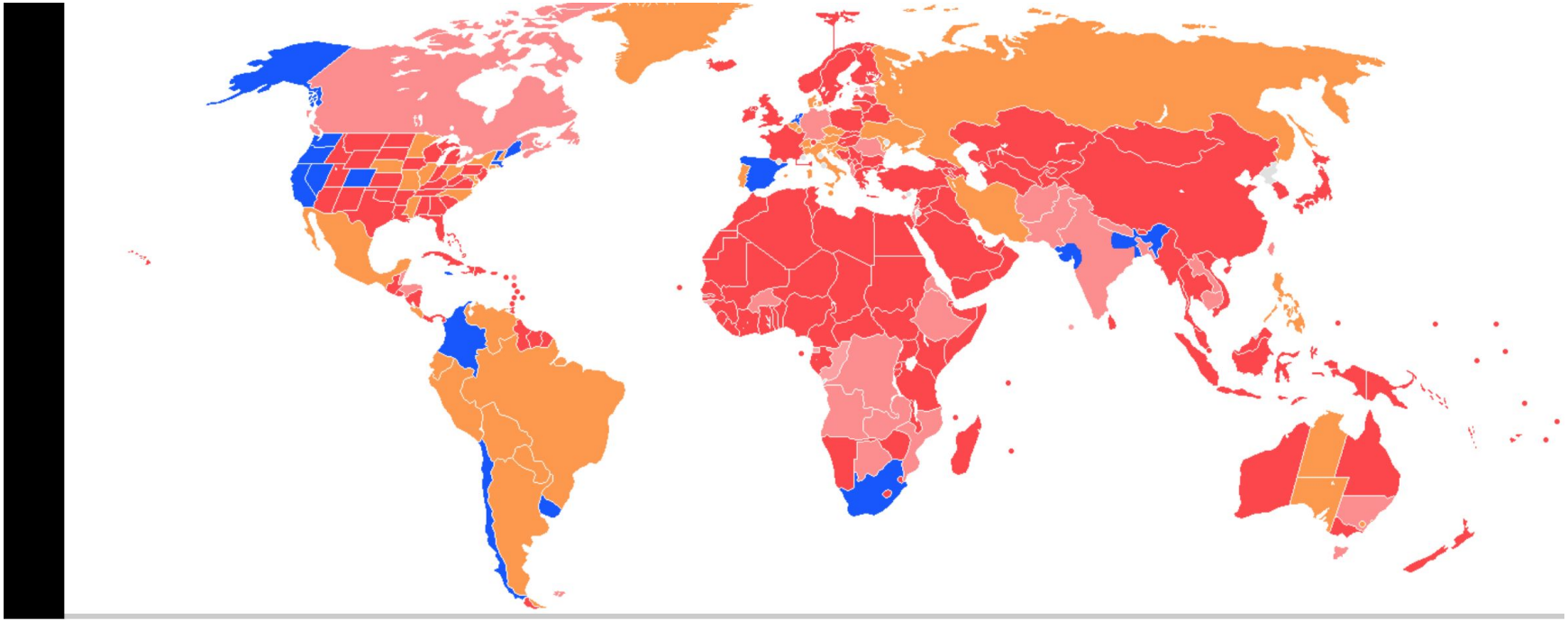
Source: MARIJUANA POLICY PROJECT
GRACE DONNELLY/FORTUNE

Medicinal Use



*Does not include regions of countries where legal HuffPo

Legalization



World laws on possession of small amounts of cannabis for personal use. Partially or essentially legal | Illegal but decriminalized | Illegal but often unenforced | Illegal | No information

More deta

Wikipedia

“Illegal but often unenforced”

- Black Canadians in Toronto are 3x more likely to be arrested for *cannabis* possession compared to white Canadians
  - Relatively similar rates of usage across all groups
- Stigma and marginalization of conviction
  - Increased likelihood of becoming “known the police”
- ...but what about upcoming legalization?

Canada Legalization

- Government set to legalize *cannabis* in summer or fall 2018
- People with criminal convictions will be denied security clearance to work as a licensed medical cannabis producers
    - Might be maintained with proposed law, but advocacy around issue
- Proposed legal limits on micro-cultivation and micro-processing
    - Will these be enforced similarly?

Canada Legalization

- Recommendations
  - Pardoning individuals convicted of activities that are no longer illegal (following example of Bill C66)
  - Distribution of tax revenue to marginalized communities most harmed by *cannabis* prohibition
  - *Cannabis* industry participation
    - Tiered licensing system and specialized business loans
    - Private companies should adopt strategies to promote inclusion

Cannabis Use

Table 14-1 Rates of Marijuana Use in 2014 Amongst U.S. Youth and Adults

	8th Graders	10th Graders	12th Graders	19–28 Year Olds	29–35 Year Olds	40–50 Year Olds
Lifetime use	15.6%	33.7%	44.4%	57.5%	—	—
Annual use	11.7%	27.3%	35.1%	31.6%	22.1%	12.3%
Past 30-day use	6.5%	16.6%	21.2%	19.2%	12.2%	7.3%
Daily use	1.0%	3.4%	5.8%	6.9%	5.4%	2.2%

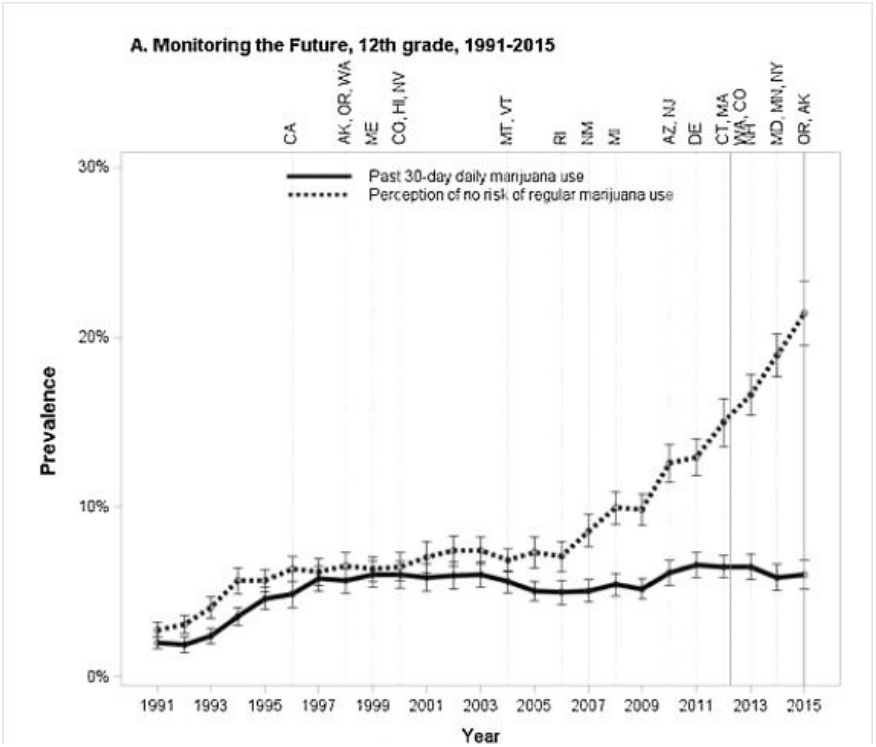
SOURCES: Miech et al. (2015); Johnston, O'Malley, Bachman, Schulenberg, & Miech, 2015.

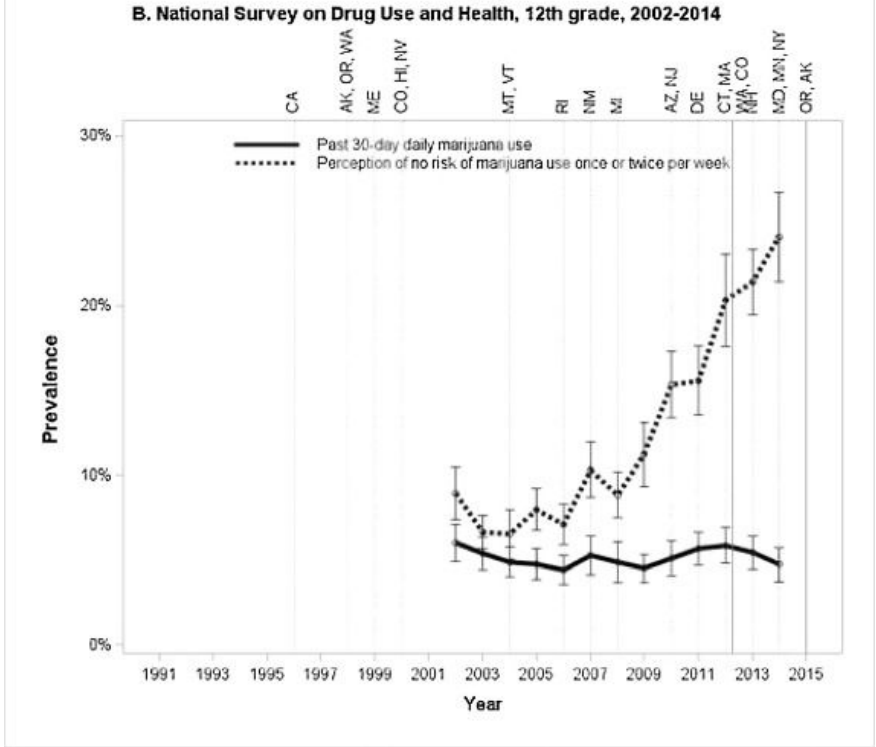
Similar, but slightly lower % in Canada

Cannabis Use

- Affecting Rate of Usage
  - Availability
  - Social acceptability
  - Perceived risk of harm

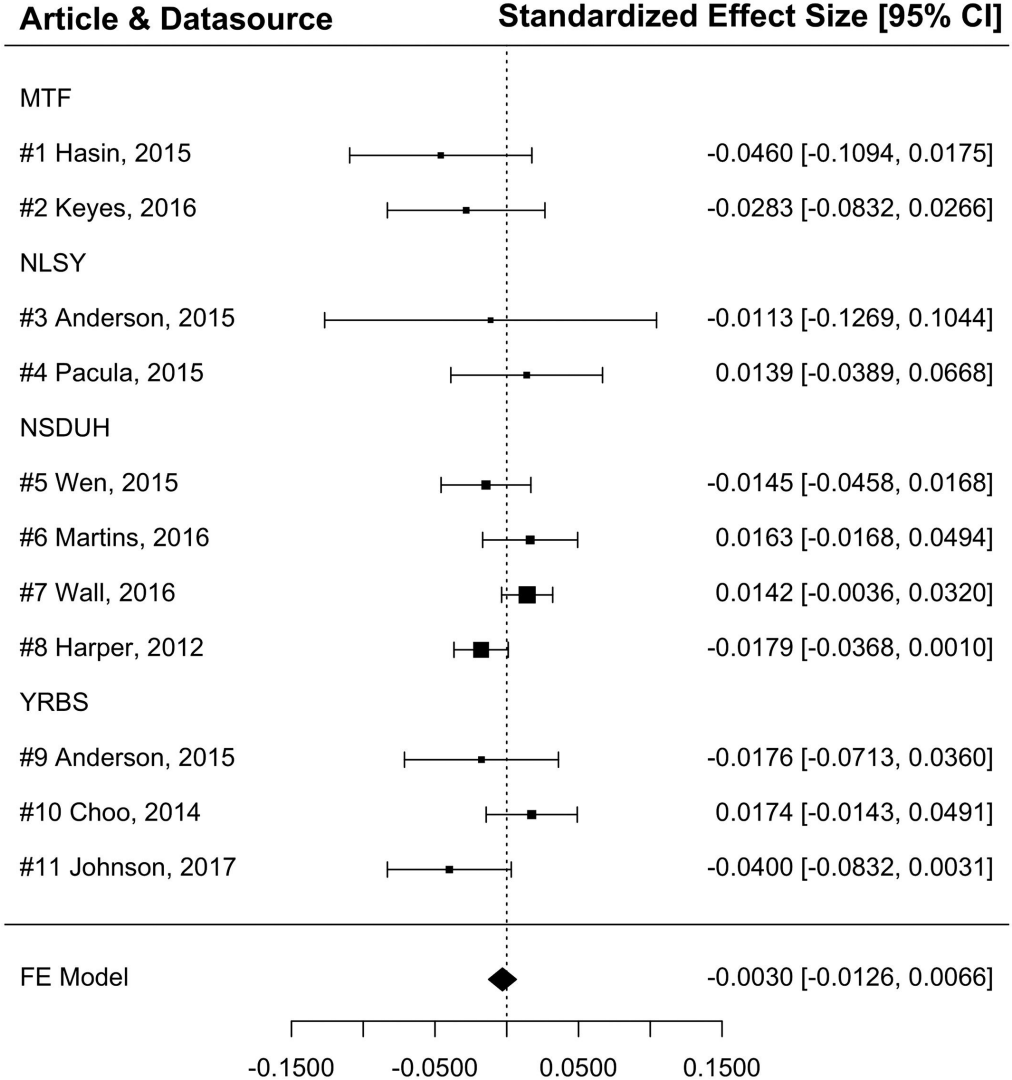
Cannabis Use and Risk Perception





Sarvet et al., 2018

Cannabis Legalization and Adolescent Usage



Sarvet et al., 2018

Summary

Cannabis History:
Cultivation, Medicine, Usage Rates and Legalization

Cannabis likely originated in central Asia, but distributed widely before written history.

Medical uses reported in Egypt, India and China all around 2000 BCE.

Brought to the Americas through the slave trade.

Summary

Cannabis History:
Cultivation, Medicine, Usage Rates and Legalization

Modern medicine's interest was piqued in 1800's. Tincture preparation spread to Europe and Americas, especially utilized by physicians.

Medical interest waned in 1930's; and, interest in smoked *cannabis* criminalization driven by racism and xenophobia.

Summary

Cannabis History:
Cultivation, Medicine, Usage Rates and Legalization

1970, classified as a Schedule 1 Drug in USA.

Changes in decriminalization and legalization—increase in jurisdictions legalizing and decriminalizing medical and recreational *cannabis*.

Consideration needs to be taken on how *cannabis* legalization can address racialized outcomes of criminalization.

Summary

Cannabis History:
Cultivation, Medicine, Usage Rates and Legalization

Cannabis use peaked in 1970s, was at a low in 1990s, before increasing again in 2000s.

Lifetime prevalence in individuals 25+ in the USA and Canada is apx. 50 % and 40 %, respectively.

Although *cannabis* use increases with availability, social acceptance and lowered perceived risk, there is no evidence this is the case for adolescents in US states where legal.

Medical Uses of *Cannabis*

Current Medicinal Uses for *Cannabis*

- Antiemetic (anti-nausea)
  - Synthetic cannabinoids (nabilone and dronabinol/Marinol) and THC*
- Cachexia (general wasting and malnutrition that occurs in the context of chronic diseases such as cancer and HIV/ AIDS)
  - Synthetic cannabinoids (Marinol) and THC*
- Pain
  - stimulation of CB 1 receptors along pain pathways in the periphery, spinal cord, and brain produces antinociception
  - THC is largely effective at alleviating chronic neuropathic pain
  - Opioid sparing effects (rev. in Donvito et al., 2017)
  - Role for CBD?

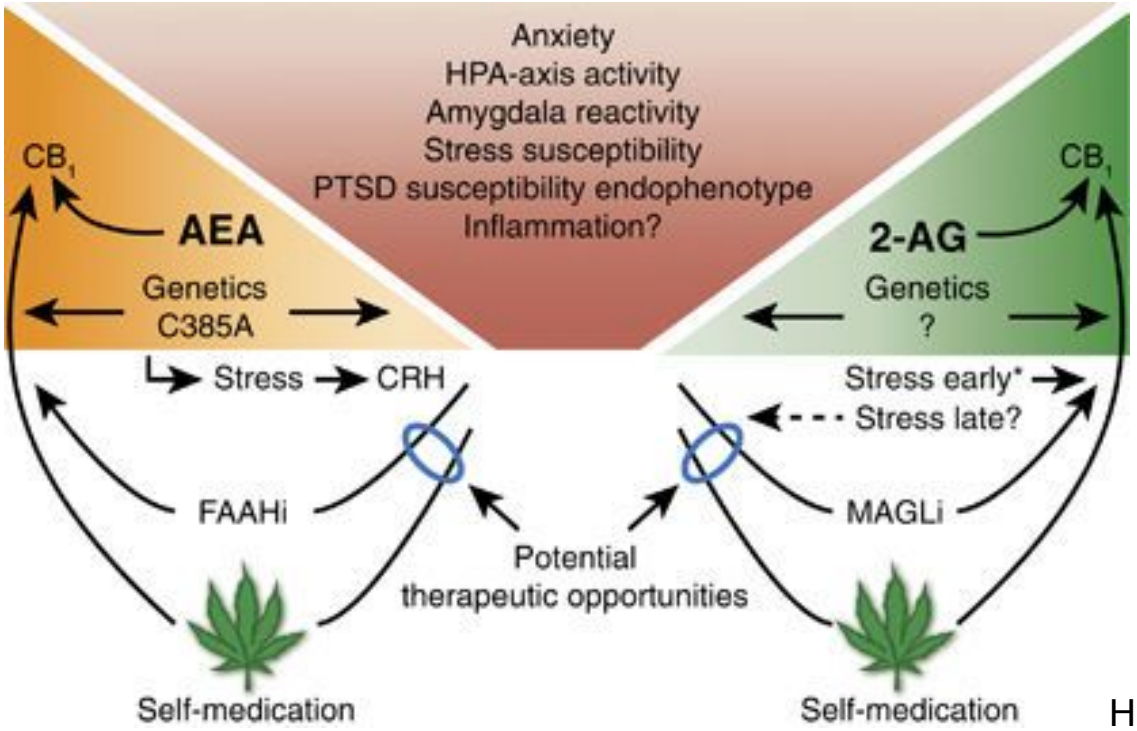
Current Medicinal Uses for *Cannabis*

- Muscle Spasticity (disordered sensorimotor control that leads to involuntary muscle activation; present in ALS and MS)
  - Oral or sublingual THC reduces spasms (smoking to a lesser degree)
  - Cannabinoids reduce spasticity largely through anti-inflammatory and neuron-inhibitory actions within the spinal cord
- Glaucoma (intraocular pressure is too high)
  - Smoking cannabis reduces pressure for about 60-65% of individuals; effect lasts for roughly 3-4 hours, thus requiring users to smoke multiple times per day to achieve relief

Current Medicinal Uses for *Cannabis*

- Epilepsy
  - potential benefit of cannabinoids in treating seizure disorders stems mostly from CBD or other non-psychoactive cannabinoids
    - Currently testing CBD in Dravet Syndrome
- Hypothesized potential for treating many other disorders
  - Research is lacking
  - Results are inconclusive
  - CB2 agonists for anti-inflammatory and immunosuppressive properties

Current Medicinal Uses for *Cannabis*



Hill et al., 2017

Summary

Medicinal Cannabinoids

Cannabinoids are used for antiemetic and anti-cachexia properties.

Cannabinoids have antinociceptive properties; opioid sparing properties.

There is still a lot of research required to understand full therapeutic properties of cannabinoids.

Adverse Effects of *Cannabis*

Drug Poisoning and Toxic Effects

- No CB1 receptors on brain stem nuclei controlling vital life functions
  - THC will not cause respiratory depression
- Toxic effects of synthetic cannabinoids
  - Lethal effects include seizures and heart attack
  - Suicidality

Mental Disturbance and Psychosis

- “Inverted U”
  - Effects on anxiety, agitation, paranoia, delusions, auditory and visual hallucinations, depersonalization, derealization, disorganized thinking, and impairments in attention and memory
- Psychosis
  - Mixed evidence, poorly designed studies
  - Likely decreases age of onset for individuals susceptible to schizophrenia and psychosis
- Higher CBD seems to blunt these effects

Persistent Intellectual Impairment

- Mixed results of prenatal, childhood and adolescent exposures
- Heavy users during childhood, adolescence and into adulthood in one cohort study had lower IQ scores (apx. 8 points)
- Prenatal exposure correlates with cognitive impairment

Amotivational Syndrome

Amotivational syndrome—changes in lifestyle, ambitions, level of motivation, and personality

- Data mixed
  - Recent studies that showed that 5 % of high school students display amotivational syndrome
  - Possibly a variety of factors, including persistent alcohol and tobacco use

Gateway Drug

Gateway drug—first step toward the use of more dangerous drugs

- No causal relationship

Common factor model

- Results of this model demonstrate that degree of drug exposure is better predictor of hard drug use than *cannabis* use

Respiratory Health & Lung Cancer

- Mixed data
- Similar to smoking tobacco, smoking *cannabis* leads to smoke containing toxins (causing oxidative stress) and carcinogens
    - Different routes of administration lead to different amounts of smoke
    - Many *cannabis* smokers also tobacco smokers
- THC, CBD and endocannabinoids have all shown anti-tumor properties in cell culture studies

Summary

Adverse Effects of *Cannabis*

Scientific evidence on potential adverse effects of *cannabis* are inconsistent and contradictory.

Cannabis use may speed up age of onset for first-onset psychosis and schizophrenia.

Little causal evidence that *cannabis* is a gateway drug.

Mixed results on links between *cannabis* and respiratory health and lung cancer.

Cannabis Dependence

Cannabis Dependence

- Annual rates of *cannabis* use has leveled off recently
- Daily use rates have increased in the past decade
- Frequency is associated with dependence
- 31 % of *cannabis* users meet DSM-V criteria for *cannabis* use disorder
- Risk highest for those who started *cannabis* use as an adolescent and continued to daily use as an adult

Cannabis Use Disorder

	DSM-IV Abuse[a]		DSM-IV Dependence[b]		DSM-5 SUD[c]	
Hazardous use (e.g., driving under the influence)	X	≥1 criteria	–		X	≥2 criteria
Social/interpersonal problems related to use	X		–		X	
Neglected major roles to use	X		–		X	
Legal problems	X		–		–	
Withdrawal[d]	–		–	≥3 criteria	X	
Tolerance	–		X		X	
Used larger amounts/longer	–		X		X	
Repeated attempts to quit/control use	–		X		X	
Much time spent using	–		X		X	
Physical/psychological problems related to use	–		X		X	
Activities given up to use	–		X		X	
Craving[d]	–		–		X	

[a] One or more abuse criteria within a 12-month period
[b] Three or more dependence criteria within a 12-month period
[c] Two or more SUD criteria within a 12-month period
[d] New criterion added in DSM-5

Rewarding Effects of *Cannabis*

http://thebrain.mcgill.ca/flash/i/i_03/i_03_m/i_03_m_par/i_03_m_par_cannabis.html#drogues

Linked to activation of CB1 on GABA neurons, not DA neurons in midbrain.

Administration of cannabinoids produces reward and reinforcement.

Tolerance

- Tolerance to repeated cannabinoid exposure
  - Due to pharmacodynamic changes not pharmacokinetic changes
    - Receptor sensitivity
- Tolerance that develops rapidly, dissipates rapidly
- Synthetic cannabinoids lead to higher levels of tolerance

Withdrawal

- Inconsistent reports of physical withdrawal from *cannabis*
- ⅓ of regular *cannabis* users will experience withdrawal
- Animals
  - Shakes, face rubbing, hypolocomotion etc…
- Humans
  - Irritability, anger, aggression
  - Anxiety
  - Restlessness
  - Difficulty sleeping
  - Changes in appetite
- Stronger effects with synthetic cannabinoids

Summary

Cannabis Dependence

Cannabis use disorder rate is 31 % in regular users.

Cannabinoids are likely rewarding and reinforcing through acting in reward circuitry on GABA neurons, not DA neurons.

Animals and humans both show tolerance and dependence (apx. ⅓) to regular use.

Synthetic cannabinoids produce greater effects than THC.

Resources

http://www.nature.com/nppr/index2_2018.html#Review-Articles

http://www.broadbentinstitute.ca/aobempah/cannabis_legalization_and_equity_in_canada

https://robynmaynard.com/another-black-life-taken-by-the-montreal-police-collateral-damage-in-a-racist-war-on-drugs/

https://www.canada.ca/en/health-canada/services/publications/drugs-health-products/summary-comments-public-consultation-regulation-cannabis.html