Reefer Madness 2015: The Science of Leaf Marijuana and Medical Cannabinoids

Dr. Merrill Norton Pharm.D.,D.Ph.,ICCDP-D
University of Georgia College of Pharmacy
Athens,Georgia
mernort@gmail.com

News

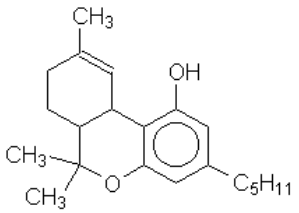
- More Americans are using marijuana, according to a new government report. About 8.4 percent of Americans ages 12 and older were current users of marijuana last year, up from 7.5 percent in 2013. The percentage of teens ages 12 to 17 who smoke, drink or use prescription narcotics nonmedically has fallen, Health Day reports.

Introduction What Do We Know About Medical Marijuana? Is that the Correct Term?

Classifying Marijuana

- Marijuana produces some **excitatory** effects but it is not generally regarded as a stimulant.
- Marijuana produces **sedative** effects, but a person faces no risk of slipping into a coma or dying.
- Marijuana produces mild **analgesic** effects (pain relief), but it is not related pharmacologically to opiates like drugs.
- Marijuana produces **hallucinations** at high doses, but its structure does not resemble LSD or any other drug formally categorized as hallucinogen.

STRUCTURE OF THC



Δ^9-TETRAHYDROCANNABINOL (Δ^9-THC)
(The primary psychoactive molecule)

Background and History of Marijuana

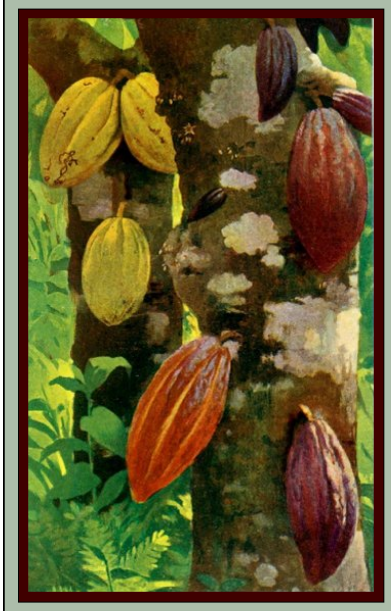
- Produced from the flowering hemp (Cannabis Sativa).
- Hemp was historically important as a major source of fiber for rope making
  - Shipping
- Contains more than 60 unique compounds collectively known as cannabinoids
- Some of these compounds are psychoactive
  - Δ^9 – tetrahydrocannabinol (THC)

Chemistry was established over 100 years ago by two chemists, the Smith Brothers.

50 cannabinoid-based compounds, with 4 major cannabinoids in the plant:

- 2 isomers, a trans-**delta-9-THC** and a delta-8-THC
- A cannabidiol [**CBD**] (the 2nd most abundant psychoactive ingredient after THC)
- A cannabinol is a decomposition product of THC that accumulates as cannabis samples age.

After ingestion, delta-9 is converted in the liver to **11-Hydroxy THC** which is **equally as potent and active.**



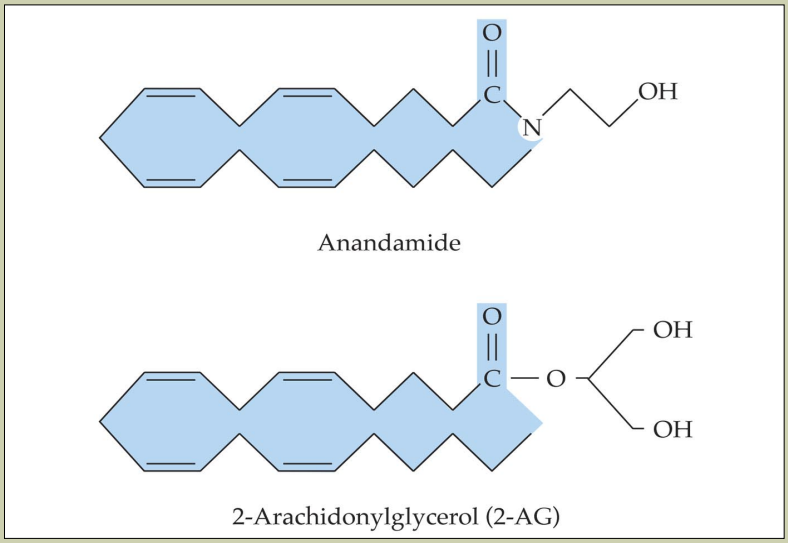
Chocolate tree

Endocannabinoids are the body's endogenous cannabinoids.

"The Bliss Molecules"

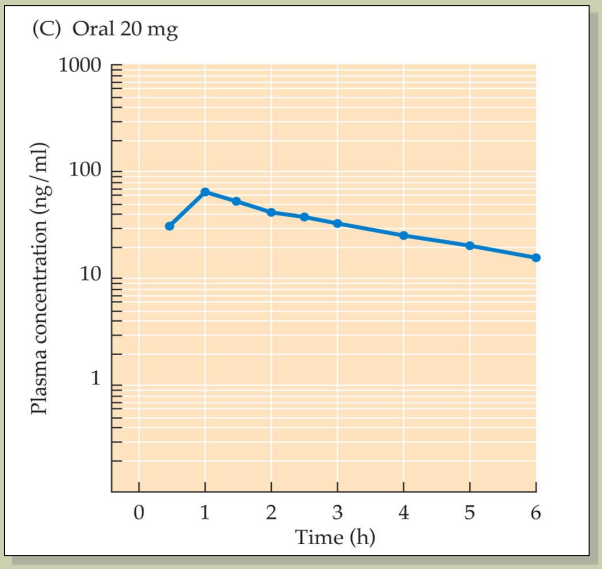
Anandamide (Sanskrit ***ananda*** **inner bliss**) is one endocannabinoid. It is found in chocolate (though there is some controversy over whether the small quantity has any effect on the body). It is **about as potent as THC**.

Chemical structures of the **endocannabinoids** anandamide and 2-arachidonylglycerol (2-AG)

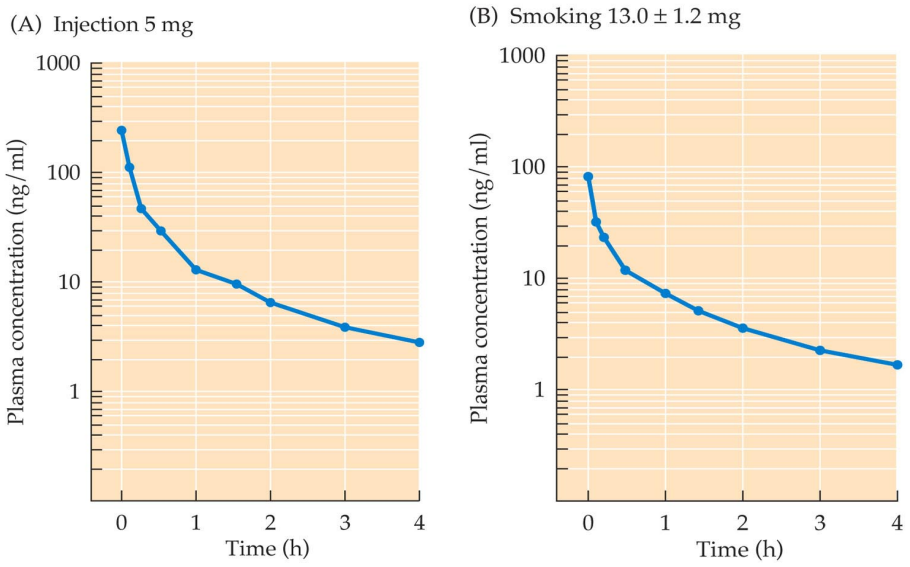


Time course of plasma THC concentrations

THC in a sesame oil suspension



Time course of plasma THC concentrations



After a 6 min smoking period, **peak blood levels reached at about 7 min** (100 ng/ml plasma).

Most THC is **absorbed from the blood within 30 min**.

Moves rapidly into the brain and across the blood/brain/ placental barrier. Because fatty chains make it very lipid soluble.

Half-life is about 19 hours. Can store in fat cells.

Established physiological effects are dose related.

Lethal dose for THC use has now been studied, and no human deaths have been reported due to intoxication from cannabis.

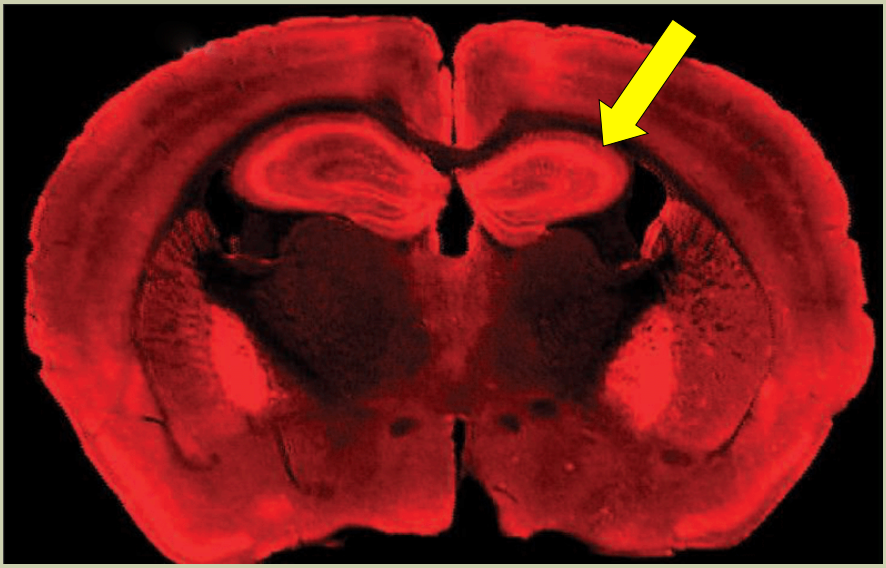
Radioactively labeled delta-9-**THC** has been found to **persist** in the body as an active metabolite **as long as 8 days after use**.

Primary metabolite has a half-life of **50 hours**. The complete elimination of the drug can take as long as **6 weeks!**

After ingestion, delta-9 is converted in the liver to 11-Hydroxy THC which is **equally as potent and active.**

2/3 of metabolites are excreted in feces.
1/3 of metabolites are excreted in urine.

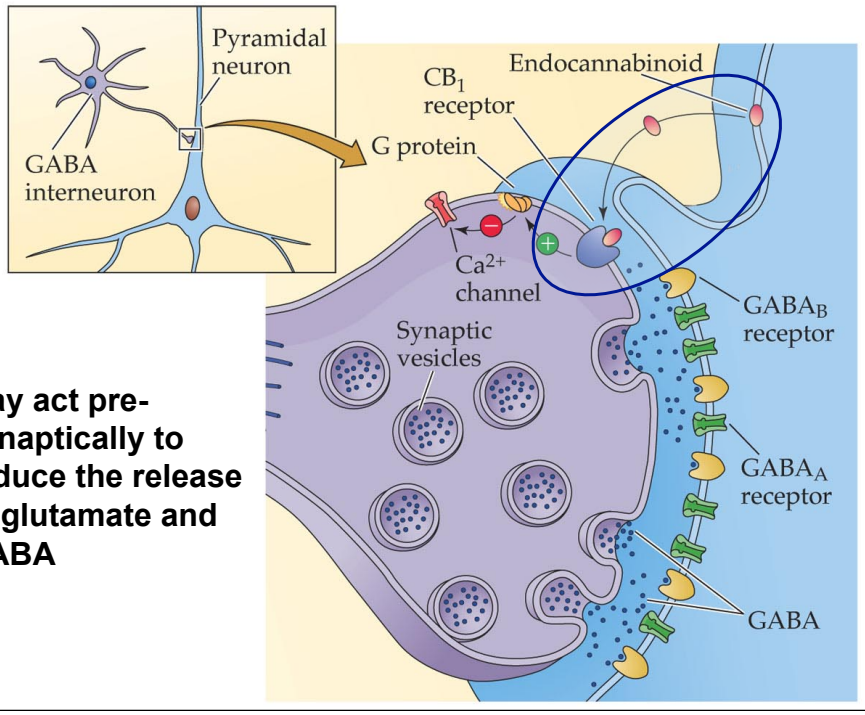
Location of endocannabinoid receptors in a rat brain



CB1 receptors (red) are widely distributed in the brain. K. MACKIE/UNIV WASHINGTON, Science, 2006

Unlike classical neurotransmitters…

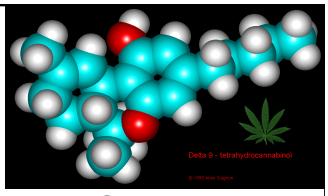
- Endocannabinoids are **not stored in vesicles**.
- Endocannabinoids are **retrograde transmitters**. They are released from the postsynaptic cell and act on the presynaptic cell.

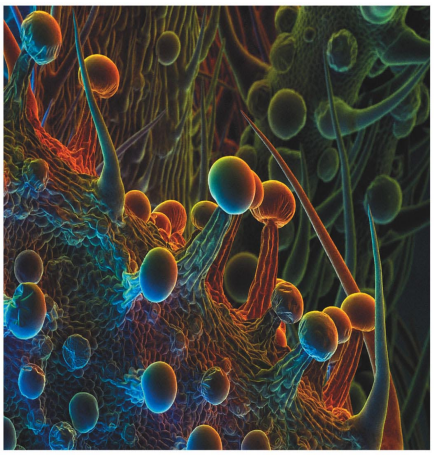


May act pre-synaptically to reduce the release of glutamate and GABA

What Does Science Tell Us About Marijuana?

Active Agents





- Δ-9-THC
- Δ-8-THC
- Cannabidiol
- Active Metabolites

PSYCHOPHARMACOLOGY, Chapter 13 Opener © 2005 Sinauer Associates, Inc.

Cannabis (sativa, indica, ruderalis)

Plant-derived cannabinoids

- Δ^9-tetrahydrocannabinol (9) - THC
- Δ^9-tetrahydrocannabivarin - THCV
- Cannabidiol (7) - CBD
- Cannabigerol (6)
- Cannabichromene (5)
- Cannabicyclol (3)
- Cannabielsoin (5)
- Cannbitriol (9)
- Cannabinol
- Miscellaneous (11)

Br J Pharmacology [illegible] 171

What are cannabinoids?

- Group of >60 dibenzopyran chemicals found in leaves and flowering tops of female cannabis plant (*Cannabis sativa* and *Cannabis indica*)
- Some common cannabinoids are:

In the plant:	In your body (endogenous):	Synthetic:
Δ^9 – THC	2-arichidonyl glycerol (2 – AG)	CP 55,940
Δ^8 – THC	anandamide	HU – 210 (Marinol)
cannabidiol and cannabinol		

CANNABIS KINETICS

- THC
  - Noncrystalline
  - Waxy liquid at room temperature
  - (-) Trans-isomer is 6 to 100 times more potent than (+) trans-isomer
  - Psychoactive effect when bound to CB1 receptor

CANNABIS KINETICS

- Typical joint (Leaf Marijuana)
  - 0.5 - 1 gram cannabis
  - THC concentration 5 - 150mg
  - 20 to 70% of THC is delivered in the smoke
    - 2 - 3 mg THC can produce a brief high
  - Lipid soluble so deposited into fat tissue

CANNABIS KINETICS

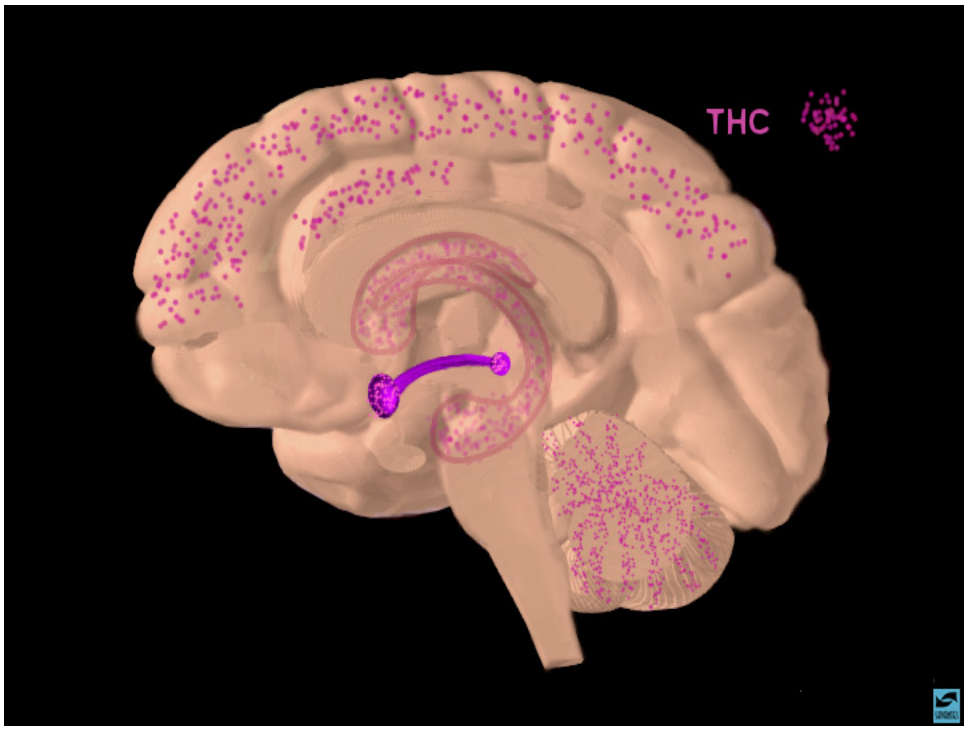
- **80-200 probable biologically inactive metabolites of THC**
- 11-hydroxy - THC is the primary active metabolite
- delta-9-THC most commonly known
- THC is eliminated in the feces and 33% in the urine

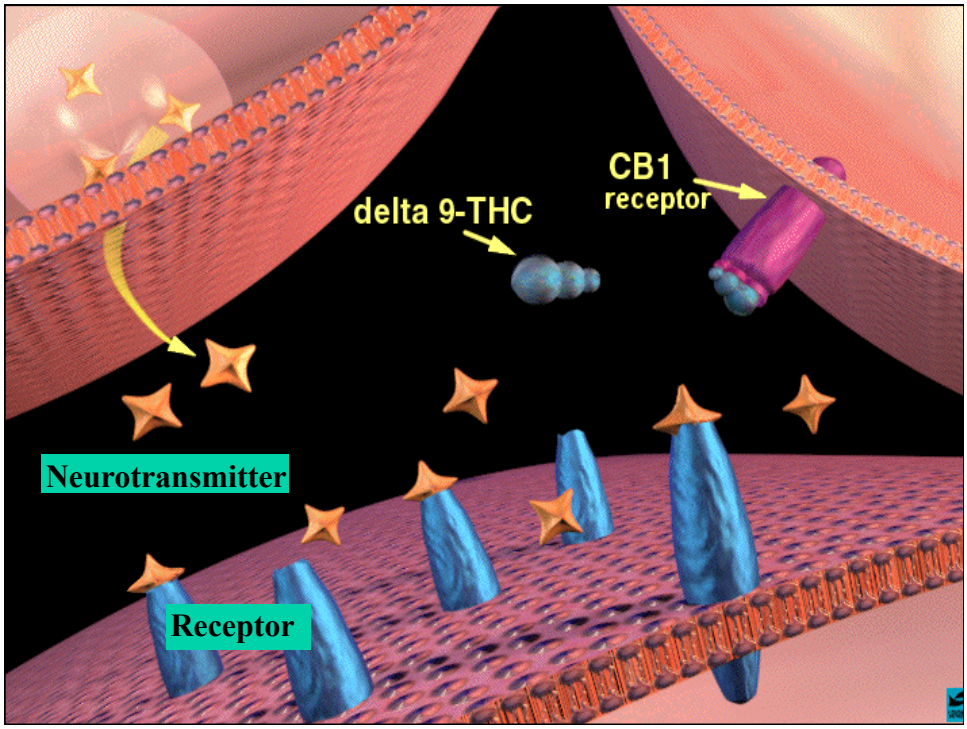
CANNABIS KINETICS

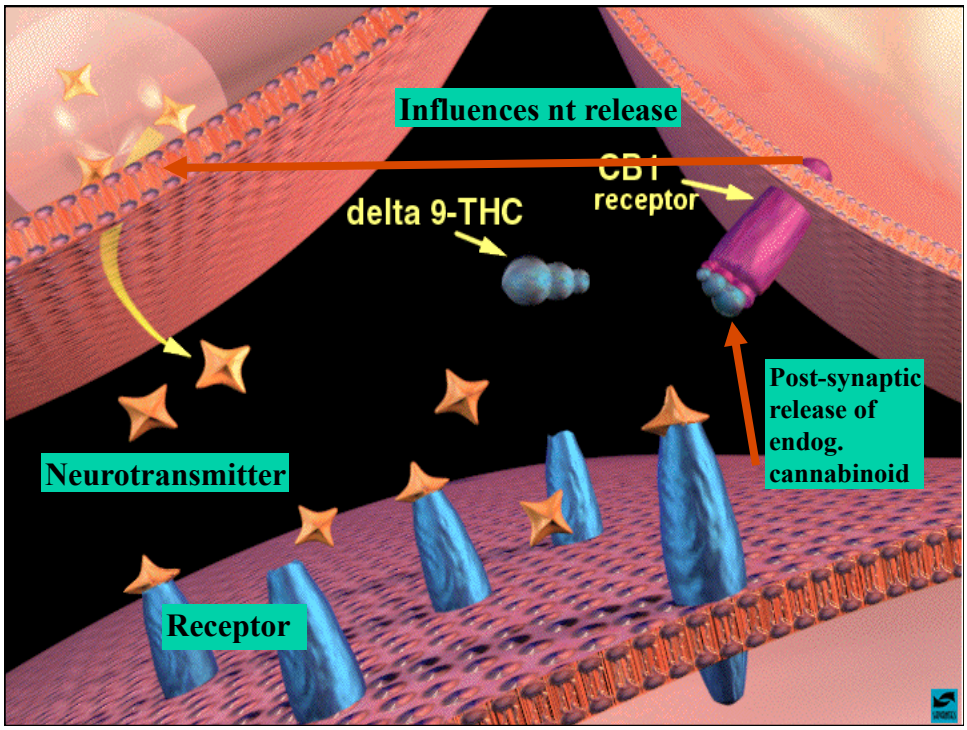
- Oral use
  - Psychoactive effects slowed to about one hour
  - Absorption is erratic
  - High is less intense, but lasts longer than if smoked
- IV use
  - Water insoluble so cannot be injected

ADDICTION LIABILITY

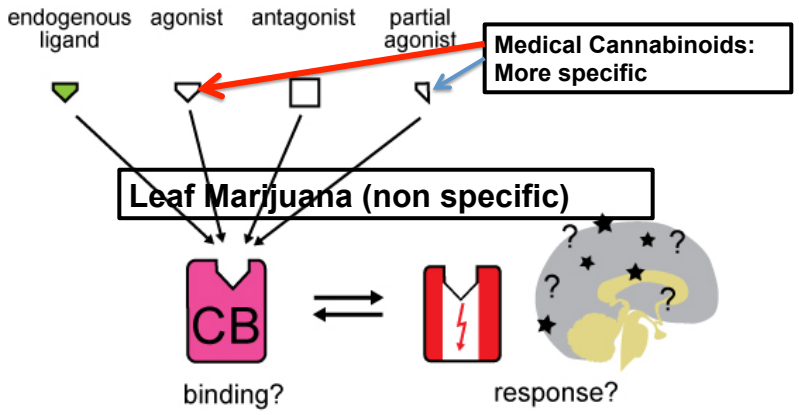
- 9% of those who ever used become dependent
- Dependence associated with gradual increase in use
- No scientific evidence that it is a “gateway” drug
  - Study by Royal Children’s Hospital Center in August 2004 showed that teenagers who smoked cannabis daily for at least a month are 4 times more likely to become addicted to nicotine by the time they reach their 20’s.
    - Reverse directionality: cannabis → tobacco → alcohol → drugs and not tobacco → alcohol → cannabis → drugs



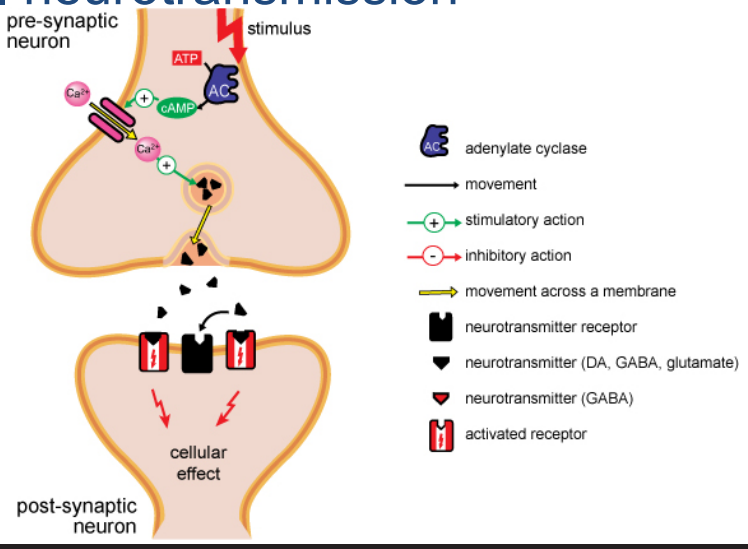

CB1
receptor
delta 9-THC
Neurotransmitter
Receptor


Influences nt release
CB1
receptor
delta 9-THC
Post-synaptic
release of
endog.
cannabinoid
Neurotransmitter
Receptor

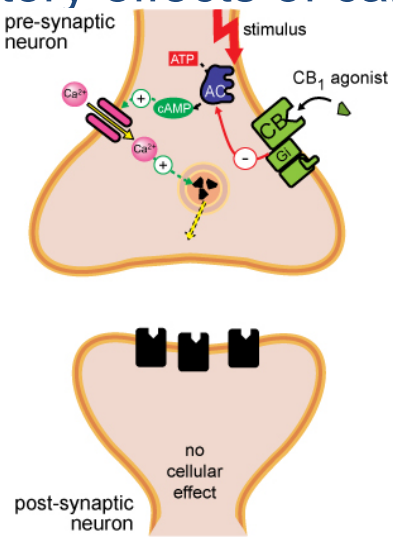
Cannabinoid/CB receptor interactions



Normal neurotransmission

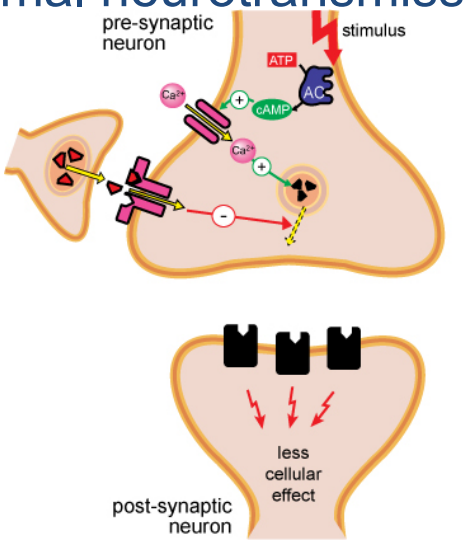


Regulatory effects of cannabinoids



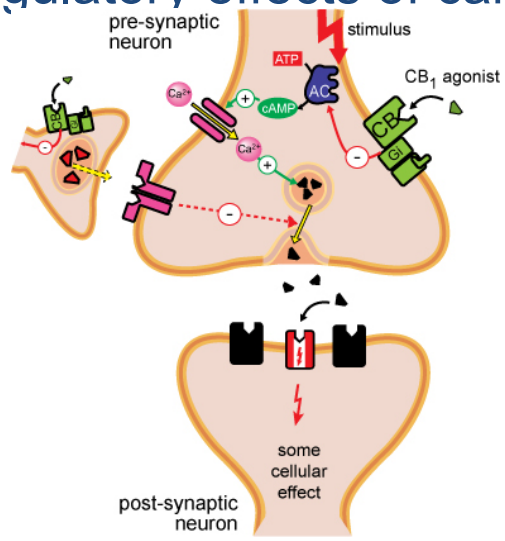
Pertwee RG, Br J Pharm, 2008

Normal neurotransmission in a network



Skaggs School of Pharmacy and Pharmaceutical Sciences
Celebrating 100 years of education, patient care and scientific discovery.

Regulatory effects of cannabinoids



Pertwee RG, Br J Pharm, 2008

Dose Response Effects

Threshold doses of 2 mg smoked, 5 mg orally, produce **euphoria**.

7 mg smoked, 17 mg orally, produces feeling **enhanced perception** and **change in sense of time** passage.

15 mg smoked, 25 mg orally, subjects report marked **changes in body image, perceptual distortion, delusions, and hallucinations**.

Oral intake associated with nausea, physical discomfort and hangover because dose level cannot be titrated as accurately as smoking.

Generally, a new user has to ***learn*** how to smoke marijuana. There are three stages:

Step 1: involves deeply inhaling the smoke (**breath-holding does not substantially enhance the effects** of marijuana smoking – lipid solubility).

Step 2: the user has to learn to **identify and control** the effects.

Step 3: the user has to learn the **label the effects as pleasant.**

Because of this learning process, usually first time users do not achieve the euphoric *stoned* or *high* condition of the repeat user.

Also because smokers *learn* to enjoy marijuana: In a study comparing effects of placebos and cigarettes containing 9 mg of THC, experienced users reported moderate levels of intoxication after use of placebo cigarettes. So, save your money!

Physiological Changes

Tachycardia (increased heart rate)
Enlarged pupils (in some users)
Dryness of mouth and throat
Reddening of the eyes
Inconsistent blood pressure changes

Eating Changes (the *Munchies*)

The presence of the cannabinoid receptor in the ventromedial **hypothalamus** may explain the *munchies*.

- Hunger may be effected by **THC concentration**, as cultural differences are observed (Jamaicans think of it as appetite suppressant).

- In a study, 9 male subjects were given THC-containing cigarettes either (1) before a private work period, or (2) during access to social periods with other subjects. (1) did not lead to increased food intake (2) did lead to increased food intake, especially between meals.

Sexual Functioning

In North America, marijuana is thought of as a sexual enhancer, in India it is considered a sexual depressant.

Low doses enhance sexual desire in males, while **high doses** tend to **suppress** it, even to the point of impotence.

(Levinthal 2006).

Psychomotor Performance

Marijuana smokers are more likely to get into an auto accident. Reaction time is the same, but slower at noticing things that should be stopped for.

Decline in sensory-motor performance as well as attention and memory will persist well after the point at which the marijuana smoker no longer feels high.

Effect on Memory

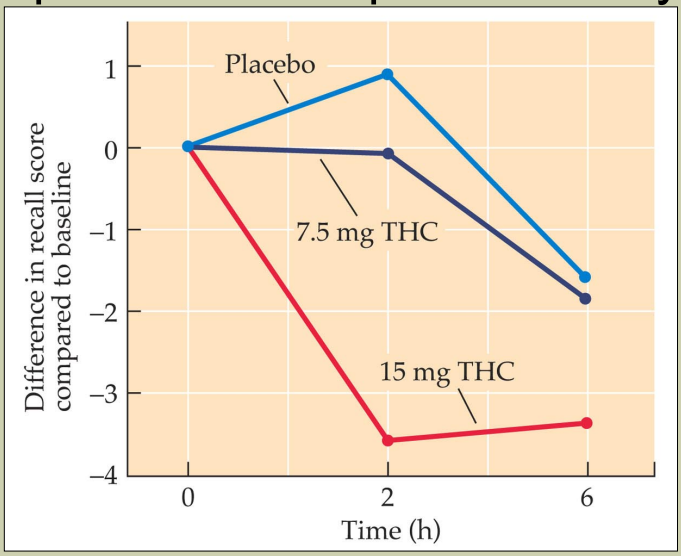
One consistent alteration in function is on **short-term memory**.

The **encoding and consolidation** of short-term to long-term memory is impaired with marijuana intoxication.

Researchers have concluded that information **retrieval is intact** and not altered by marijuana intoxication.

The effects on memory are different from those seen with alcohol.

Oral THC produces a dose-dependent impairment in explicit memory

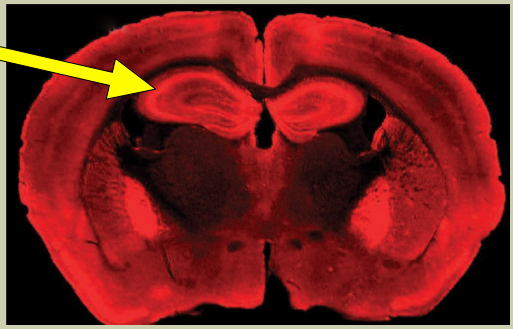


Effects of Marijuana on the Brain

The **hippocampus** is a part of the brain's limbic system necessary for learning and memory. The **prefrontal cortex** is involved in information processing and higher processes.

CB1 Receptors in Hippocampus

Hippocampus and prefrontal cortex both rich in CB1 receptors.



Marijuana: What Does The Medical Evidence Show?

Allen C. Bowling, MD, PhD
Physician Associate
Colorado Neurological Institute (CNI)

Merrill Norton Pharm.D.,D.Ph.,ICCDP-D
Clinical Associate Professor
University of Georgia College of Pharmacy

Marijuana and Neurological Disease

- Increasing legalization and availability
- Neurologically relevant medical studies
- BUT huge challenges for public and professionals:
  - Emotional response
  - Political/media/business interests
  - Difficult to find objective safety and effectiveness information

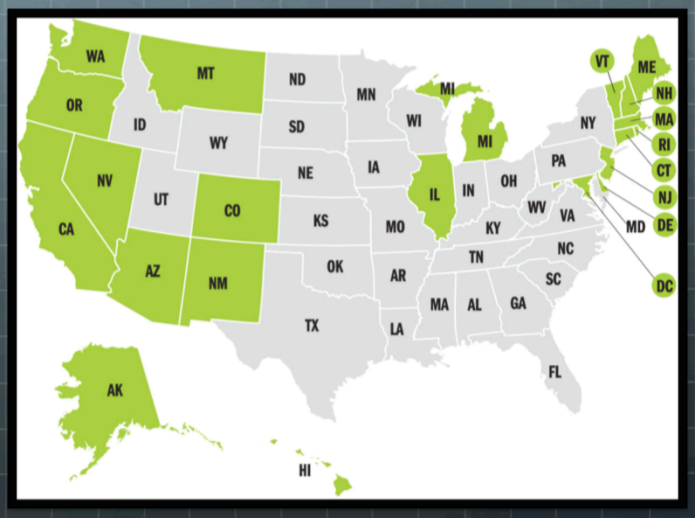
Marijuana Information

- "Cannabis is effective for treating epilepsy, Parkinson's disease, depression, and migraine."
- "[In MS], numerous studies have reported improvement in tremor, sexual dysfunction,… vision dimness, dysfunctions of walking and balance (ataxia), and memory loss."
- "Research has shown that medical marijuana… can alleviate symptoms of Tourette's."

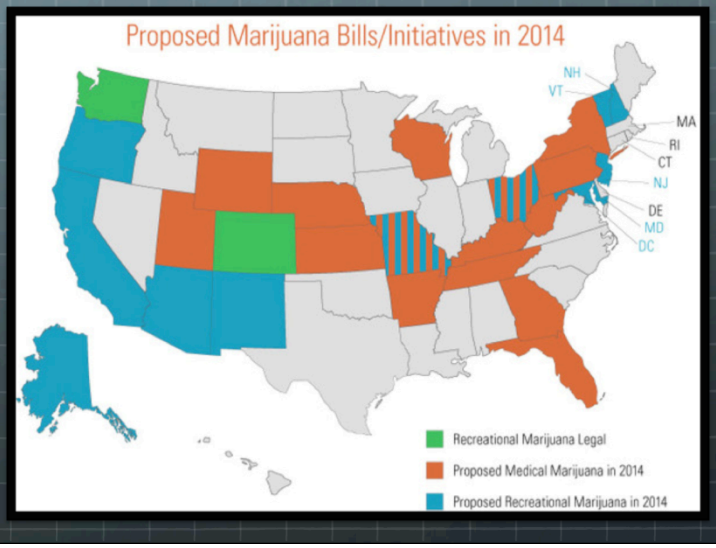
Summary

- Basics of Marijuana
- The Evidence
  - Scientific studies
  - Clinical studies
    - MS, epilepsy, Parkinson's disease and other movement disorders
    - Pain, anxiety, sleep
  - Safety
- Information Resources

States with Medical/Recreational Marijuana (Illegal at Federal Level)



Proposed Marijuana Bills/Initiatives in 2014



Medical Marijuana in Colorado: "Approved Conditions"

- "persistent muscle spasms, including those that are characteristic of multiple sclerosis"
- "seizures, including those that are characteristic of epilepsy"
- "severe pain"

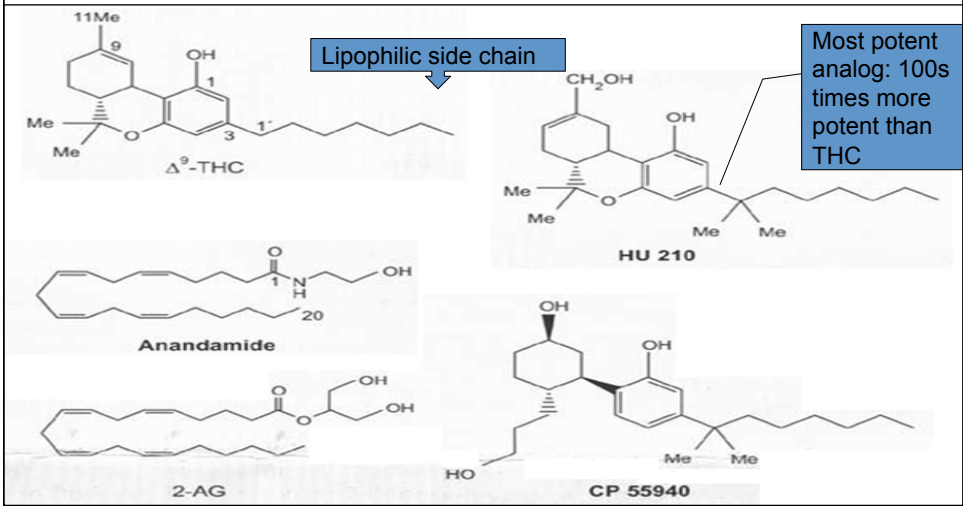
Variability of Marijuana Plants and Products

- Two major "subspecies"
  - *Cannabis sativa:* mainly THC
  - *Cannabis indica:* THC and CBD
- Many different hybrids
- Other variables
  - Growing and storage
  - State of maturity
  - Processing/formulation

Forms of Marijuana

- Leaf
  - Smoked, eaten ("edibles"), vaporized
- Plant resin: "hashish"
  - Smoked, eaten
- Oil extracts
  - Nabiximols (Sativex), Cannador, many others that are unregulated and non-standardized
- Single molecule preparations
  - THC: Marinol, dronabinol
  - Chemical variant of THC: Cesamet, nabilone

Structure of THC and Synthetic Analogs



Location of Cannabinoid Receptors

Location	Structure	Function
CB_1 receptors		
CNS	Hippocampus	Memory storage
	Cerebellum	Coordination of motor function, posture, balance
	Basal ganglia	Movement control
	Hypothalamus	Thermal regulation, neuroendocrine release, appetite
	Spinal cord	Nociception
	Cerebral cortex	Emesis
Periphery	Lymphoid organs	Cell-mediated and innate immunity
	Vascular smooth muscle cells	Control of blood pressure
	Duodenum, ileum, myenteric plexus	Control of emesis
	Lung smooth muscle cells	Bronchodilation
	Eye ciliary body	Intraocular pressure
CB_2 receptors		
Periphery	Lymphoid tissue	Cell-mediated and innate immunity
	Peripheral nerve terminals	Peripheral nervous system
	Retina	Intraocular pressure
CNS	Cerebellar granule cells mRNA	Coordination of motor function

Croxford, JL. CNS Drugs 2003; 17(3)

Medical Marijuana

- Marijuana is the most commonly abused illicit drug in the United States. A dry, shredded green/brown mix of flowers, stems, seeds, and leaves of the plant Cannabis sativa, it usually is smoked as a cigarette (joint, nail), or in a pipe (bong). It also is smoked in blunts, which are cigars that have been emptied of tobacco and refilled with marijuana, often in combination with another drug. It might also be mixed in food or brewed as a tea. As a more concentrated, resinous form it is called hashish and, as a sticky black liquid, hash oil. Marijuana smoke has a pungent and distinctive, usually sweet-and-sour odor.
- Marijuana is a Schedule I substance under the Controlled Substances Act (CSA). Schedule I drugs are classified as having a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use of the drug or other substance under medical supervision.

Vaporization of medical cannabis

- Cannabinoids vaporize at a temp lower than combustion
- Increasingly popular
- Lower % of noxious chemicals

http://www.volcanovaporizer.com/products-page/complete-sets/ Accessed 08/31/2012

The truth is coming out about marijuana's therapeutic benefits.

How much should a person use to get 25 mg of THC?

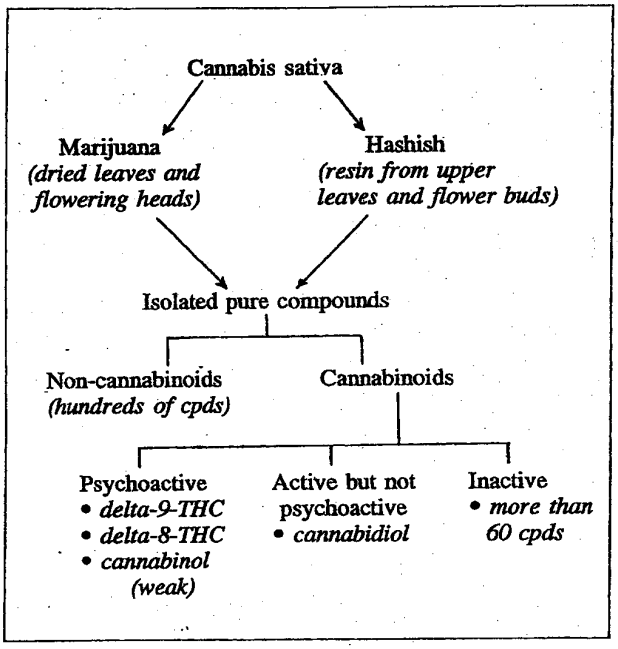
- 20% THC
- Net weight 1/8 oz or 3.5 gm
- Single serving 50 mg

http://bothcollective.com/page/6/?app-download=windowsphone

http://onehumanbeing.com/the_mmj_project/2009/03/granddaddy-purple-at-cclb/

Skaggs School of Pharmacy and Pharmaceutical Sciences

Celebrating 100 years of education, patient care and scientific discovery.



Kalant, 2001

Figure 1) Relationships between crude cannabis products and pure cannabinoids. cpds Compounds; THC Tetrahydrocannabinol

TABLE 2.1 Landmark Discoveries Since the 1982 IOM Report

Year	Discovery	Primary Investigators
1986	Potent cannabinoid agonists are developed; they are the key to discovering the receptor.	M. R. Johnson and L. S. Melvin[75]
1988	First conclusive evidence of specific cannabinoid receptors.	A. Howlett and W. Devane[36]
1990	The cannabinoid brain receptor (CB_1) is cloned, its DNA sequence is identified, and its location in the brain is determined.	L. Matsuda[107] and M. Herkenham et al.[60]
1992	Anandamide is discovered—a naturally occurring substance in the brain that acts on cannabinoid receptors.	R. Mechoulam and W. Devane[37]
1993	A cannabinoid receptor is discovered outside the brain; this receptor (CB_2) is related to the brain receptor but is distinct.	S. Munro[112]
1994	The first specific cannabinoid antagonist, SR 141716A, is developed.	M. Rinaldi-Carmona[132]
1998	The first cannabinoid antagonist, SR144528, that can distinguish between CB_1 and CB_2 receptors discovered.	M. Rinaldi-Carmona[133]

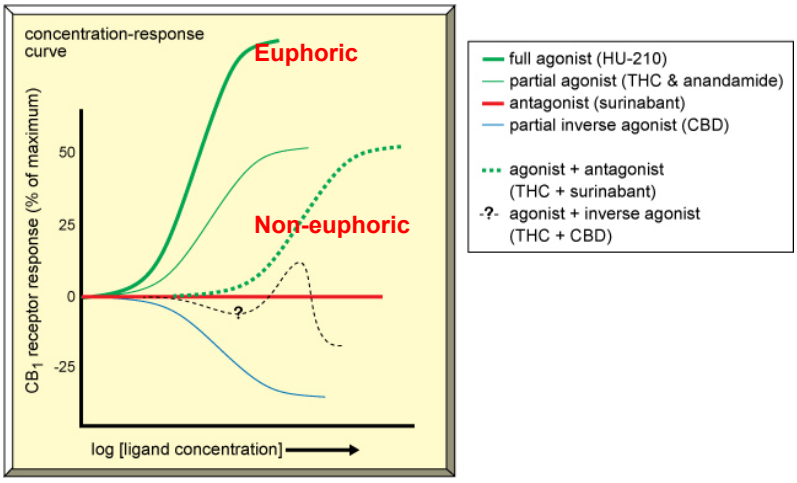
Mechanisms of Action

- first thought to be non-specific membrane action due to very high lipid solubility
- late 1980s - identification of specific receptors
- CB_1 subtype - primarily in CNS but also in periphery
  - shorter variant CB_{1A}
  - found in cerebral cortex, basal ganglia, cerebellum, limbic system, hypothalamus, hippocampus

Mechanisms of Action (cont'd)

- CB_2 subtype - only in periphery
  - immune system, bone marrow, lung, pancreas, smooth muscle
- endogenous ligands are formed *in situ* in cell membrane, act directly on receptors, and are broken down by amidases in membrane

Cannabinoid receptor active ligands

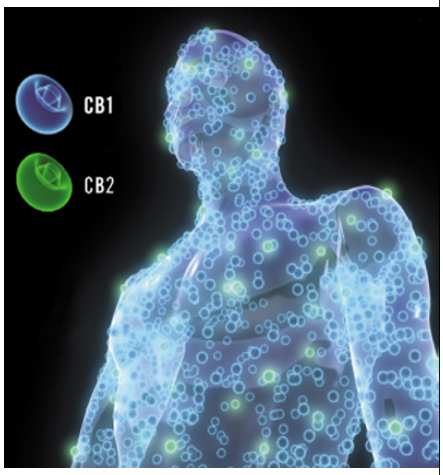


Skaggs School of Pharmacy and Pharmaceutical Sciences

Celebrating 100 years of education, patient care and scientific discovery.

The Ubiquitous CB1

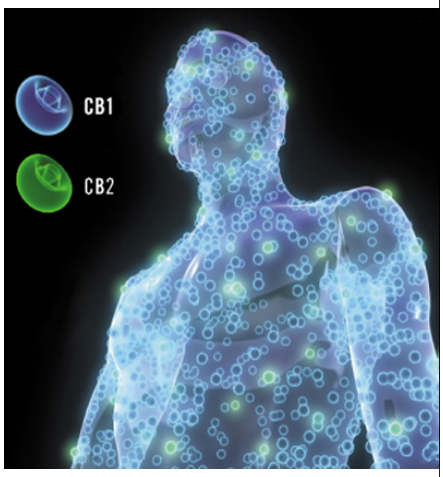
- Endogenous CBs are a major class of neuromodulators, acting through receptors, CB1 and CB2
- CB1 receptors are primarily located on CNS neurons
  - Levels exceed those of nearly all neurotransmitter receptors
- Exogenous CBs exert their effects by driving this innate system, often mimicking and enhancing its natural functions



66

The Ubiquitous CB1

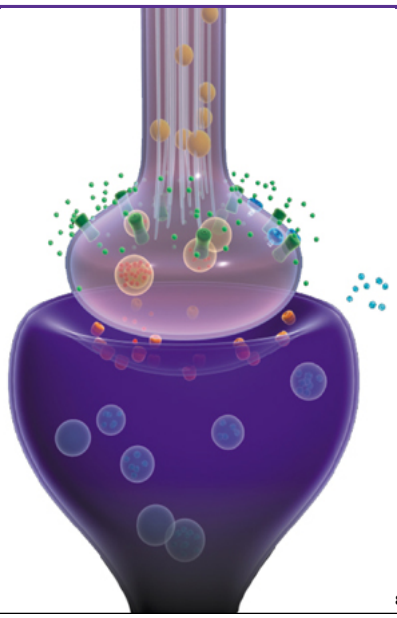
- The omnipresent central distribution of CB1, has led to the term, **Omnineuromodulator,** to describe CB action
- Therapeutic effects are primarily due to agonist action in brain regions that mediate nausea/vomiting, appetite, and neuropathic pain



67

Omnineuromodulation

- Nabilone acts on presynaptic CB1 receptors, similar to endocannabinoids
  - Inhibits the release of excitatory (e.g., glutamate) and inhibitory (e.g., GABA) neurotransmitters
- The primary effect on neuronal signaling appears to be inhibitory, but network effects may be complex and hence **modulatory** in nature
- Endogenous CB1 ligands act "backwards" from classical neurotransmitters by serving as retrograde synaptic messengers



8

Pardon Me, Officer, While I Finish My Beer

Associated Press

Despite the fact that an officer is pointing a gun at him, a passenger from a stopped vehicle decides to finish his beer. Police stopped the vehicle because they thought it was stolen; it wasn't, but another passenger was taken into custody on an outstanding warrant and was also charged with resisting arrest. Five people were in the vehicle, and drinking was obviously occurring, but the police didn't arrest anyone else. The incident occurred in Klamath Falls, Ore., on Wednesday.

Addiction can occur to THC, but only at dose and use levels far above what is now used recreationally.

1977 Report stated that *moderate* marijuana smoking **does not cause changes in the physical structure of the brain**, at least those that can be detected. (Does not kill cells – no "dormancy")

Sensitization develops with prolonged use at recreational levels i.e. less drug being necessary with each succeeding use.

This is related to its high lipid solubility. Desensitization occurs, but as more THC **accumulates** in the body, less is needed to reach the threshold of effect.

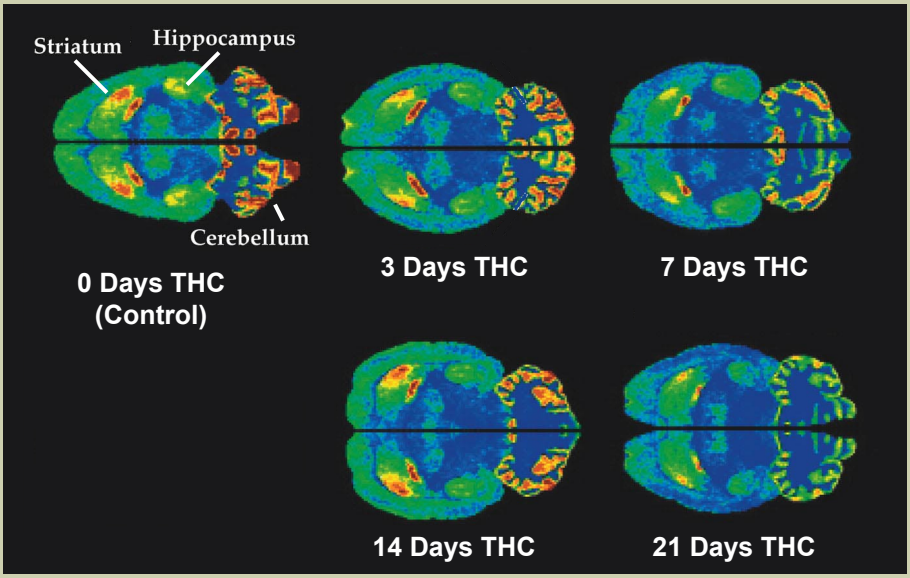
Sensitization- Positive Reinforcement to Negative Reinforcement

Liking

Wanting

Craving

Desensitization of cannabinoid receptors produced by chronic THC exposure



Psychopharmacology

Medical Concerns

Usually **no obvious high frequency physiological effects** of moderate use of marijuana over a 5-10 year period. But, in comparison, there are no obvious high frequency serious effects of moderate use of cigarettes over a 5-10 year period either.

Concern usually arises when use is more frequent that 2 or 3 uses per week.

- Lungs & Heart
- Immune system
- Reproduction
- Cognition
- Psychological effects
- Amotivational Syndrome

Effects on Immune System?

Two types of receptors are known. CB1 is in the brain and **CB2 are on immune cells**.

Most research concludes that it **does suppress some** aspects of the immune system. But this is subtle.

Effects on Reproduction

There is not evidence of long term reproductive problems from cannabis use, yet hormonal changes do occur.

Males:

- Reduces level of testosterone (still within normal levels)
- Reduces sperm count (10 joints/day, effect disappears when use stopped)
- Changes in shape and morphology of sperm
- Effects of THC can be estrogen-like producing breast development (gynecomastia).

Females:

- Reduction in luteinizing hormone, necessary for egg implantation into the uterus. (Not seen in regular users – implies tolerance).
- Reduction of prolactin levels (associated with increased release of dopamine in the hypothalamus), effecting lactation

Effects on Cognition

There is evidence that long term use may lead to **deficits in learning memory and attention.**

However, it is unknown how long these deficits may persist after abstinence from the drug.

Effects of Heavy Marijuana Use on Attention, Learning, & Memory in Undergraduates

Researchers compared 65 "heavy users," (smoked a median of 29 of the past 30 days), and 64 "light users," (smoked a median of 1 of the past 30 days).

After 19-24 hours of abstinence from marijuana and other illicit drugs and alcohol, the undergraduates were given several standard tests measuring aspects of attention, memory, and learning.

Heavy marijuana users made more errors and had more difficulty sustaining attention, shifting attention to meet the demands of changes in the environment, and in registering, processing, and using information.

However, the question remains open as to whether this impairment is due to a residue of drug in the brain, a *withdrawal* effect from the drug, or a frank neurotoxic effect of the drug.

H. G. Pope Jr and D. Yurgelun-Todd, 1996

Significant prior usage may reduce the adverse cognitive effects of acute marijuana exposure.

This has led to the hypothesis that behavioral ("cognitive") tolerance develops in heavy marijuana smokers (Hart, 2001).

Does marijuana lead to Psychosis ?

There is evidence that cannabis use is **correlated** with degradation in mental health, especially in those with a predisposition to mental illness. However, it is uncertain whether cannabis use is a cause, contributing factor, associated social phenomenon, or type of self-medication. (Henquet, 2004)

In North Africa and India, higher incidence of psychiatric problems associated with THC are reported. The THC is usually more concentrated, used more frequently, and exposure over a lifetime is generally greater than the US.

The **DSM-IV** has a classification called **'cannabis psychosis'** which is very rare. In susceptible individuals, ingestion of sufficient quantities of the drug can trigger an *acute* psychotic event.

Pharmacology books stated that people who had a history of repeated frustrations, and deprivations, who were sexually maladjusted, especially homosexuals, or those who seek escape and sometimes possess major personality defects and are often psychopathic, are the kinds of people who smoke marijuana.

1971, Reported that “Moderate to heavy use of marijuana in adolescents and young people without predisposition to psychotic illness may lead to ego decomposition, ranging from mild ego disturbance to psychosis.” (Kolansky and Moore)

They concluded that marijuana smoking leads to psychosis.

The *psychosis* theory was tested by Altman and Evenson:

They administered questionnaires to people who were being admitted to mental institutions in Missouri.

They did this until they identified 38 individuals who had used marijuana prior to having shown psychiatric symptoms.

Found out **what else** these patients were doing prior to being admitted, and discovered 10 other events that occurred more often than marijuana use….

These included the following (in order of frequency):

10. Growing long hair
9. Masturbation
8. Driving a car
7. Taking a sex education class
6. Having sexual intercourse
5. Beer drinking
4. Dancing
3. Tobacco use
2. Kissing

And the most frequent thing they did that may have correlated best with psychosis…

1. **Watching late night television!!**

Amotivational Syndrome.

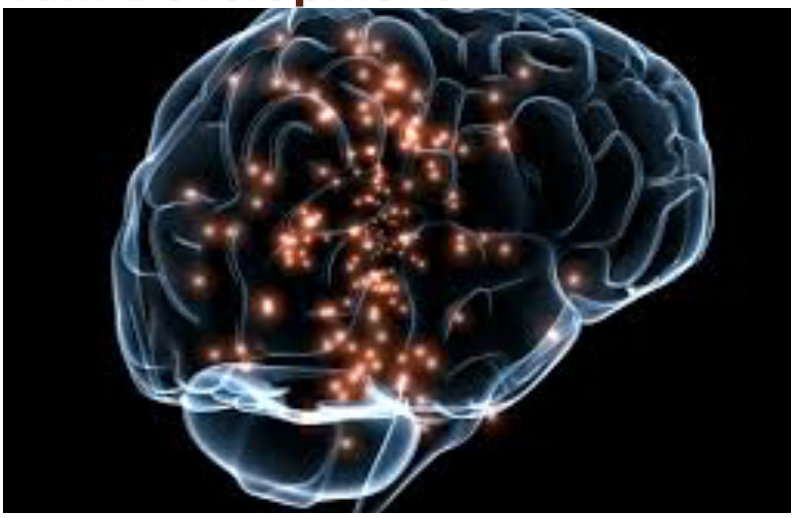
Recent studies have found that users of moderate amounts of marijuana show no personality disturbances, but heavy users were characterized as suffering from **apathy, dullness, lethargy, and impairment of judgment.**

However, heavy users were defined as people who smoked 17-200 marijuana cigarettes per day! (1 joint ever waking 5 mins!)

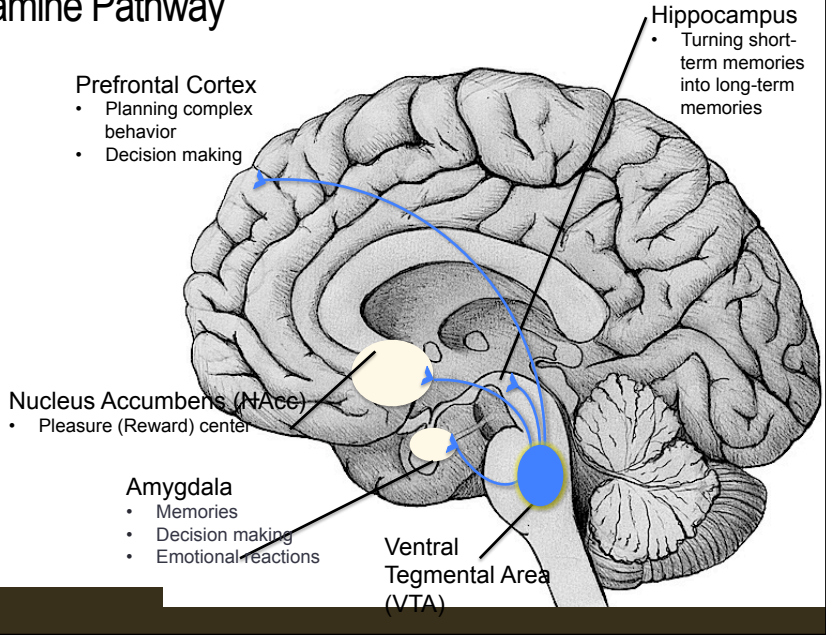
This is also correlational evidence.

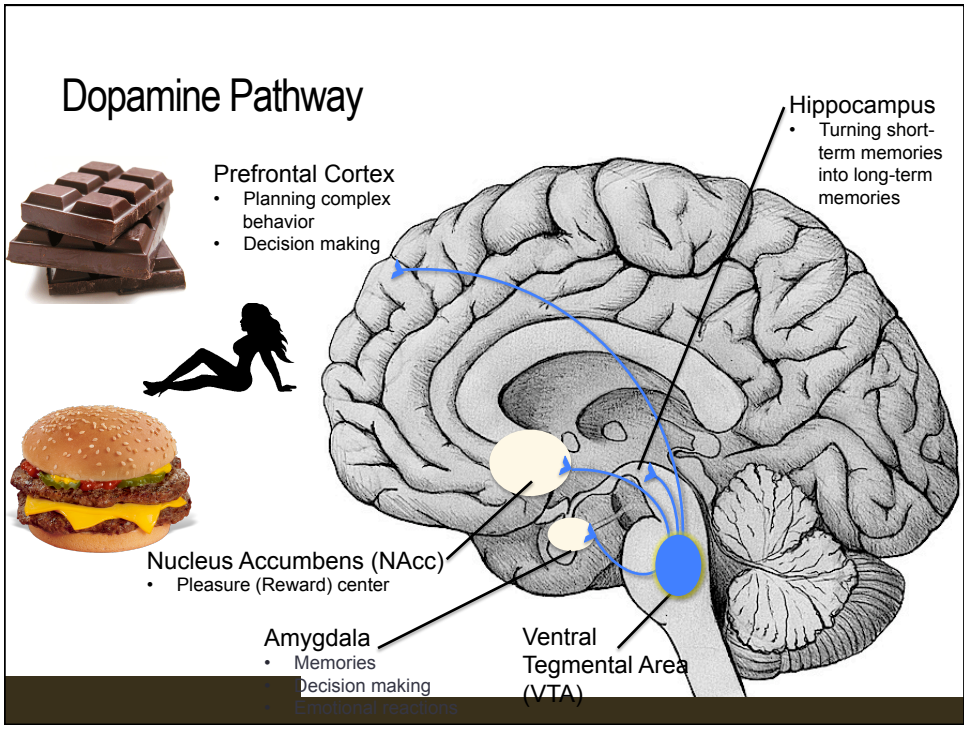
Is Marijuana Addicting?

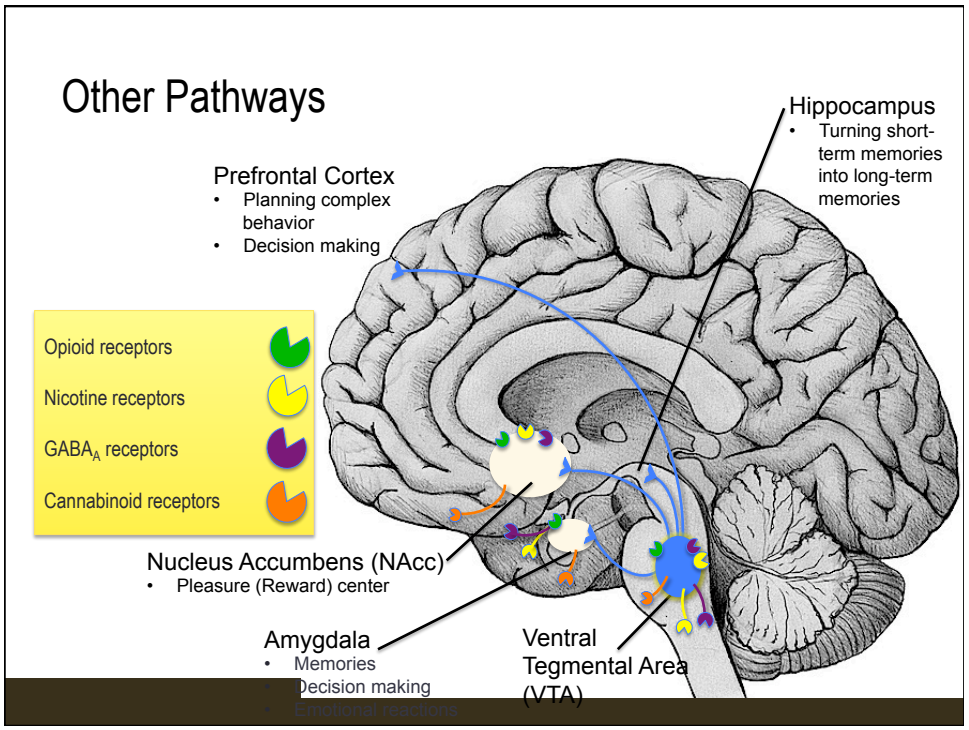
The Importance of Dopamine on Brain Development



Dopamine Pathway




Dopamine Pathway
Prefrontal Cortex
• Planning complex behavior
• Decision making
Hippocampus
• Turning short-term memories into long-term memories
Nucleus Accumbens (NAcc)
• Pleasure (Reward) center
Amygdala
• Memories
• Decision making
• Emotional reactions
Ventral Tegmental Area (VTA)


Other Pathways
Prefrontal Cortex
• Planning complex behavior
• Decision making
Hippocampus
• Turning short-term memories into long-term memories
Opioid receptors
Nicotine receptors
GABA$_A$ receptors
Cannabinoid receptors
Nucleus Accumbens (NAcc)
• Pleasure (Reward) center
Amygdala
• Memories
• Decision making
• Emotional reactions
Ventral Tegmental Area (VTA)

The Impact of Dopamine

- **This enhanced natural dopamine release can give adolescents a powerful sense of being alive when they are engaged in life. It can also lead them to focus solely on the positive rewards they are sure are in store for them, while failing to notice or give value to the potential risks and downsides.**
- **The brain's increased drive for reward in adolescence manifests in teens' lives in three important ways. One is simply increased *impulsiveness*, where behaviors occur without thoughtful reflection. In other words, impulse inspires action without any pause. Pausing enables us to think about other options beyond the immediate dopamine-driven impulse pounding on our minds. Telling that impulse to chill out takes time and energy so it's easier just not to do it. This said, with the drive for reward stronger and more pressing than ever when we are teens, taking the time needed for processing—for reflection and self-awareness—becomes very important. If any notion turns immediately into an action without reflection, we are living our lives all gas pedal and no brakes.**
- Daniel J. Siegel's Brainstorm: The Power and Purpose of the Teenage Brain

The Impact of Dopamine

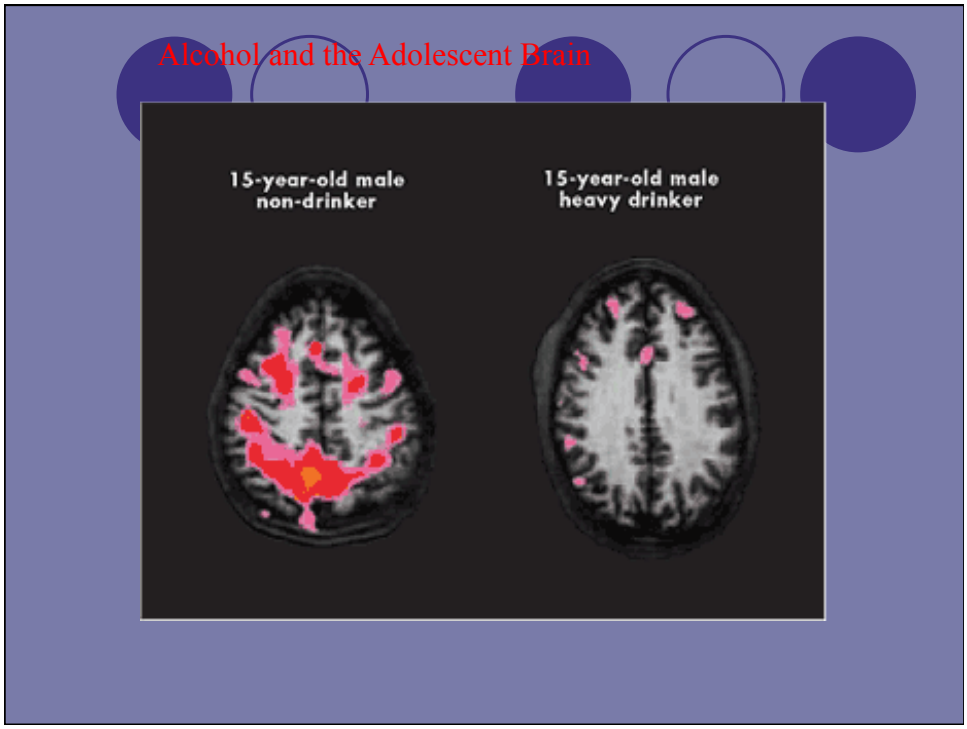
- **A second way in which increased dopamine release affects us during adolescence is the documented increase in our susceptibility to addiction. All behaviors and substances that are addictive involve the release of dopamine. As teens not only are we more likely to experiment with new experiences, we are also more prone to respond with a robust dopamine release that for some can become part of an addictive cycle. A drug, alcohol for example, can lead to release of dopamine, and we may feel compelled to ingest beer or wine or hard liquor. When the alcohol wears off, our dopamine plummets. We then are driven to use more of the substance that spiked our dopamine circuits.**
- Daniel J. Siegel's Brainstorm: The Power and Purpose of the Teenage Brain

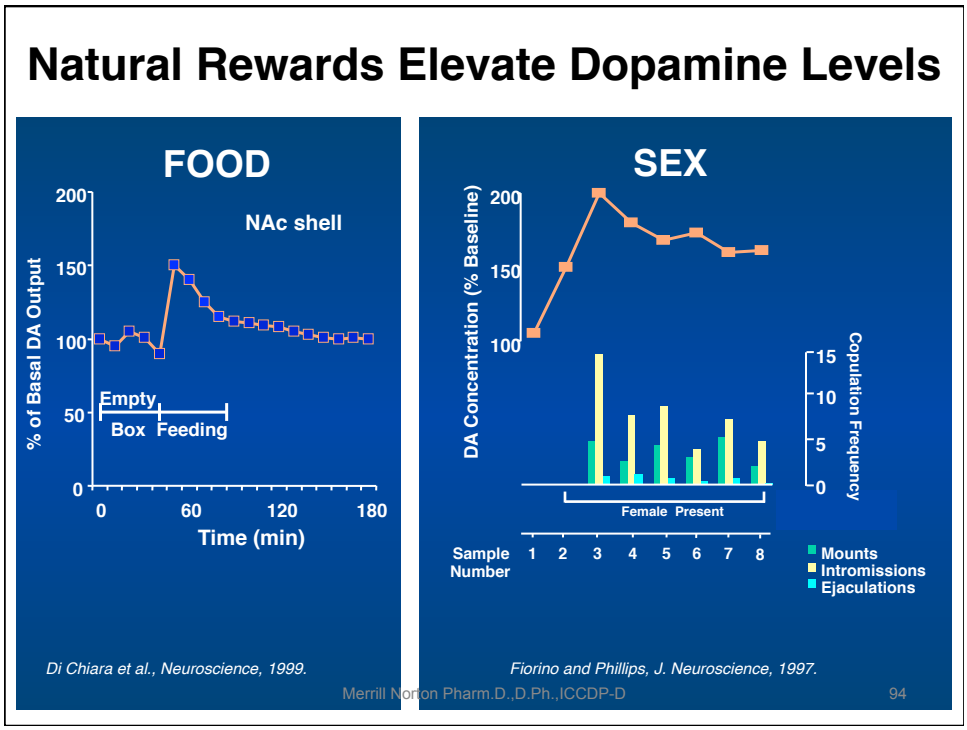
The Impact of Dopamine

- **The third type of behavior shaped by the increased reward drives of the adolescent brain is something called *hyperrationality*. This is how we think in literal, concrete terms. We examine just the facts of a situation and don't see the big picture; we miss the setting or context in which those facts occur. With such literal thinking, as adolescents we can place more weight on the calculated benefits of an action than on the potential risks of that action. Studies reveal that as teens we are often fully aware of risks, and even at times overestimate the chance of something bad happening; we simply put more weight on the exciting potential benefits of our actions.**
- Daniel J. Siegel's Brainstorm: The Power and Purpose of the Teenage Brain

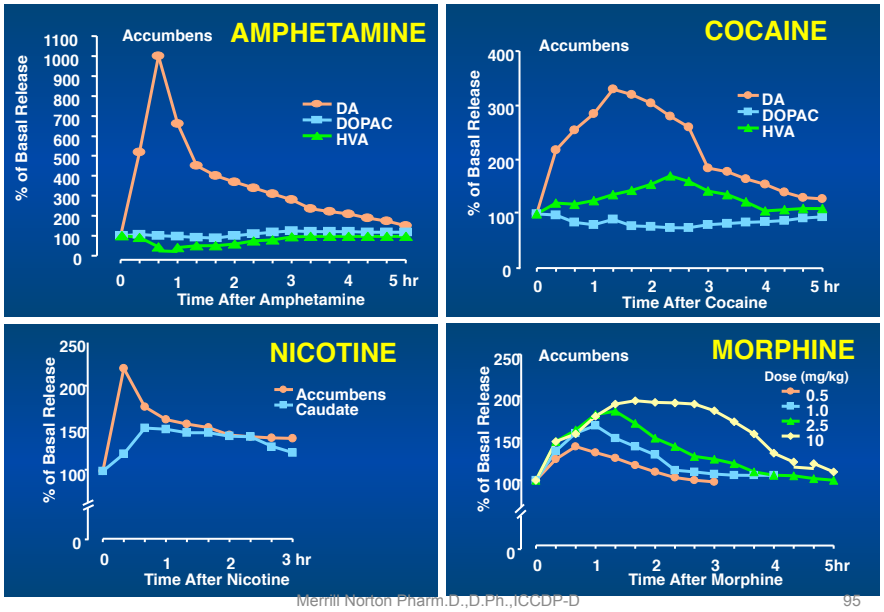
The Impact of Dopamine

- **This is not as simple as saying that teens are just impulsive. And it's also not as simple as saying, "Oh, raging hormones," as its sometimes stated. Research suggest that risky behaviors in adolescence have less to do with hormonal imbalances than with changes in our brain's dopamine reward system combined with the cortical architecture that supports hyperrational decision-making—creating the positive bias that is dominant during the teen years.**
- Daniel J. Siegel's Brainstorm: The Power and Purpose of the Teenage Brain


Alcohol and the Adolescent Brain
15-year-old male non-drinker
15-year-old male heavy drinker

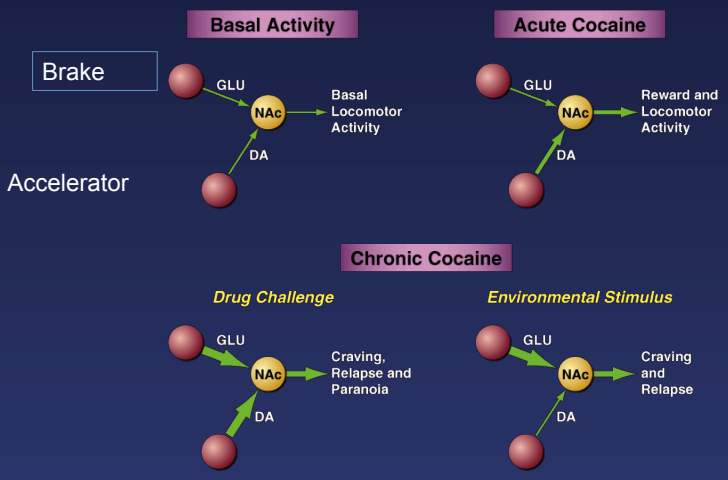

Natural Rewards Elevate Dopamine Levels
FOOD
NAc shell
% of Basal DA Output
200
150
100
50
0
Empty
Box
Feeding
0
60
120
180
Time (min)
Di Chiara et al., Neuroscience, 1999.
SEX
DA Concentration (% Baseline)
200
150
100
Copulation Frequency
15
10
5
0
Female Present
Sample Number
1 2 3 4 5 6 7 8
Mounts
Intromissions
Ejaculations
Fiorino and Phillips, J. Neuroscience, 1997.
Merrill Norton Pharm.D.,D.Ph.,ICCDP-D
94

Effects of Drugs on Dopamine Release



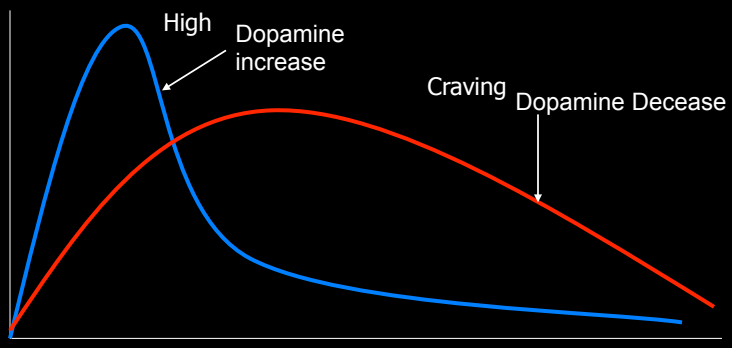
Di Chiara and Imperato, PNAS, 1988

Role of Glutamate and Dopamine Neurotransmission in Relapse to Drug-Seeking Behavior



From: Cornish JL and Kalivas PW, J Addict Dis, 2001, 20:43-54.

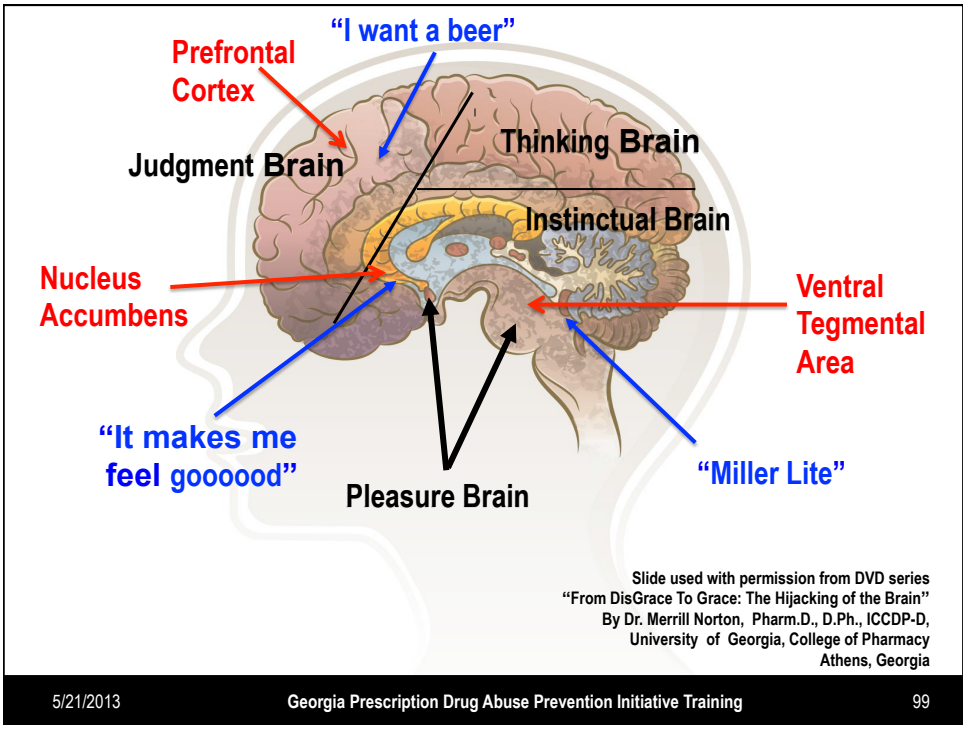
Drug-induced Craving



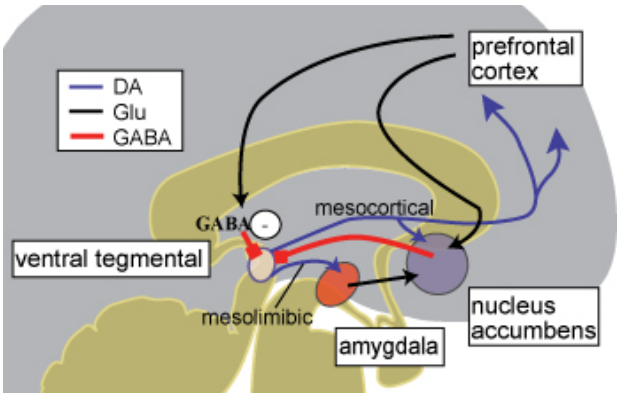
Positive and Negative Reinforcement- Definitions

Positive Reinforcement — defined as the process by which presentation of a stimulus (drug) increases the probability of a response (non dependent drug taking paradigms).

Negative Reinforcement —defined as a process by which removal of an aversive stimulus (negative emotional state of drug withdrawal) increases the probability of a response (dependence-induced drug taking)



Cannabis effect on reward pathway



DA: reward and motivation

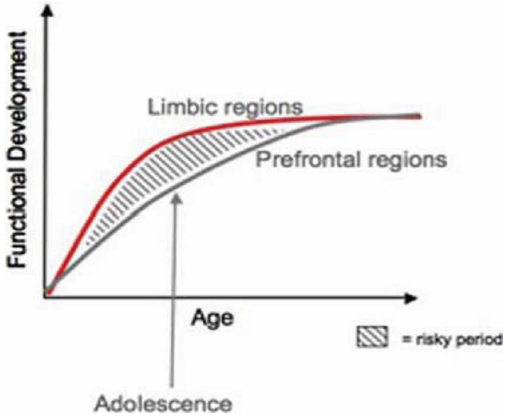
Glu: learning and memory

GABA: inhibition of neuronal activity

Skaggs School of Pharmacy and Pharmaceutical Sciences

Celebrating 100 years of education, patient care and scientific discovery.

Brain development in adolescence



Accumbens

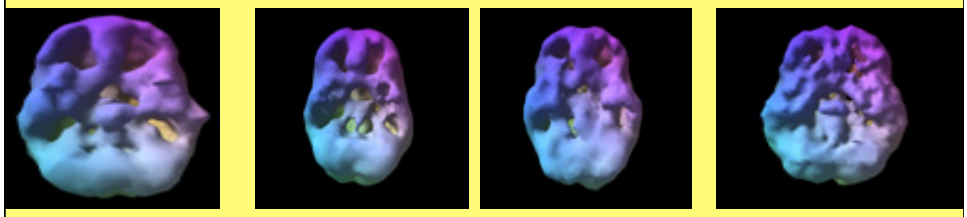
- Immediate rewards
- Impulsive behavior

Cortex

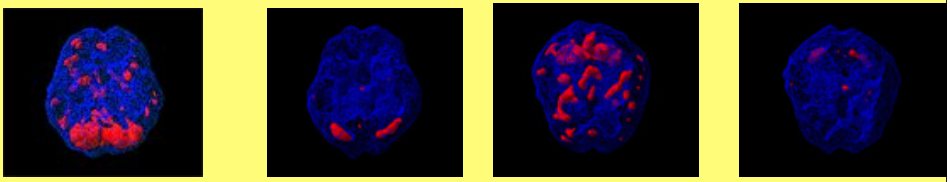
- Long term gain
- Thoughtful behavior

http://erichengelhardt.net/neuro-facts.html accessed 5/28/2013

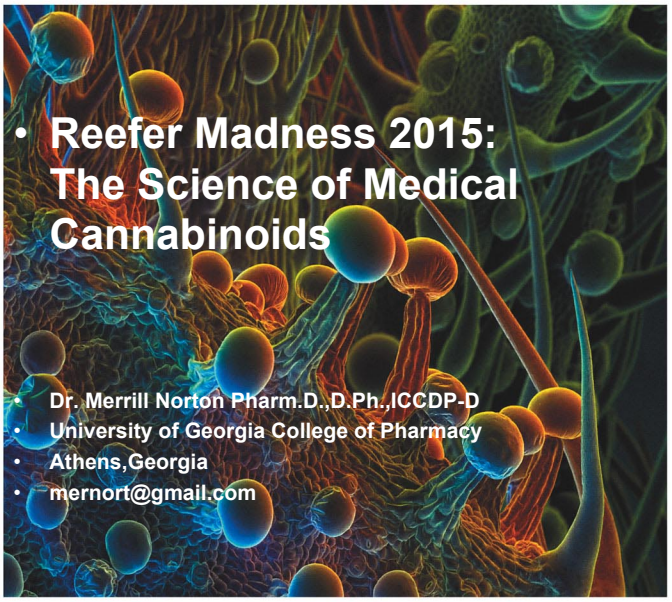
Leaf Marijuana Spect Scans



4 Years | 7 Years | 9 Years | 12 Years



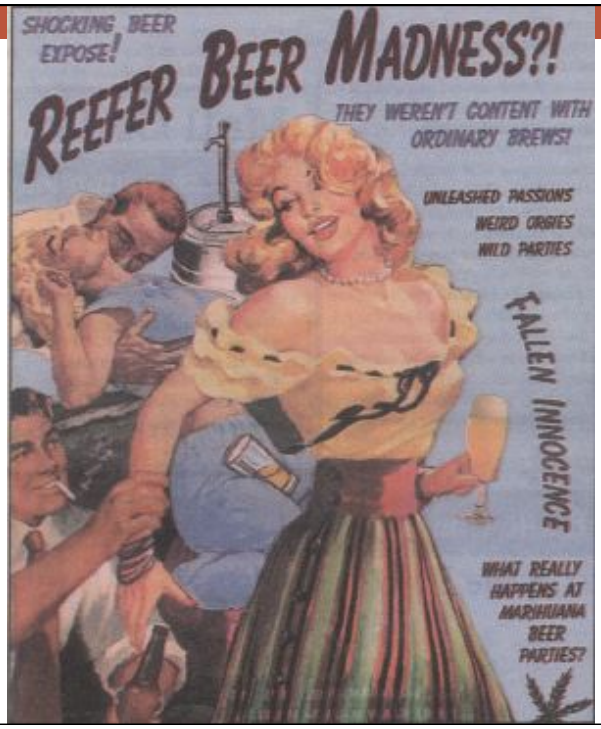
With Permission Amens Clinics



"Very few drugs, if any, have such a tangled history as a medicine. In fact, prejudice, superstition, emotionalism, and even ideology have managed to lead cannabis to ups and downs concerning both its therapeutic properties and its toxicological and dependence-inducing effects."

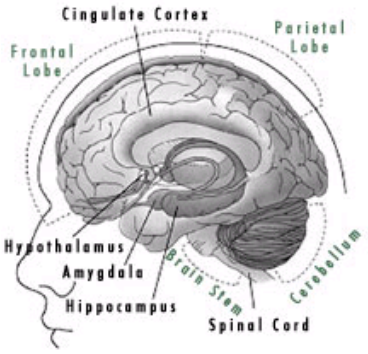
EA Carlini 2004

104



CANNABINOIDS

- Receptors have also been found in the
  - Cerebellum – body movement and coordination
  - Cortex – higher cognitive functions
  - Nucleus accumbens – reward
  - Basal ganglia – movement control
  - Hypothalamus – body temperature, salt and water balance, reproductive functions
  - Amygdala – emotional responses, fear



Forms of Cannabinoids

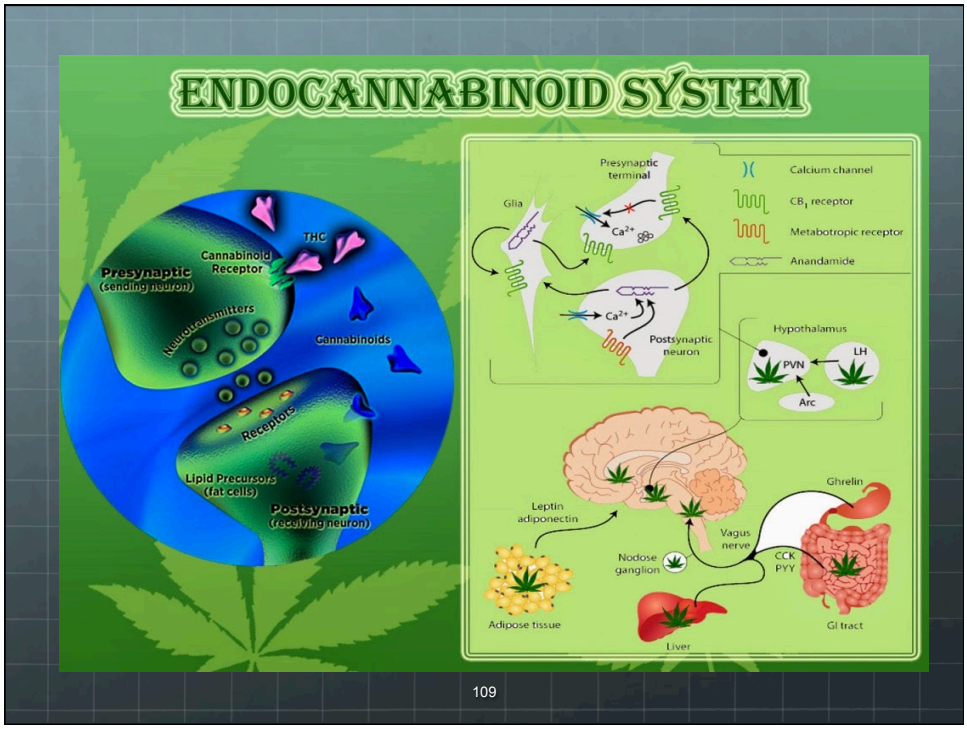
- Endocannabinoids
  - Derivatives of arachidonic acid
  - Endogenous
- Phytocannabinoids
  - Include hundreds of naturally occurring compounds in *C. sativa*
  - Includes THC and cannabidiol
- Synthetic cannabinoids
  - Laboratory produced congeners of THC and cannabidiol

107

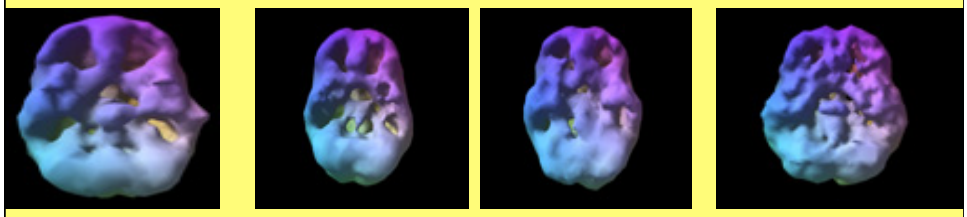
Endocannaboid System

- Finely tuned physiologic modulator
- Regulates synaptic transmitter release
- Works in conjunction with
  - Adrenergic
  - Cholinergic
  - Dopaminergic
  - Opioidergic

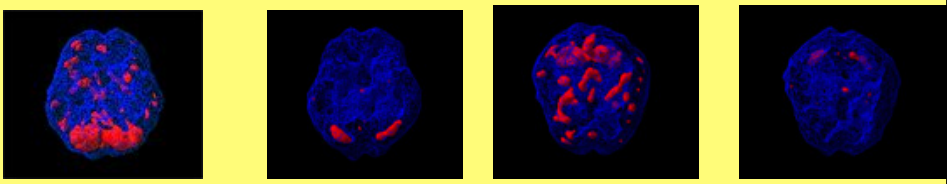
108



Leaf Marijuana Spect Scans

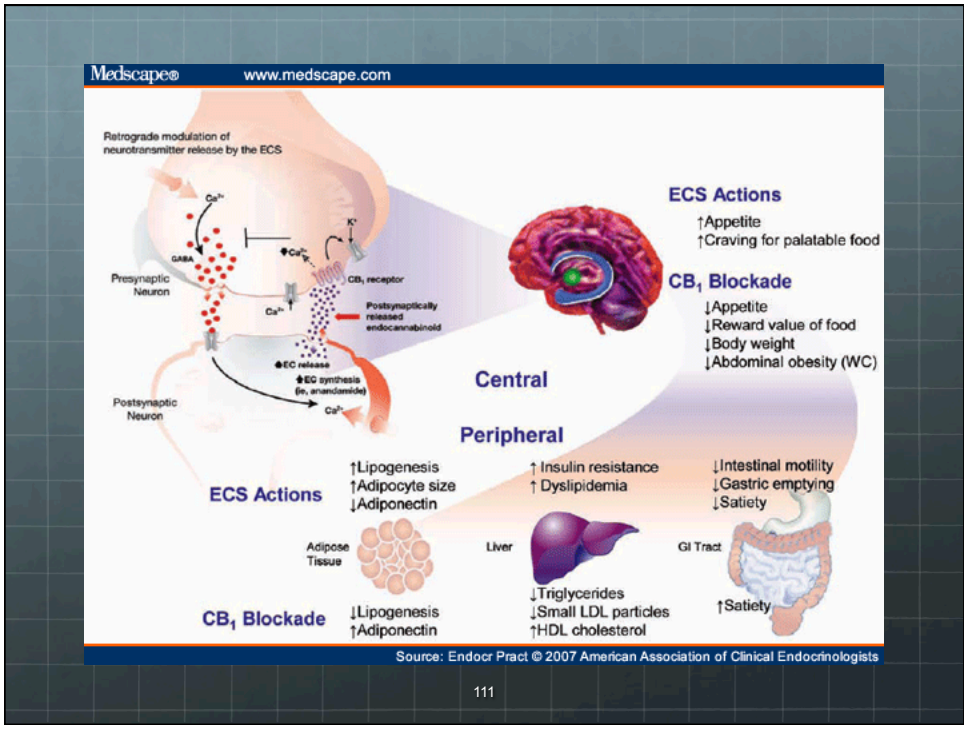


4 Years **7 Years** **9 Years** **12 Years**



With Permission Amens Clinics

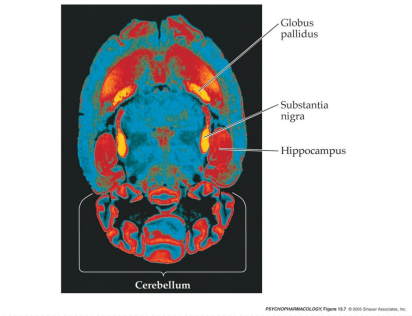
Merrill Norton Pharm.D.,D.Ph.,ICCDP-D 110



111

Two Receptor Types

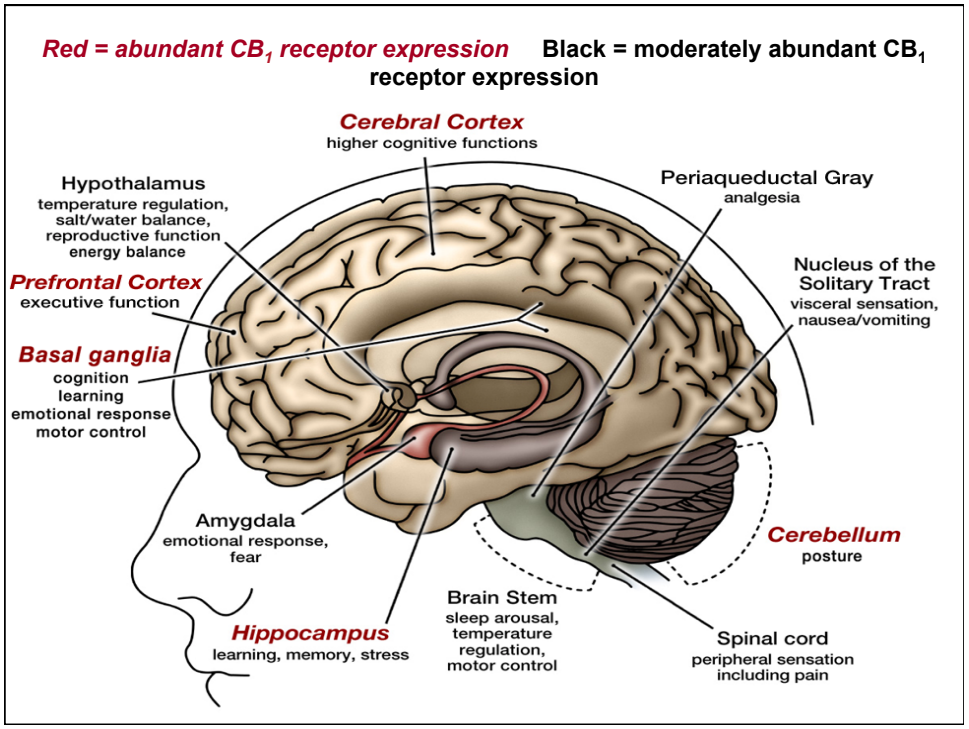
CB-1 Receptor

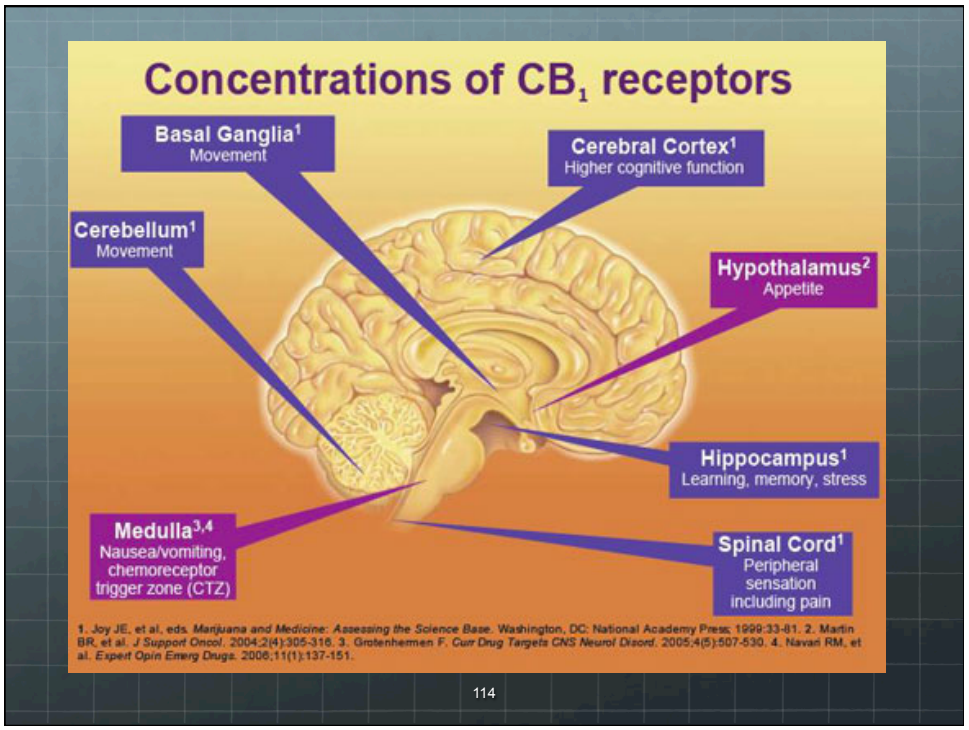


- Located in CNS and PNS

CB-2 Receptor

- Mostly in periphery
- Found primarily in immune system
- Found on heart – protects from inflammation?


Red = abundant CB1 receptor expression
Black = moderately abundant CB1 receptor expression
Cerebral Cortex
higher cognitive functions
Hypothalamus
temperature regulation, salt/water balance, reproductive function energy balance
Periaqueductal Gray
analgesia
Prefrontal Cortex
executive function
Nucleus of the Solitary Tract
visceral sensation, nausea/vomiting
Basal ganglia
cognition learning emotional response motor control
Amygdala
emotional response, fear
Cerebellum
posture
Brain Stem
sleep arousal, temperature regulation, motor control
Hippocampus
learning, memory, stress
Spinal cord
peripheral sensation including pain


Concentrations of CB1 receptors
Basal Ganglia[1]
Movement
Cerebral Cortex[1]
Higher cognitive function
Cerebellum[1]
Movement
Hypothalamus[2]
Appetite
Hippocampus[1]
Learning, memory, stress
Medulla[3,4]
Nausea/vomiting, chemoreceptor trigger zone (CTZ)
Spinal Cord[1]
Peripheral sensation including pain
1. Joy JE, et al, eds. Marijuana and Medicine: Assessing the Science Base. Washington, DC: National Academy Press; 1999:33-81. 2. Martin BR, et al. J Support Oncol. 2004;2(4):305-316. 3. Grotenhermen F. Curr Drug Targets CNS Neurol Disord. 2005;4(5):507-530. 4. Navari RM, et al. Expert Opin Emerg Drugs. 2006;11(1):137-151.
114

CB-1 Receptors

- Concentrated in CNS
  - Frontal cortex, basal ganglia, hippocampus, cerebellum
    - Pleasure, movement, learning, memory, pain
  - Mesolimbic reward center
    - Reinforce pleasurable activities
- Presence in cerebellum and basal ganglia
  - Negative - Discoordination and clumsiness (recreational users)
  - Positive - Amelioration of spasticity in upper motor neuron diseases (multiple sclerosis

115

CB-1 Receptors

- Hippocampus - modulate mood
- Prefrontal cortex and hippocampus - influence concentration, short-term memory, attention, and tracking behavior
- Hypothalamus - appetitie ("munchies")
- Spinal cord dorsal primary afferent tracts and central pain pathways - analgesic actions

116

CB-1 Receptors

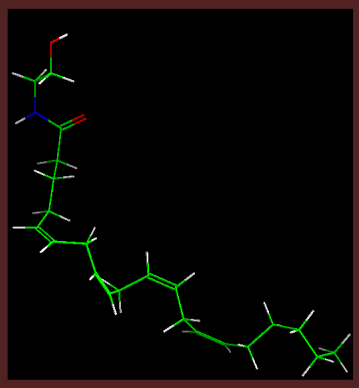
- Dopaminergic pathways in reward center - abuse and dependence
- Very few receptors in brainstem - minimal effect on ANS
  - No known lethal overdose reported with THC

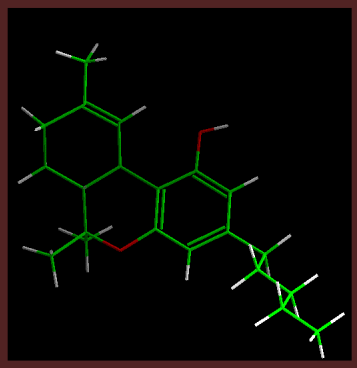
117

CB-2 Receptors

- Primarily found in immune system and hemopoetic cells
- May have a role in antinociception (some located on peripheral nerve terminals)

118





Both compounds bind to CB-1 and CB-2 receptor sites on humans' and many other species' neurons, primarily in the brain.

What Does This Science Mean????

The adolescent brain is biologically incomplete until the age of 24-26. Drug abuse will cause changes in neurohormonal and neurochemical in both the prefrontal cortex and the subcortical limbic regions. The end result is limited learning and memory capability. Drug abuse will increase the risk of future brain limitations.

What Benefits Would Medical Cannabinoids Provide To Society?

Recent Clinical Trials of Cannabinoids for the Treatment of CNS Disorders

Disorder	Target Symptoms	Therapeutic Cannabinoid	Clinical Outcome
Multiple Sclerosis	Spasticity	Oral THC, CBD	In progress
	Neurogenic pain	Sublingual THC, CBD	Phase II trial in progress
	Bladder dysfunction	Sublingual THC, CBD	Phase II trial in progress
Parkinsons's disease	Dystonia	Nabilone	No effect
	Dyskinesia	Nabilone	↓ Dyskinesia
	Tremor	Δ9-THC	No effect
Cancer	Pain	Sublingual THC, CBD	Phase III trial in progress
Postoperative pain	Pain	IM levonantradol	↓ pain, but less effective than existing therapies

CBD = cannabidiol

THC = tetrahydrocannabinol

Croxford, JL. CNS Drugs 2003; 17(3)

Recent Clinical Trials of Cannabinoids for the Treatment of CNS Disorders (cont'd)

Disorder	Target Symptoms	Therapeutic Cannabinoid	Clinical Outcome
Spinal cord injury	Pain	Sublingual THC, CBD	Phase II trial in progress
GI tract pain	Pain	THC	↓ Morphine requirement
Traumatic Brain Injury / Stroke	Neurodegeneration	IV dexanabinol (HU-211)	↓Intracranial pressure, ↓ mortality, phase III trial in progress
	Neurodegeneration	CBD	In progress
HIV wasting syndrome	Appetite loss, nausea	Smoked cannabis	In progress
	Appetite loss, nausea	Dronabinol	↑ appetite, ↓ nausea
Tourette's syndrome	Behavioural disorders	THC	undetermined

Croxford, JL. CNS Drugs 2003; 17(3)

Medical Marijuana (Medical Cannabinoids)

- Cannabis has been used for medicinal purposes for over 4,800 years.
- Surviving texts from Ancient India confirm that its psychoactive properties were recognized, and doctors used it for a variety of illnesses and ailments. (gastrointestinal disorders, insomnia, headaches and as a pain reliever)

Medical Marijuana (Medical Cannabinoids)

- Cannabis as a medicine was common throughout most of the world in the 1800s, It was used as the primary pain reliever until the invention of aspirin.
- The term *medical marijuana* post-dates the U.S. Marijuana Tax Act of 1937, the effect of which made cannabis prescriptions illegal in the United States.

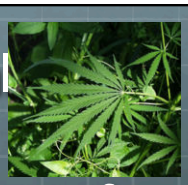
Medical Marijuana (Medical Cannabinoids)

- Later in the century, researchers investigating methods of detecting cannabis intoxication discovered that smoking the drug reduced intraocular pressure. (High intraocular pressure causes blindness in glaucoma patients)
- In the 1970s, a synthetic version of THC, the primary active ingredient in cannabis, was synthesized to make the drug Marinol.
- Users reported several problems with Marinol, however, that led many to abandon the pill and resume smoking the plant.

Medical Marijuana (Medical Cannabinoids

- Patients complained that the violent nausea associated with chemotherapy made swallowing pills difficult. The effects of smoked cannabis are felt almost immediately, and is therefore easily dosed.
- Marinol (Dronibanol), like ingested cannabis, is very psychoactive, and is harder to titrate than smoked cannabis.
- Marinol has also consistently been more expensive than herbal cannabis. Some studies have indicated that other chemicals in the plant may have a synergistic effect with THC.

Medical Marijuana (Medical Cannabinoids)



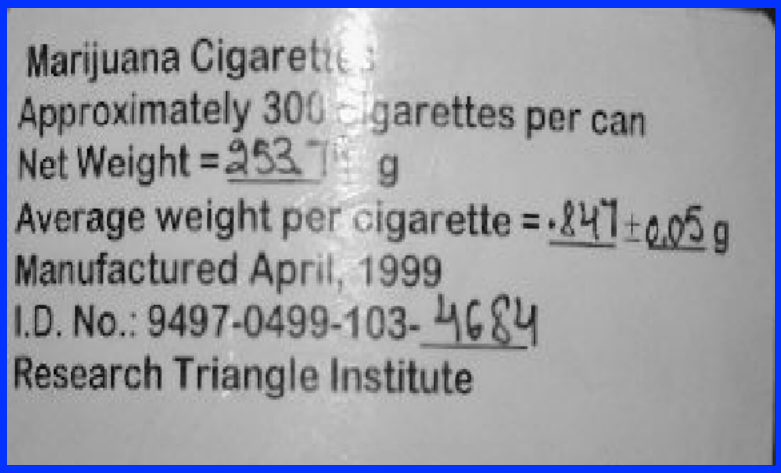
- Medical cannabis refers to the use of the drug *Cannabis* as a physician recommended herbal therapy, most notably as an antiemetic.
- Medical cannabinoids is the appropriate term to describe the legal use of cannabis products for medical purposes.

Facts On Medical Marijuana

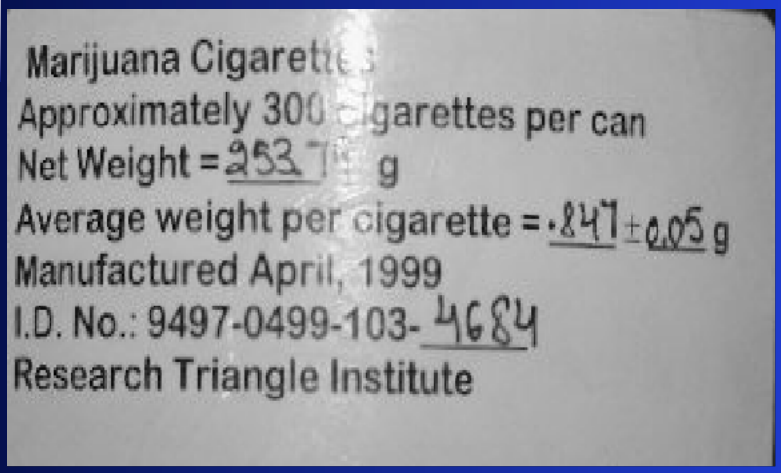
- University of Mississippi has grown marijuana since 1968 funded by Nature Institution on Drug Abuse (NIDA), then later by National Institution Health (NIH). Grow 1.5 to 6.5 acres of marijuana.
- Every state residence voted for medical marijuana except South Dakota which is 48% to 52%
- According to the US government marijuana alone has never cause a death from overdose.
- The British Lung Foundation reports that 3-4 marijuana cigarettes a day are as dangerous to the lungs as 20 or more tobacco cigarettes a day.
- A UCLA study found no association between marijuana and lung cancer.
- In 1978 the U.S. government started the Compassionate Investigational New Drug (IND) program, which supplies about 300 marijuana cigarettes per month to seriously ill patients approved for the program. The program was shut down in 1991, but seven of those patients (as of 7/31/06), continue to receive the free government marijuana.
- Marijuana extracts were one of the top three most prescribed medicines in the United States each year from 1842 until the 1890s.

Cannabis

NIDA Marijuana Label



NIDA Marijuana Label



NIDA likes "Pall Mall"™ Rolling Papers

Unrolled NIDA Marijuana: Mostly Leaf

Stems and Seeds in 3 NIDA-Supplied Marijuana Cigarettes

Four Categories of Pharmaceutical Drugs Based on Marijuana

- Drugs that contain chemical taken directly from the Marijuana Plat (1)

Name	Manufacturer	Medical Use	Related Properties
Sativex	GW Pharmaceuticals	neuropathic pain and spasticity	chemical compound is derived from natural extracts of the cannabis plant

Four Categories of Pharmaceutical Drugs Based on Marijuana

- Drugs that contain synthetic versions of chemicals naturally found in marijuana (2)

Name	Manufacturer	Medical Use	Related Properties
Dronabinol	Solvay Pharmaceuticals	nausea and vomiting, appetite stimulant, ease neuropathic pain	Synthetic Delta-9 THC

Four Categories of Pharmaceutical Drugs Based on Marijuana

- Drugs that contain chemicals similar to those in marijuana but not found in the plant (6)

Name	Manufacturer	Medical Use	Related Properties
Dexanabinol	Pharmos	Neuroprotective (protects brain from damage)	Synthetic non-psychotropic cannabinoid which blocks NMDA receptors

Four Categories of Pharmaceutical Drugs Based on Marijuana

- Drugs that do not work like marijuana but use the same brain pathways (4)

Name	Manufacturer	Medical Use	Related Properties
Rimonabant	Sanofi-Aventis	Anti-obesity	Synthetic chemical that blocks endocannabinoids from being received in the brain

Current Medical Use of Cannabinoids

Cannabinoids have found medical use in the treatment of nausea and vomiting in **chemotherapy** patients and as an appetite stimulant in **AIDS** patients.

They've been shown to attenuate the pathogenesis of **multiple sclerosis**.

Cannabinoids also have potential in the treatment of **degenerative diseases** such as Parkinson's Disease and Alzheimer's by turning off overactive immune cells.

Hempfest 2004 Seattle, Washington (AFP/ Getty Images/Ron Wurzer)

Cannabinoids in Neuroprotection

Cannabinoids are both **neuroprotective and anti-inflammatory** due to their ability to stimulate the production endogenous cytokine receptor antagonists (turn down immune system).

THC and cannabidiol (a non-psychoactive cannabinoid), both **reduced glutamate induced excitotoxicity**. Neuroprotection was not affected by cannabinoid receptor antagonist, indicating a cannabinoid receptor-independent mechanism of action. It was demonstrated that Cannabidiol, THC and other cannabinoids are **potent antioxidants**.

Hampson AJ, Grimaldi M, Lolic M, Wink D, Rosenthal R, Axelrod J. 2001

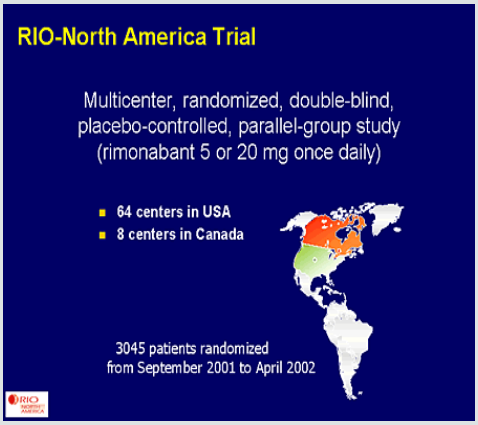
In the future Cannabinoids may be further explored for usefulness in:

Pain (via its actions in the periventricular hypothalamus), anxiety, insomnia, cough, excessive menstrual bleeding, withdrawal from narcotics and alcohol, poor appetite, epilepsy, migraines, multiple sclerosis, Parkinson's disease, and Alzheimer's disease.

Synthetic cannabinoids have been created, including **dexanabinol** which is a noncompetitive antagonist of NMDA glutamate receptors and potent anti-oxidant, but does not bind to CB1 receptors, so it does not produce associated euphoria.

The Anti-Cannabinoid

Rimonabant

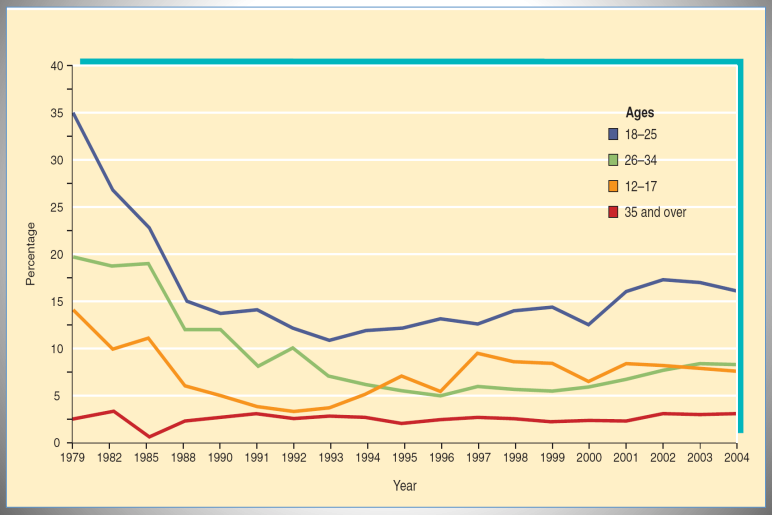


What Are The Dangers of Medical Cannabinoids To Society?

Reefer Madness 2015: The Science of Medical Cannibinoids

Dr. Merrill Norton Pharm.D.,D.Ph.,ICCDP-D
University of Georgia College of Pharmacy
Athens,Georgia
mernort@gmail.com

Current Marijuana Use



Marijuana (2010)

- Stats and Facts:
  - 2010: 15 States and DC approved Marijuana for medical purposes
  - 2009: 25% of U.S. teens had smoked MJ in the past month
  - Not much cross-tolerance with other drugs
  - Doesn't produce anesthesia, coma or death in high doses
  - Highly controversial drug
  - 2010: CA attempted to legalize MJ for recreational use with Prop 09-0024

Marijuana(2010)

- History:
  - Earliest evidence of use: 10,000 years ago during Stone Age
  - Pharmacological use recorded in China ~2700BC
  - Important crop in U.S. since 1611 (Hemp for rope)
  - Mind-altering properties not discovered until 1850s
  - Napoleon's troops brought back recreational use to France after war with Egypt
  - 1920s: Prohibition: led to increase in MJ use
  - 1937: Marijuana Tax Act made recreational use illegal and taxed Rx's

What is Marijuana?(2010)

- Cannabis plant
- 3 Types:
  - C. Sativa (hemp)
  - Indica (grown in India--higher THC)
  - Ruderalis (grown in Northern Europe and Asia—low potency)
- Active ingredients: over 80 known cannabinoids
  - Most common: delta-9-tetrahydrocannabinol (THC)
- Hashish: dried resin; most potent 10-20% THC
- Ganja: dried material from top of plant; 5-8% THC
- Marijuana: dried remainder (leafy portion); 2-5% THC

Pharmacokinetics

Pharmacokinetics(2010)

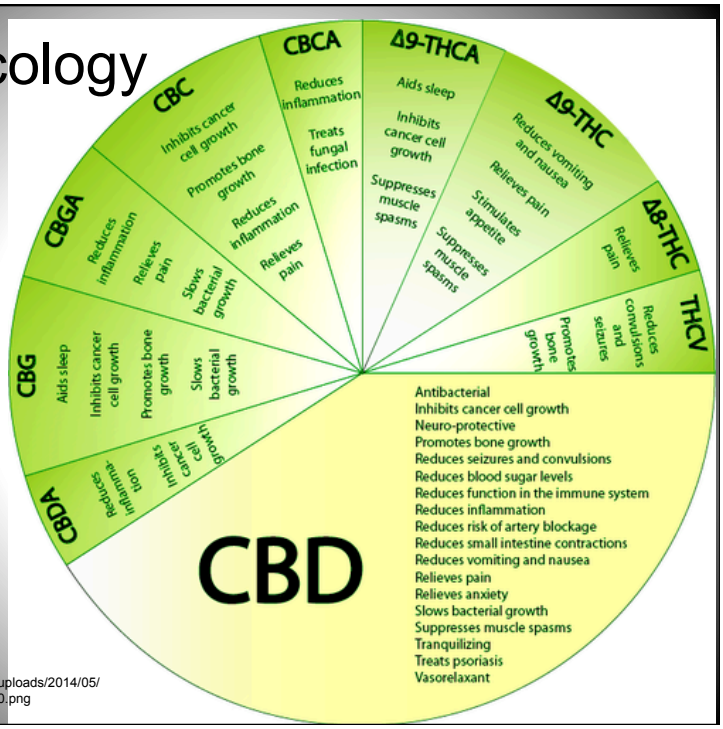
- Routes of Administration
  - Oral
    - Solid or liquid form
    - Larger dose needed for same effect as inhalation (Liver clears much of the THC)
    - Effects longer/more sustained
    - Peak effect: 1-2hrs
    - Lasts 4-6hrs
  - Inhalation
    - Rapid effect (reaches brain in ~30 seconds)
    - Peak effect: 30-60 min
    - Lasts 2-4hrs
    - Subjective state for ~12hrs

Pharmacokinetics(2010)

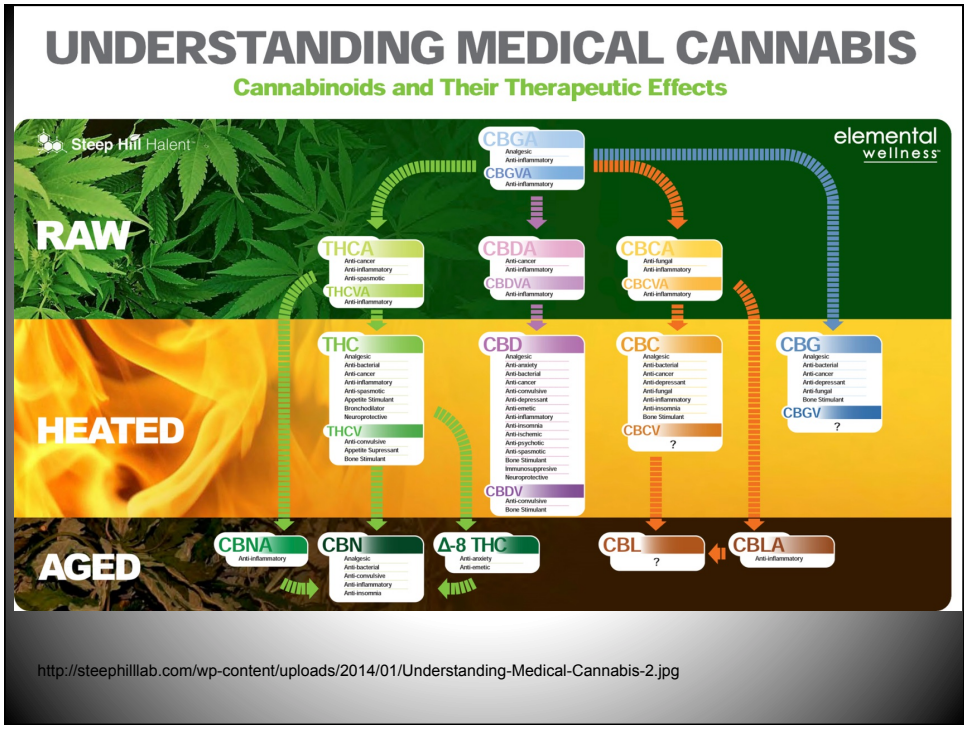
- Distribution, Metabolism, Excretion
  - THC is water insoluble
  - It is absorbed in fatty tissue throughout the body
  - 25-30% of dose may remain in tissue for a week
  - 2 weeks to clear from tissues
  - Metabolized primarily by liver
  - Excreted via urine and feces
  - Detectable in urine
    - Frequent smokers: 7-21 days
    - Infrequent smokers: 1-3 days
    - Daily users: 30 days or more

Marijuana Standards(2015)

Pharmacology



https://cbdbrothers.com/wp-content/uploads/2014/05/tumblr_mmt475oMxO1s85ojqo1_500.png



http://steephilllab.com/wp-content/uploads/2014/01/Understanding-Medical-Cannabis-2.jpg

Pharmacology(2015)

- **Marinol (Dronabinol)**
  - **Reduction of nausea and vomiting in chemotherapy**
  - **Increase appetite in HIV-wasting disease**
  - **Potential New Indications**
    - **Reduction of spasticity, analgesia, agonist-replacement in cannabis dependency**

Kinetic Profile after a single oral dose (10mg of THC)

- **mean peak conc found 1-2 hours post dose**
  - **THC: 3.8 ng/ml (1.1-12.7 ng/ml)**
  - **11-OH-THC: 3.4 ng/ml (1.2-5.6 ng/ml)**
  - **THC-COOH: 26 ng/ml (14-46 ng/ml)**

Huestis, M. 2009, Human Cannabinoid Pharmacokinetics, *National Institute of Health: Chem Biodivers*, v. 4(8), p. 1770-1804.

Pharmacology(2015)

- **Cultivation methods have been developed to reproducibly produce plants with defined THC or CBD concentrations. *GW Pharmaceuticals* has produced two standardized extract preparations, *Tetranabinex*®, which is high in THC, and *Nabidiolex*®, which is high in CBD. *Sativex*® contains equal proportions of *Tetranabinex*® and *Nabidiolex*®, and, hence, almost equal amounts of THC and CBD**

Huestis, M. 2009, Human Cannabinoid Pharmacokinetics, *National Institute of Health: Chem Biodivers*, v. 4(8), p. 1770-1804.

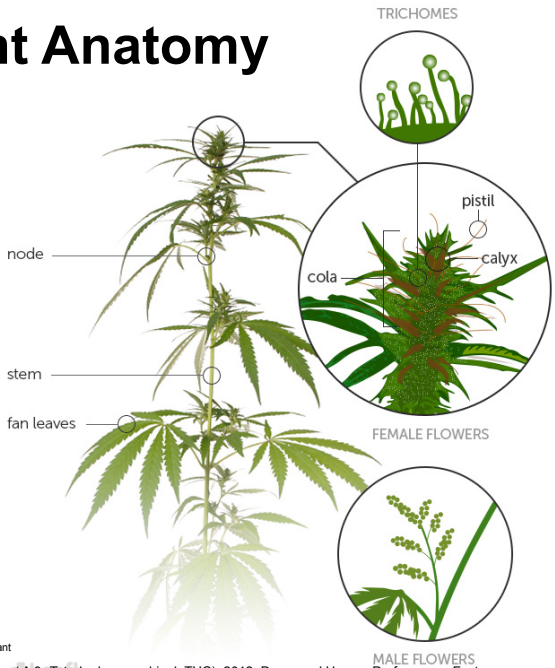
Drug Interactions(2015)

- **Stimulants**
  - **Cocaine, Amphetamines, etc**
    - **increased hypertension**
    - **tachycardia**
    - **cardiotoxicity.**
- **Depressants**
  - **Benzodiazepines, Barbiturates, Ethanol, Opioids, Antihistamines, muscle relaxants, etc.**
    - **increase drowsiness**
    - **CNS depression**
- **Alcohol**
    - **greater impairment**
    - **decreases in function**
    - **less likely to react appropriately**
    - **increased reaction times**

National Highway Traffic Safety Administration, Cannabis / Marijuana (Δ 9 -Tetrahydrocannabinol, THC), 2012, Drugs and Human Performance Fact Sheets, http://www.nhtsa.gov/people/injury/research/job185drugs/cannabis.htm , (August 3, 2015)

Cannabis Plant Anatomy

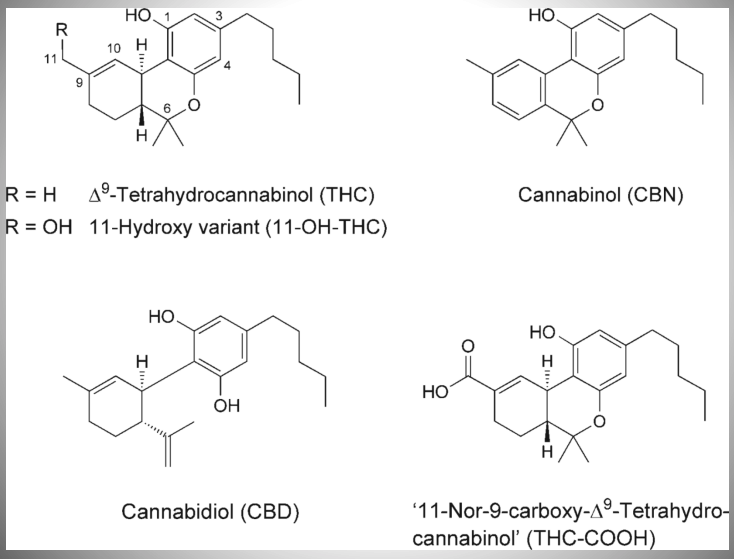
- Cannabinoid Concentration
  - 30,000 cannabis preparations confiscated in the U.S. between 1980 and 1997 were
    - Average Concentrations
      - 3.1% THC
      - 0.3% CBD
  - Influencing Factors
    - Plant sex, age/ developmental stage, environment, genetic makeup
- Medical species are grown to produce similar levels of THC and CBD
- *Sinsemilla* is derived from the unpollinated female cannabis plant
  - preferred for its high THC content (up to 17% THC)
- Concentrations of cannabinoids in the body (parent or metabolite) are dependent use and dose



P: https://www.leafly.com/news/cannabis-101/cannabis-anatomy-the-parts-of-the-plant

National Highway Traffic Safety Administration, Cannabis / Marijuana (Δ 9 -Tetrahydrocannabinol, THC), 2012, Drugs and Human Performance Fact Sheets, http://www.nhtsa.gov/people/injury/research/job185drugs/cannabis.htm , (August 3, 2015)

Cannabinoids(2015)



Huestis, M. 2009, Human Cannabinoid Pharmacokinetics, *National Institute of Health: Chem Biodivers*, v. 4(8), p. 1770-1804.

Cannabinoids(2015)

- THC
  - psychoactive, euphoria, increased reaction time, loss of memory/cognitive functioning decreases, clearance half-life of less than 30 minutes and is not detectable in urine
- CBN
  - Pain relief, Anti-insomnia, Promotes growth of bone cells, Antibacterial, Anti-inflammatory, Anti-convulsive, Appetite stimulant
- CBD
  - may modify THC effects, inhibits conversion of THC to 11-OH-THC (CYP450), formation of CBD from THC does not occur by heat from smoking nor by human metabolism, blocks anxiety and psychological side effects produced by THC intake
- THC-COOH
  - Lipid soluble component (metabolite), can be stored in fat cells for weeks to months, found in blood and urine, typically appears in the urine within 60 minutes, but can take as long as 4 hours, presence of the major THC-COOH >LOQ indicates exposure to THC within 3 days after a single use, to approximately 30 days in heavy chronic users

Marijuana Δ^9-Tetrahydrocannabinol (THC), 2015, Mayo Clinic: Drugs of Abuse Testing, http://www.mayomedicallaboratories.com/test-info/drug-book/marijuana.html (August 10, 2015)
Huestis, M. 2009, Human Cannabinoid Pharmacokinetics, *National Institute of Health: Chem Biodivers*, v. 4(8), p. 1770-1804.

Modifying Concentrations

- Why
  - Seeking better high
  - More THC and less CBD
    - CBD limts psychoactive effects of THC
    - terpenes, delay or modulate the onset of effects of cannabinoids
      - anti-inflammatory terpenes that protect the lungs from irritation
- What
  - Honey Oil, Wax, Hash Oil
- How
  - Using burning techniques and solvents to rid plant and plant resins of CBD
  - pure THC preparations may be the presence of residual solvents (e.g., ethanol) that are needed to solubilize the sticky pure THC

De Backer, B., Maebe, K., Verstraete, A., Charlier, C., 2012, Evolution of the Content of THC and Other Major Cannabinoids in Drug-Type Cannabis Cuttings and Seedlings During Growth of Plants, Journal of Forensic Sciences, v. 57(4)

National Highway Traffic Safety Administration, Cannabis / Marijuana (Δ 9 -Tetrahydrocannabinol, THC), 2012, Drugs and Human Performance Fact Sheets, http://www.nhtsa.gov/people/injury/research/job185drugs/cannabis.htm , (August 3, 2015)

But Is THC Toxic???

- 2009 study from American Scientist on the relative toxicity of recreational drugs showed that using only 10 times the "effective" dose of alcohol could be fatal, whereas more than 1,000 times the effective dose of marijuana would have to be used to be possibly fatal.
- The toxic dose of THC in a 65kg adult would be 8.45kg.

But is THC Toxic???

- The tachycardia almost invariably produced in acute intoxication, combined with the sensory alterations and increased tremor commonly reported, probably contribute to the affective components of these reactions. CNS and respiratory depression are noted with high doses, which in severe overdose may be life-threatening (Rosencrantz, 1983). These effects are, of course, more dangerous to those with pre-existing cardiac irregularities. Because of the large effective to lethal dose ratio in humans (probably in excess of 1:1000 in non-tolerant users) the risk of experiencing severe toxic effects of cannabis is limited by the aversive psychotropic effects of high doses, which usually lead to cessation of use before the onset of dangerous physical consequences.

Evolving Cannabis Administration

- What?
  - New routes
- Why?
  - Provide more direct delivery
- Considerations:
  - Mathematical models have been developed to estimate the time of marijuana exposure within a 95% confidence interval based on blood concentrations
  - Marijuana has been shown to impair performance on driving simulator tasks and on open and closed driving courses for up to approximately 3 hours

National Highway Traffic Safety Administration, Cannabis / Marijuana (Δ 9 -Tetrahydrocannabinol, THC), 2012, Drugs and Human Performance Fact Sheets, http://www.nhtsa.gov/people/injury/research/job185drugs/cannabis.htm , (August 3, 2015)

New Types of Concentrates

- Kief
- Water Hash
- CO2 Oil
- Butane Hash Oil (BHO)
- Rosin

Concentration: Kief

- Also known as dry sieve (sometimes “dry sift”) hash, kief is the simplest of concentrates. Kief is composed of the trichomes (the crystalline structures coating the outside surface of the flowers) broken away from the dried plant material, usually via specialized filtering screens and a little elbow grease. Kief is generally considered a lower-quality extract, but some top-flight extractors can produce an extremely clean and flavorful product using this method. THC content can range from 20 percent to 60 percent. This process at its highest level yields nothing but the largest, most perfect trichome gland heads and none of the gland stems, plant matter, etc. that generally clouds the quicker, lower-quality kief extractions. While it is certainly available in Colorado dispensaries, compared to three years ago, it is much harder to find because of the prevalence of solvent extracts and the low return that it provides to commercial growers.

De Backer, B., Maebe, K., Verstraete, A., Charlier, C., 2012, Evolution of the Content of THC and Other Major Cannabinoids in Drug-Type Cannabis Cuttings and Seedlings During Growth of Plants, Journal of Forensic

Concentrates of Water Hash

- There are various techniques used in the production of water hash, and the resulting products have many forms (bubble hash, solventless wax, ice wax, among others). The basic principle is this: plant material (either dry or fresh-frozen generally) is mixed with cold water and ice, then agitated manually or mechanically in order to break off the now-brittle trichome heads. This solution is then filtered through specifically-sized screens to remove anything undesirable, leaving behind a relatively pure finished product that typically tests between 50 percent and 80 percent THC. The most common way that water hash is extracted is using a series of microscreen fabric bags (generally referred to as “bubble bags”) which remove various grades of

Concentrates of CO2 Oil

- This variety of extract is created using carbon dioxide compressed at high pressures until it becomes what is known as a "supercritical fluid," which then is able to strip the essential oils of the cannabis plant much like hydrocarbon solvents. CO2 oil is generally a loose, orange-tinted oil that can be either clear or opaque depending upon the finishing processes used after extraction, and THC content tests between **50 percent and 75 percent.** The appeal of this method for many is that it is non-flammable and contains no chemical solvents. The machines required to do CO2 extractions at any kind of commercial scale can cost hundreds of thousands of dollars.

Concentrates of Butane Hash Oil (BHO)

- Perhaps the most common type of extract on the market, BHO has a variety of names (wax, shatter, crumble, oil, errl, honeycomb, moon rock, nectar, etc.) but like water hash, the basic principles of extraction are the same across all of them, with the variations in appearance and texture mostly coming in finishing processes. To make a butane concentrate, butane is pressurized in a vessel and washed over plant material (usually dry, but sometimes fresh-frozen — more on that below), then the resulting solution is collected. The hashmaker must remove any residual solvent from this solution, so the next step generally is applying heat (butane has a low boiling point) and vacuum (which lowers the boiling point further) in order to make this process easier and faster while retaining the highest amount of flavorful terpenes and cannabinoids in the finished product. BHO generally tests between **60 percent and 90 percent THC**, making it perhaps the strongest concentrate on the mainstream market.

Concentrates of Rosin

- The newest and hottest type of extract on the scene right now, rosin is extracted from either dried buds, trim, or lower-grade water hash/kief. What is unique about rosin is that it can be made with nothing more than a standard hair straightener, parchment paper and some hand-applied pressure. When the material is smashed and heated quickly between the parchment sheets, it extrudes some of the essential oils present in the plant, resulting in a golden shatter or oil-like extract that looks similar to pressed high-quality water hash or even solvent-extracted shatter. Rosin is a fairly recent development, so its availability in dispensaries is still somewhat limited, as is data about its potency; but early reports on some rosin extracts have showed numbers **between 50 percent and 70 percent**

Inhalation and Smoking

- **Absorption**
  - **Rapid and efficient delivery from lungs to brain**
  - **Exposing drug effects to CNS (abuse potential)**
  - **Slightly lower peak concentrations that IV administered THC**
  - **Bioavailability: 2-56%**
    - **Due to variability in smoking dynamics/ability**
      - **Number, duration, spacing between puffs, hold time, inhalation volume, smoking topography, and expectation**
  - **Formation of 11-OH-THC and THC-COOH occurred later and with much lower concentrations**

Huestis, M. 2009, Human Cannabinoid Pharmacokinetics, *National Institute of Health: Chem Biodivers*, v. 4(8), p. 1770-1804.

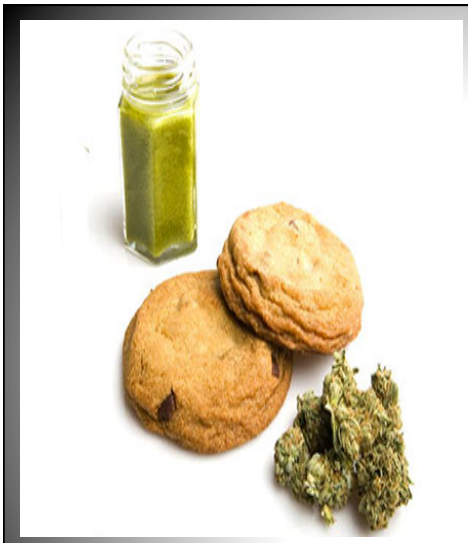
Vaping

- **Absorption**
  - **vaporizers reported the onset of effects more rapidly with pure THC (mean 2.5 min) than herbal cannabis (mean 6.5 min)**
  - **vaporizer resulted in higher plasma concentrations of THC compared to smoked marijuana at 30 and 60 min at each strength**
- **Technique**
  - **heating cannabis to a temperature between 180 and 2001C, it is possible to vaporize the cannabinoids that reside on the trichomes on the surface of cannabis flowers and leaves, while avoiding combustion**
- **Thought on safety/delivery**
  - **volatizes components such as THC, CBD, and terpenes, but with significant reduction of pyrolytic byproducts**
  - **release substantial**
  - **amounts of the THC while producing no measurable amounts of the benzene, toluene, and naphthalene, which are generated when marijuana is smoked**
  - **vaporizer to inhale some form of pure THC (likely dissolved in alcohol or another solvent)**

Hazekamp, A., Ware, M., Muller-Vahl, K., Abrams, D., Grotenhermen, F., 2013, The medicinal use of cannabis and cannabinoids--an international cross-sectional survey on administration forms, Journal of Psychoactive Drugs, 45(3), p. 199-210

Colorado Marijuana Analysis – March 2015

- **Denver lab analyzed more than 600 samples of bud provided by certified growers and sellers**
- **average THC level was 18.7%, and some retail pot contained 30% THC or more**
- **Little or no cannabidiol (CBD) —the average CBD amount: 0.1%**
  - **Recall: CBD lacks detectable psychoactivity and instead has anti-inflammatory, analgesic, anti-nausea, anti-emetic, anti-psychotic, anti-ischemic, anxiolytic, and anti-epileptiform effects – the "medical" in medical marijuana.**



Edibles

Edibles

- **Absorption**
  - **Readily absorb due to high octanol/water partition coefficient**
    - **Circulation Concentrations are Dependent on: subject determination, dose, vehicle, physiological factors, and excretion rate**
    - **Occurs slower with lower peak THC concentrations**
    - **Ohlsson Study: Ingesting 20 mg of THC in a Chocolate Cookie Vehicle**
      - **Peak: 4.4 to 11 ng/ml occurred at 1-5 hours Vehicle**
      - **Oral Bioavailability: 6% (range 4-20%)**
        - » **Variable absorption, degradation of drug in the stomach, first pass metabolism to active 11-OH-THC, inactive metabolites in the liver**

Huestis, M. 2009, Human Cannabinoid Pharmacokinetics, *National Institute of Health: Chem Biodivers*, v. 4(8), p. 1770-1804.

Edibles

- Gelatin capsules, glycocholate, sesame oil: improved bioavailability
  - Considerable variations in peak concentrations and rates of absorption
    - » Occurred even when administer in the same vehicle more than once
  - Sesame Oil based Administration
    - » Oral THC bioavailability: 10-20%
      - Men ingested 20 mg
      - Women ingested 15 mg
    - » Plasma Peak at 4-6 hours, but were considered over estimated because of radioactive labeling not being subject to only THC and extending to its metabolites

Edibles

- Technique
  - THC Containing Foods
- Thought on safety/delivery
  - Hemp Oil (derived from seeds): source of essential amino acids and fatty acids
    - THC conc is dependent on seed cleaning and oil filtration processes
    - THC contents greater than or equal to 300 and up to 1500 mg/g are available

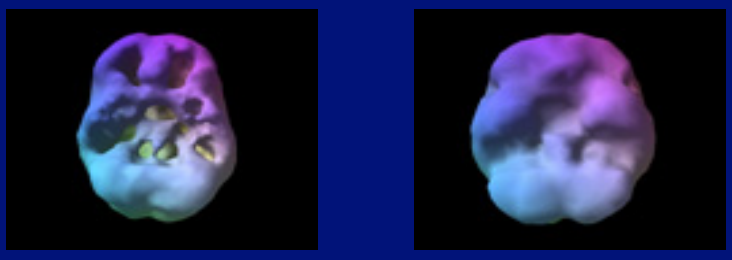
Other Administrations

- **Routes**
  - **Oromucosal**
    - ***Sativex*® is administered sublingually to avoid first-pass metabolism by the liver. *Sativex*® is approved in Canada for the treatment of neuropathic pain associated with multiple sclerosis, and in three European countries for a number of indications.**
  - **Rectal**
    - **THC-hemisuccinate provided the highest bioavailability of 13.5% (Marinol suppository)**
    - **bioavailability of the rectal route was approximately twice that of the oral route**
    - **THC did not accumulate in the blood following 10−15 mg daily doses**
    - **administration of 2.5−5 mg of THC produced maximum plasma concentrations of 1.1−4.1 ng/ml within 2−8 h.**
  - **Transcutaneous**
    - **mean steady-state plasma concentration of Δ8-THC was 4.4 ng/ml within 1.4 h, and was maintained for at least 48 h**
    - **Permeabilities of CBD and CBN were found to be 10-fold higher than for Δ8-THC**
    - **Low abuse potential due to slow delivery of THC to the brain**
  - **Intravenous**
    - **THC produced schizophrenia-like positive and negative symptoms and euphoria, and altered aspects of cognitive function**
      - **Acute paranoia, panic, hypotension, withdrawal, behavior and cognitive defects (endogenous psychosis)**

Huestis, M. 2009, Human Cannabinoid Pharmacokinetics, *National Institute of Health: Chem Biodivers*, v. 4(8), p. 1770-1804.

Impact of Addiction

- MARIJUANA:



16 y.o.
2 year history of daily abuse

Normal

underside surface view of prefrontal and temporal lobe activity

Withdrawal According to the DSM 5

- A. Cessation of cannabis use that has been heavy and prolonged
- B. 3 or more of the following develop within several days after Criterion A
- 1. Irritability, anger or aggression
- 2. Nervousness or anxiety
- 3. Sleep difficulty (insomnia)
- 4. Decreased appetite or weight loss
- 5. Restlessness
- 6. Depressed mood
- 7. Physical symptoms causing significant discomfort: must report at least one of the following: stomach pain, shakiness/tremors, sweating, fever, chills, headache

Questions???????