THE IRRATIONAL USE OF MEDICAL MARIJUANA IN CANADA

THE ENDOCANNABINOID SYSTEM

- Located in brain & throughout peripheral nervous systems
- Neuromodulatory lipids acting via cannabis receptors
- Influencing: appetite, pain-sensation, mood, and memory

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- (☺) Executive Summary
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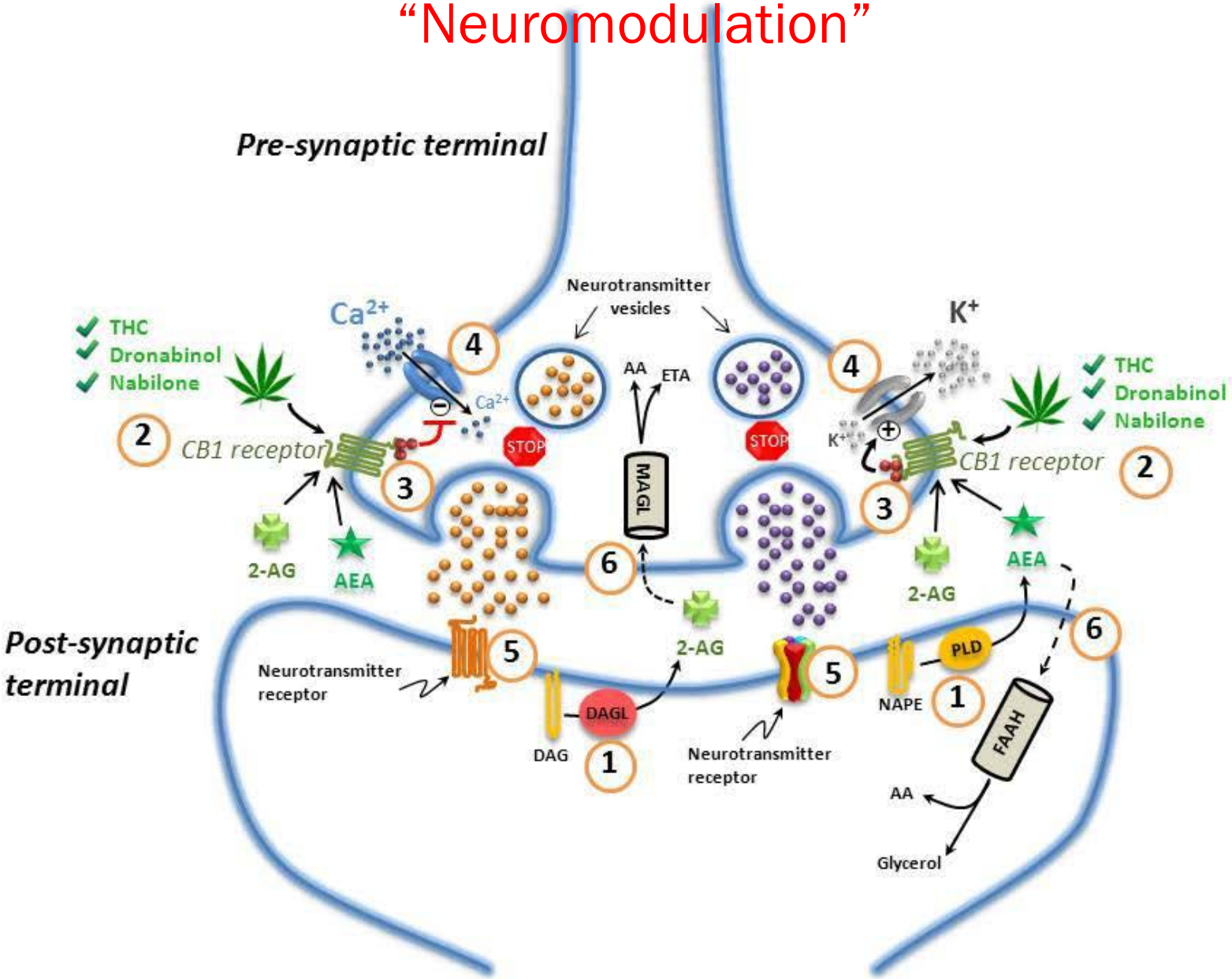
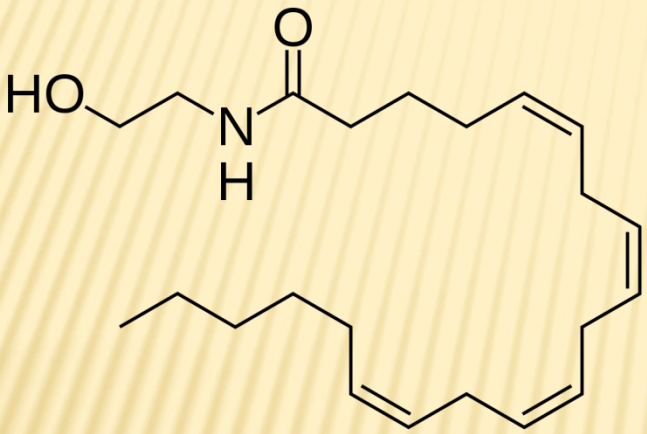
“Neuromodulation”

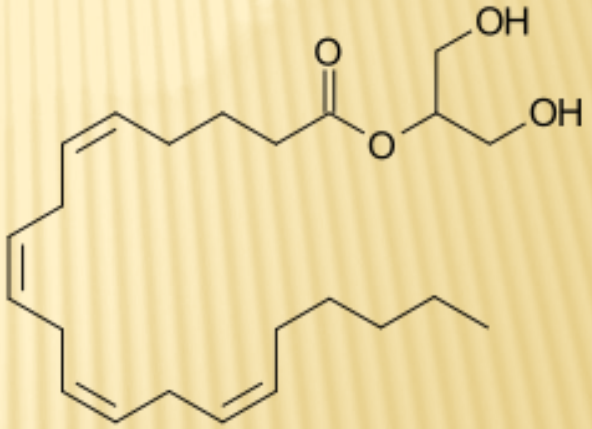


THE ENDOCANNABINOIDS

Anandamide



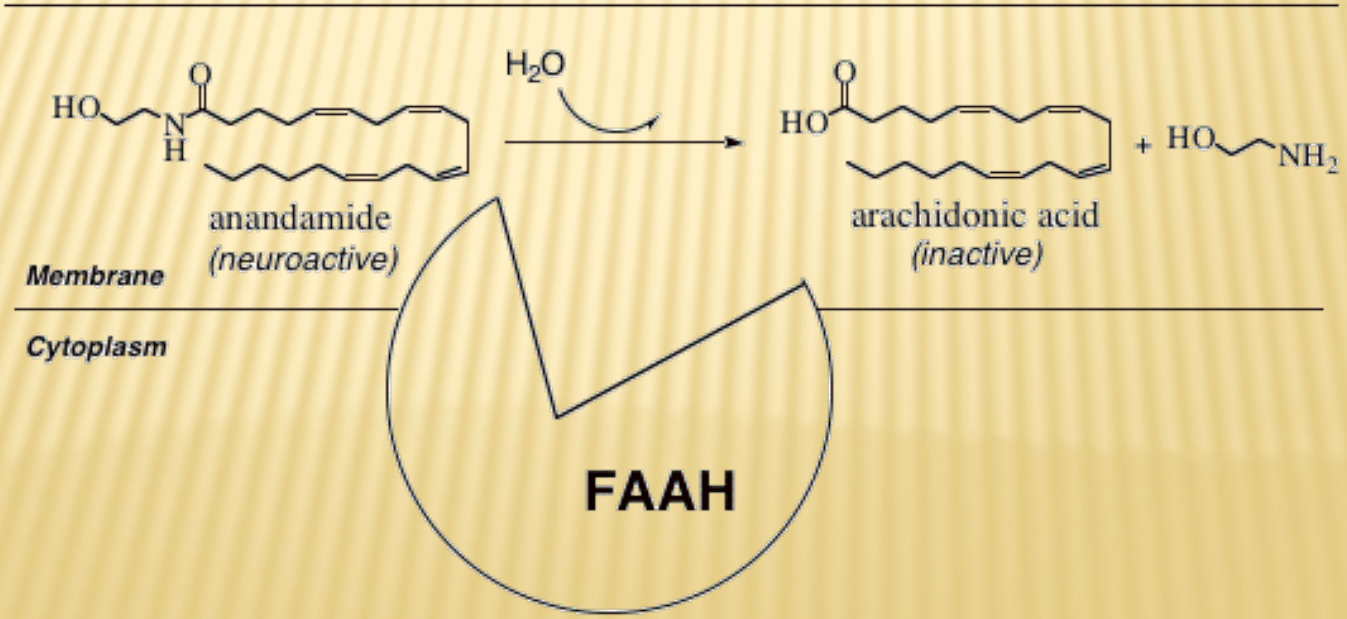
2-Arachidonoylglycerol (2-AG)



In Cannabis plant: **Tetrahydrocannabinol THC** – mimics Anandamide effect

THE ENDOCANNABINOIDS

- Lipids (Eicosanoids) neurotransmitter
- Synthesized from arachidonic acid like all eicosanoids
- Degraded by fatty acid amide hydrolase (FAAH)



THC RECEPTORS

- CB_1
  - Basal ganglia & cerebellum (motor control), hippocampus (short term memory), neocortex (abstract thinking), hypothalamus & limbic system (appetite, sedation), etc. responsible for "high"
- CB_2
  - Mainly expressed in the immune system (WBC) and in hematopoietic cells (bone marrow)
  - Keratinocytes, on peripheral nerve terminals, (role in nociception - Pain), microglial cells in CNS
  - Also in few brain locations
- Cannabinoids that bind more selectively to certain receptors are more desirable for medical usage

CANNABINOID RECEPTORS

- 473 aa with 7 trans-membrane domains
- **G-protein coupled rec. far reaching effects via signal transduction cascades, incl. change in transcription (protein synthesis)**
- Effect on neuronal activity – generally inhibitory
  - Effects on Ca^{++} and K^{+} channels, cAMP levels – very complex

CB_1 KNOCKOUT MICE

- Viable and live into adulthood
- On high-fat diet **60% leaner** and slightly less hungry than wildtype
- **Severe deficits in motor learning, memory retrieval,** and increased difficulty in completing the Morris water maze
- Increased incidence and severity of strokes and seizures

CB_2 KNOCKOUT MICE

- Long-term contextual **fear** memory impaired
- Cued **fear** memory normal
- Enhanced **spatial working memory**
- Motor activity and anxiety intact
- Acute blockade of CB_2 receptors via antagonist - no effect on memory, motor activity, or anxiety
- CB_2 cannabinoid receptors play diverse roles in regulating memory depending on memory types and/or brain areas

CB_2 VARIATION IN HUMANS

- A polymorphism of *CNR2 gene*, which encodes CB2R related to schizophrenia, depression & bipolar disorder

$CB_{1\&2}$ KNOCKOUT MICE

- KO-mice for <u>both</u> CB_1 and CB_2 rec. Cannabis still has some effects
- Other additional receptor?
- E.g. **transient receptor potential cation channel subfamily V member 1 (TrpV1)**
- **Capsaicin receptor** and the **vanilloid receptor 1**
- Member of the TRPV group of transient receptor potential family of ion channels
- **Function:** detection and regulation of **body temperature sensation of scalding heat and pain nociception**
- Excited by: acidic conditions; capsaicin(hot chili peppers)& allyl isothiocyanate (mustard & wasabi)

FAAH (DEGRADING ENZYME FOR ENDOS)

- People with defective enzyme function
- Elevated anandamide levels
- Reduced pain perception, anxiety, PTSD
- FAAH inhibitors in drug development
- Neuropathic pain treatment, inflammatory bowel and Chrohn's disease, etc.

- *FAAH* KO mice >15-fold levels of *N*-acylethanolamines and *N*-acyltaurines in various tissues.
- Significantly elevated anandamide levels
- Reduced pain sensation in the hot plate test and other tests
- Super-sensitivity to exogenous anandamide

EFFECTS OF ENDOS

- Memory
  - **Inhibition of long-term memory formation**
  - CB_1- rec KO-mice – enhanced memory
    - Physiological purpose: erase unnecessary memory, free up space (“RAM”)

EFFECTS

- Appetite
  - Stimulated via CB_1 rec.
  - Activity reduces leptin (satiety hormone)
  - Leptin KO-mouse – extremely obese, very high levels of anandamide
  - **The munchies in pot users**
  - **Rimonabant Acomplia®(THC antagonist) reduced appetite**
    - **Was briefly on market as appetite suppressant, withdrawn due to suicidal side effects**
  - **Modulation of taste perception – sweet preference (☺)**

EFFECTS

- **Stress**
  - Acute stress (adrenalin release – within seconds-minutes)
  - Prolonged stress – cortisol release – within hours
- **Moderation of cortisol secretion**
  - **Lesser stress response**

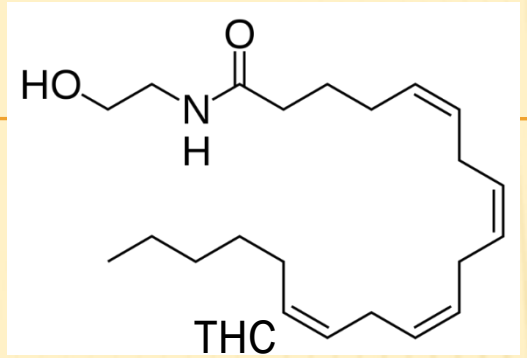
EFFECTS

- **Exploration, social behavior, and anxiety**
  - Modulation of neurons using: CB_1 KO mice
  - Endocannabinoid – decrease release of NT
  - **Glutamate as NT (excitatory)**
    - decreased object exploration, social interactions, and increased aggressive behavior (in absence of endocannabinoid)
  - **GABA as NT (inhibitory NT)**
    - increased exploration of objects, socialization, and open field movement (in absence of endocannabinoid)

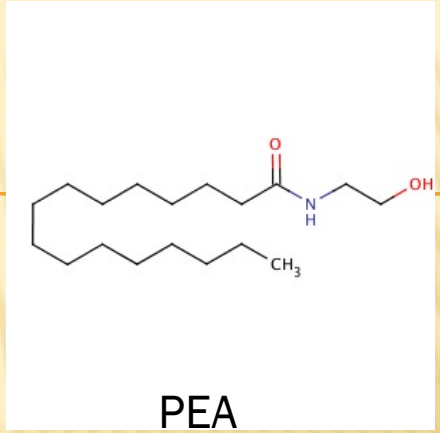
EFFECTS

- Immune system
  - CB_1 rec. found on several types of WBC
    - Weak evidence for direct effects
- Multiple sclerosis
  - Two medical issues:
    - 1. Origin is autoimmune attack on myelin protein of neurons
    - 2. Demyelination of neurons – neurological symptoms
  - THC beneficial effect on patients with MS
    - Less tremor, less pain via effect on neurons – probably not on autoimmune attack perse

EFFECTS



THC



PEA

- **Analgesia (Pain)**
  - Suppression of pain conduction in spinal cord
  - Very convoluted mechanism
    - Another endogenous eicosanoid: **Palmitoylethanolamide** (**PEA**) binds to two other receptors: peroxisome proliferator-activated receptor alpha (PPAR-α)
    - PEA also has affinity to cannabinoid-like G-coupled receptors GPR55 and GPR119
    - Relation to inflammation and chronic pain

EFFECTS

- Thermoregulation
  - Vasodilation (as in response to heat challenge)
  - Not mediated via CB_1 rec. (KO-mice) rather via two other receptors
  - TRPA1 channels receptor by releasing CGRP from perivascular sensory neurons
- Also activated by endocannabionoids and THC
  - Red eyes in pot smokers (☺)

EFFECTS

- Sleep
  - promotes sleep-inducing effects incl. REM sleep
  - In rats: circadian changes in endocannabinoid levels
  - Highest during day (nocturnal animals)

EFFECTS

- Dopamine release in reward circuit indirect via opioid neurons – effect blocked by naloxone
- Overstimulation of cannabinoid receptors via THC
- Disruption of endogenous cannabinoids' normal homeostasis
- Gradual degradation of some cannabinoid receptors
- Possibly producing permanent adverse effects and contributing to addiction and risk for a withdrawal syndrome

ACUTE EFFECTS - TIMING

- Not relevant for the “normal endogenous cannabinoid system”
- Smoking: effects begin immediately after the drug enters the brain
- Inhalation causes very high, short-lived plasma levels
  - The Buzz (☺)
- duration 1 to 3h
- Oral route: onset slower (½ –2 h) duration 4 h

ACUTE EFFECTS

- Heart rate increase by 20 to 50 bpm
- Bronchial relaxation/dilation
  - Chronic use - constriction
- Vasodilation in eyes
- Euphoria via reward system
- Possible experience of pleasant sensations, colors and sounds may seem more intense
- Time appears to pass very slowly
- Dry mouth, sudden hunger or thirst
- Hands may tremble and grow cold
- After euphoria sedation or depression
- Occasionally, anxiety, fear, distrust, or panic

ACUTE EFFECTS

- Impaired ability to form memories (anterograde amnesia), recall events and shift attention from one thing to another
- Disruption of coordination and balance
  - (Potential cause of accidents)
- 6 – 11% of fatal accident victims test positive for THC. In many of these cases, alcohol is detected as well
- High doses: Hallucination, delusion, paranoia

ACUTE EFFECTS

- Person's risk of heart attack during the first hour after smoking marijuana increased 4x
  - Via increased heart rate
- Appetite stimulation
  - *Munchies*

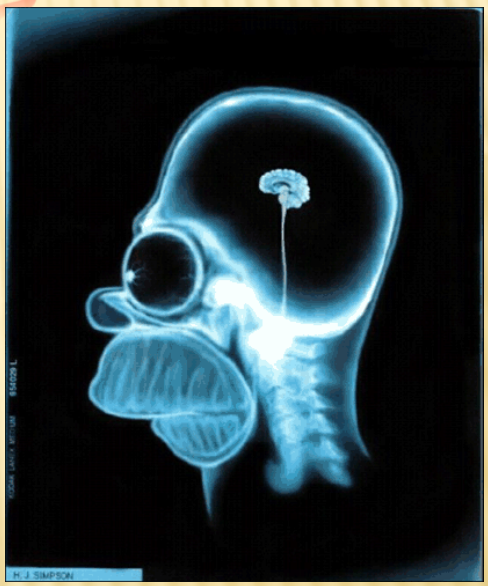
ACUTE TOXICITY OVERDOSES?

- No fatal overdose known (LD_{50})
- Rare acute complications
  - (e.g. panic attacks, psychoses, convulsions, etc.) that present to hospital Emergency Departments

PHYSICAL HEALTH

- Respiratory problems
- Daily cough and phlegm production
- More frequent acute chest illnesses, a heightened risk of lung infections, and a greater tendency toward obstructed airways
- Tar content in *joints* higher that in tobacco cigarettes
- Inhalation deeper/more prolonged
- Carbon monoxide, PAH (carcinogens)

CHRONIC LONG-TERM EFFECTS



- Depression
- Anxiety
- Personality
  - Amotivational Syndrome
- Compromises ability to learn and remember information
- Psychosis in genetically pre-disposed people (especially in adolescence)

PSYCHOSIS

- Some people with COMT gene (Catechol O-methyl transferase) variant coding for Val instead of Met
- *Val/Val* genotype higher enzymatic activity
  - lower dopamine levels in the prefrontal cortex
  - Homozygous carriers for Val allele - increase in the incidence of hallucinations after cannabis exposure
  - conditional on prior psychometric evidence of psychosis liability
- *Met/Met* genotype low enzyme activity higher dopamine levels
- *Val/Met* genotype intermediate

ADDICTION POTENTIAL

- 30% of users with some degree of addiction
- Individuals using before the age of 18 addiction increases 4–7 fold
- 17% of users since adolescence become dependent

CANNABIS SATIVA MARIJUANA

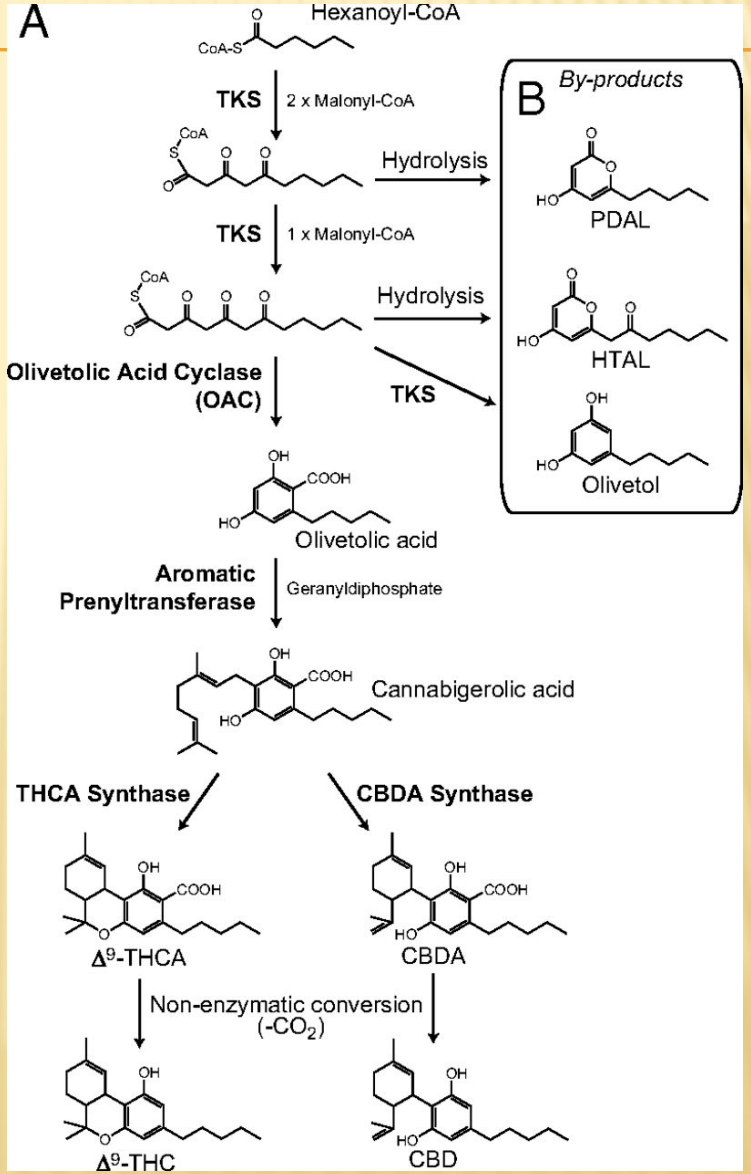
- Buds and leaves of female plant
- Main active compound:
- THC (Tetrahydrocannabinol)
- Content of product highly variable:
- 1-30% avg.: 10% at present
- BC world leading for highest content!
- Problem with research of “pot smokers”
  - Used very weak “legal” products (produced by government labs)
  - Clean pharmacology: use pure THC! Need to document plasma levels in smokers or stick at least to known exact doses in oral administration

HASHISH

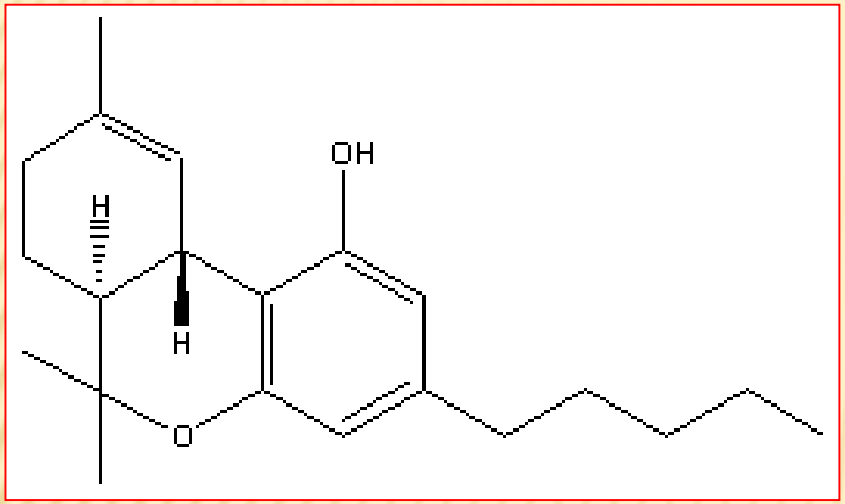
- Tetrahydrocannabinol (THC) content of hashish comes in wide ranges from almost none to 65% and that of hash oil from 30% to 90%
- Extracted product composed of compressed or purified preparations of stalked resin glands

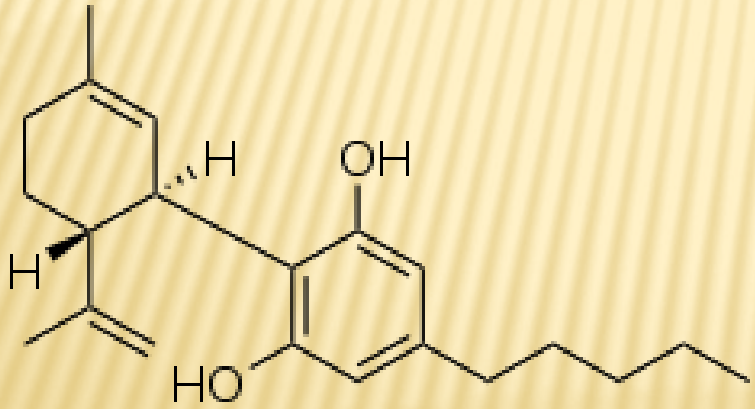
CANABINOIDS

- A member group of the "terpenes"
- Total number of cannabinoids isolated varies in literature 70 – 113 (?)



CANNABINOIDS





- Main Cannabioids THC and cannabidiol
- THC responsible for main psychoactive effect
- Via CB_1 rec.

CANNABIDIOL (CBD)

- Lacks psychoactivity
- No affinity at CB_1 or CB_2 receptors
- Acts via a number of other targets including ion channels, receptors, and enzymes
- anti-inflammatory, analgesic, anti-nausea, anti-emetic, anti-psychotic, anti-ischemic, anxiolytic, and anti-epileptiform effects

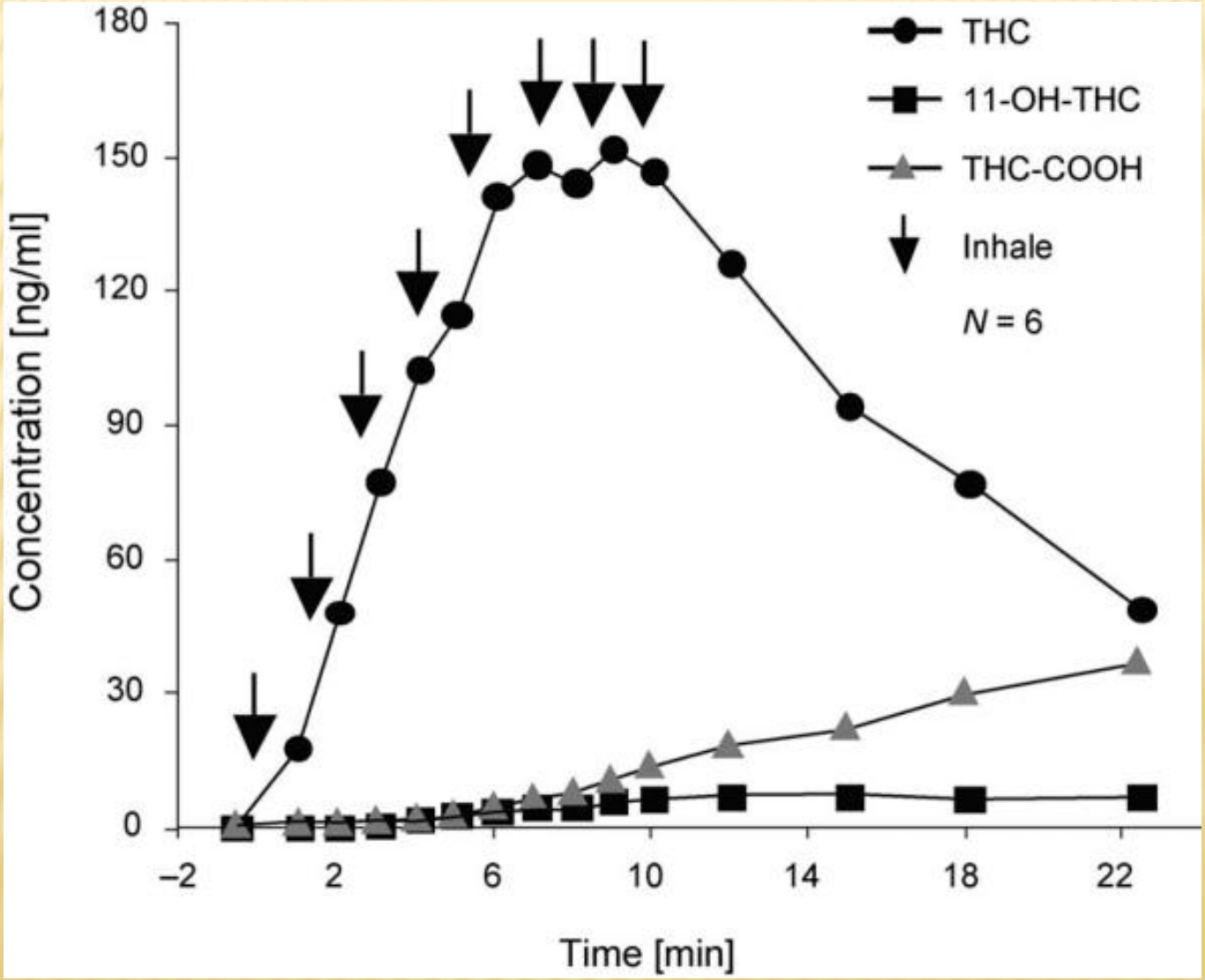
SMOKE OF A DOOBIE

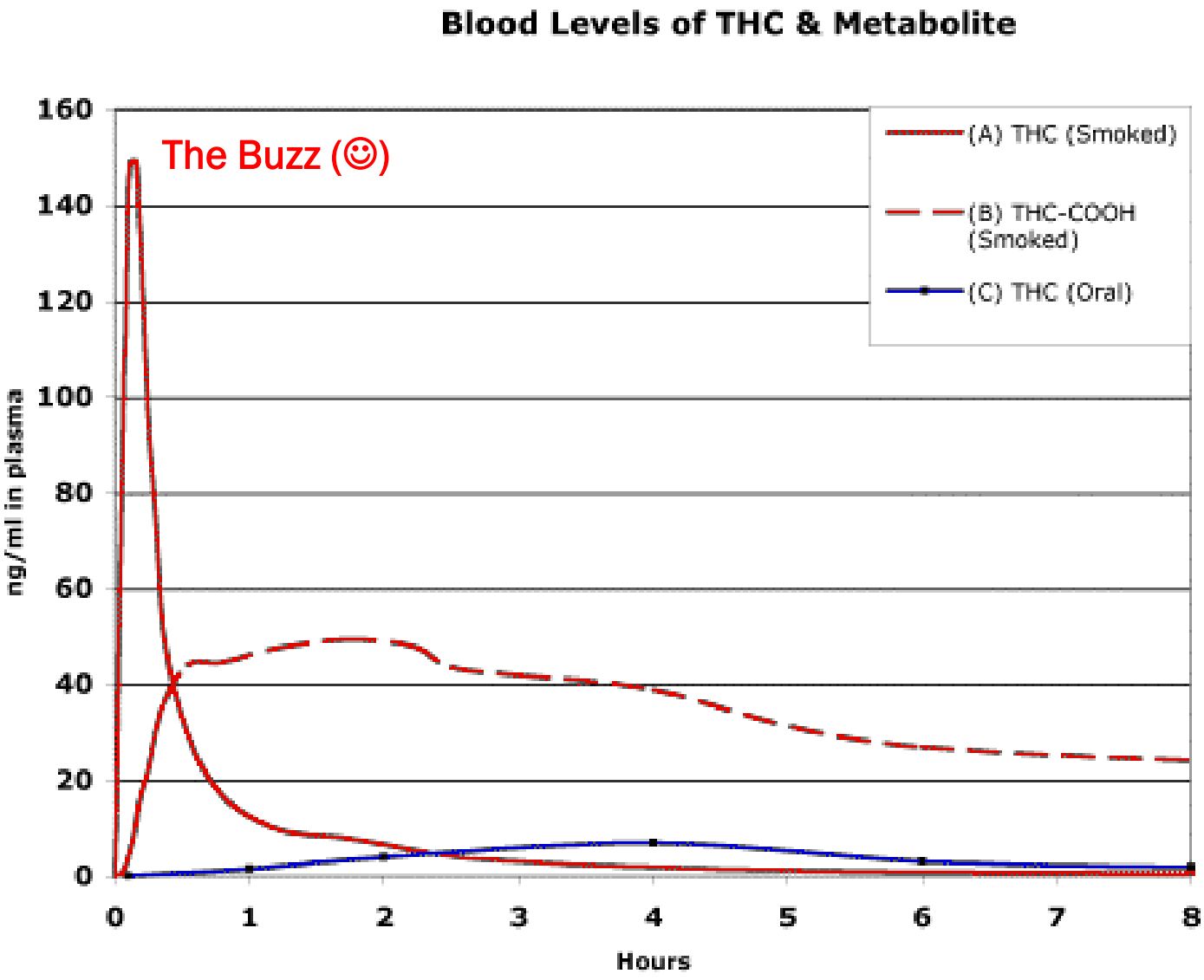
- Pyrolysis transforms each of the hundreds of compounds in cannabis into a number of other compounds
- *"Marihuana (cannabis) can be considered a very crude drug containing a very large number of chemical and pharmacological constituents, the properties of which are only slowly being understood."* Health Canada – see reference at end
- Similar composition of tar and carcinogens as tobacco smoke

PHARMACOKINETIC

- THC highly lipophilic
- Smoking of joints
- Rapid pulmonary absorption of THC vapours
  - Short lived very high plasma levels
  - Smoking extremely variable doses absorbed
    - Type, quality of plant, technique of burning, inhalation, etc.
    - bioavailability of 2 - 56%
  - Vaporization – many of the same dosing issues

SMOKING OF A SINGLE CANNABIS CIGARETTE CONTAINING 3.55% OF THC. ARROWS (↓) INDICATE ONE INHALATION OR PUFF




Blood Levels of THC & Metabolite
The Buzz (☺)
(A) THC (Smoked)
(B) THC-COOH (Smoked)
(C) THC (Oral)
ng/ml in plasma
160
140
120
100
80
60
40
20
0
0
1
2
3
4
5
6
7
8
Hours

ORAL USE OF PURE THC (MARINOL®)

- Dose highly variable b/w patients used in loss of appetite in AIDS pts. & chemotherapy associated nausea
  - 2.5 – 40 mg/day
  - Plasma levels:

Dose [mg]	Peak plasm [ng/ml]
2.5	1.3
5	3.0
10	7.9

  - Smoking of joint with 3.55% THC – levels b/w 100-250 ng/ml
  - Some cannabis today: up to 30%
  - Legal limit in Colorado for driving 5 ng/ml

PHARMACOKINETIC

- Well absorb after oral intake, but high first pass effect (bioavailability ca. 10%)
- Reaches all organs throughout body
  - Redistribution to adipose tissue
- t ½ ca. 30 h
- Accumulation of THC in fat tissue – prolonged t ½
- THC accumulation with frequent use

SOME WISDOMS OF PHARMACOLOGY

- Use as few drugs and as little as possible to achieve desired effect
- "Polypragmatic shotgun therapy"
  - Fixed combinations of several drugs with particular effects combined
  - Not recommended
  - E.g. cold remedy: antihistamine, analgesic, decongestant, antitussive, sedative – all in one tablet as fixed dosages

MARIJUANA

- Very complex mixture of cannabinoids
- Pharmacological jungle of complexity (mess)
- Popular believe among non-scientist “natural” mixtures of compounds is a “naturally benign” combination
- Evolution: Cannabis has no intention to be nice to suffering humans (☹)

SOME STATEMENTS FROM HEALTH AUTHORITIES

- FDA (U.S. Food and Drug Administration)
- The term *medical marijuana* refers to using the whole unprocessed marijuana plant or its basic extracts to treat a disease or symptom. The (FDA) has not recognized or approved the marijuana plant as medicine.

FDA

- The FDA requires carefully conducted studies (clinical trials) in hundreds to thousands of human subjects to determine the benefits and risks of a possible medication. So far, researchers have not conducted enough large-scale clinical trials that show that the benefits of the marijuana plant (as opposed to its cannabinoid ingredients) outweigh its risks in patients it is meant to treat.

FDA

- THC increases appetite and reduces nausea. The FDA-approved THC-based medications are used for these purposes. THC may also decrease pain, inflammation, and muscle control problems.
- CBD is a cannabinoid that does not affect the mind or behavior. It may be useful in reducing pain and inflammation, controlling epileptic seizures, and possibly even treating mental illness and addictions.

HEALTH CANADA

Health Canada Santé Canada

- Cannabis is not an approved therapeutic product and the provision of this information should not be interpreted as an endorsement of the use of this product, or cannabis generally, by Health Canada.
- *But: they do supply medical pot:*
- **12.5 ±2% total THC (Δ^9-THC and Δ^9-THCA), and less than 0.5% CBD**

CANNABIS IN GERMANY

- " Bundesaerztekammer" official body of German Physicians
- Only indication approved for cannabinoids: Advanced MS
- Re: Nausea associated with chemotherapy
  - Clear statement that better, more powerful anti-emetics are available with less adverse effects(☺) than cannabinoids
- Re: anorexia treatment in AIDS
  - Not clinically proven

CANNABIS IN GERMANY

- Re: Chronic pain
  - Recommendation is to use cannabinoids in patients with chronic pain especially in palliative setting
  - "Adverse effects are of positive value"
  - Euphoria, sleep promoting, anti-nausea effect, somewhat increased appetite
- Re: Schizophrenia, Parkinson's
  - No use

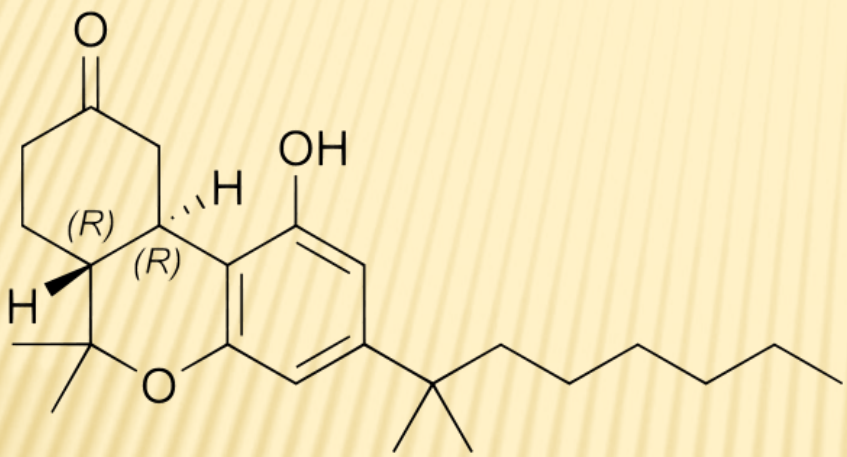
CANNABIS IN GERMANY

- The German statement does not even mention the use of “smoking” cannabis
- Neither does it approve any “whole extract” of cannabis
- Recommends only use of pure cannabinoids

PURE CANNABINOIDS AS DRUGS

- Sativex® combination of THC and cannabidiol (aka: Nabiximols) aerosolized mist for oral administration
  - Approved in Canada for pain relief in MS & cancer (since 2005) oro-mucosal mouth spray
  - Each spray delivers a dose of 2.7 mg THC and 2.5 mg CBD
- Pure CBD (Epidiolex®) oil extracted from the cannabis
  - in clinical trials for refractory epilepsy syndromes
- Dronabinol (Marinol®)
  - Pure THC not on market in Canada

PURE CANNABINOIDS AS DRUGS



- Nabilone (Cesamet®) man made THC-related drug
- CB_1 rec. agonist
- Adverse effect: euphoria (high)
- On market in Canada
- Antiemetic, analgesic

GOOD REFERNCES

- Health Canada for Professionals (1,000 references)
- http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php#chp11
- Canadian Center on Substance Abuse: (97 pages – referenced)
- “Effect of Cannabis during adolescence”
- http://www.ccsa.ca/Resource%20Library/CCSA-Effects-of-Cannabis-Use-during-Adolescence-Report-2015-en.pdf
- In German: Official statement of the Body of German Physicians:
- http://www.akdae.de/Stellungnahmen/Weitere/20160114.pdf