# Marijuana

**Daniel D. Langleben, MD**
**langlebe@mail.med.upenn.edu**

**Treatment Research Center**
**Department of Psychiatry**
**University of Pennsylvania**

# Pre-Lecture Exam

1. Cannabis use can lead to all except:
    a. Euphoria
    b. Impaired memory
    c. Weight gain
    d. Altered perception
    e. Anxiolysis

# Pre-Lecture Exam

2. Cannabis has been used as a therapeutic agent for the following conditions:
    a. Extreme nausea
    b. Increased intraocular pressure
    c. Inflammation
    d. AIDS-related wasting
    e. All of the above

# Pre-Lecture Exam

3. Which of the following is/are not true:
   a. About 40% of Americans over the age of 12 have tried marijuana
   b. A single joint can lead to a positive urine test for 8-96 hours
   c. It is absolutely legal to prescribe marijuana in some states, but not in others
   d. Marijuana is Schedule 1 substance under the Controlled Substance Act E
   e. All of the above statements are false

# Pre-Lecture Exam

4. Which statement about cannabinoids is/are true:
   a. Cannabinoid agonists can be used for the treatment of obesity
   b. Cannabinoid antagonists can be used to treat nausea associated with chemotherapy
   c. Cannabinoid CB1 receptors can be found in the basal ganglia, cerebellum, hippocampus, and cortex D
   d. All of the above are true

# Pre-Lecture Exam

5. Which is true about schizophrenia and cannabis:
   a. The risk for developing schizophrenia is higher for those using cannabis at an early age versus those starting in late adolescence
   b. The risk for developing schizophrenia is highest for those who use cannabis at an early age and who have the MET-MET COMT genotype
   c. The risk for developing schizophrenia is higher for those using alcohol at an early age versus those starting in late adolescence.
   d. All of the above are true

# Teaching Points

- Cannabis has potentially toxic effects regarding cognition, bronchopulmonary irritation, endocrine changes, and immunomodulation
- Cannabis has been used as a therapeutic agent as an antiemetic, for glaucoma, as an analgesic, as a muscle relaxant, and as an anti-inflammatory agent
- Although theoretically “legalized” in several states for medicinal use, cannabis remains a Schedule 1 substance under the Federal Controlled Substance Act, and thus illegal outside an FDA-approved research program

# Teaching Points (cont.)

- Synthetic cannabinoid agonists (for example, dronabinol) are commercialized and FDA-approved for chemotherapy-related nausea and AIDS-related wasting
- Cannabinoid antagonists (for example, rimonabant, not approved in the US) may be useful for the treatment of obesity and possibly substance use disorders
- There may be a gene x environment interactions regarding cannabis use and the development of schizophrenia

# Outline

- What is marijuana?
- Desirable and undesirable cognitive effects
- Therapeutic and toxic somatic effects
- Chemistry and pharmacokinetics
- Synthetic THC
- Cannabinoid receptors
- Cannabinoids and obesity
- Cannabis and schizophrenia

# Marijuana = Dried and shredded

**Cannabis sativa** (hemp)

- Native of Central Asia, now worldwide
- Blooming buds of the female plants: highest concentration of THC
- Smoked (joints, bongs and blunts) or eaten

# Clinical effects - cognitive

## Desirable

- **Euphoria** : ***"high"***
- **Anxiolysis:** ***"mellowing out"***

## Toxic

- **Balance and orientation**
- **Motivation**
- **Memory**
- **Perception**
- **Consciousness**

# Clinical effects - somatic

## Therapeutic

- Antiemetic
- Reduction of intra-ocular tension
- Analgesic
- Muscle relaxant
- Anti-convulsant
- Anti-inflammatory
- ⇑appetite: “the munchies”

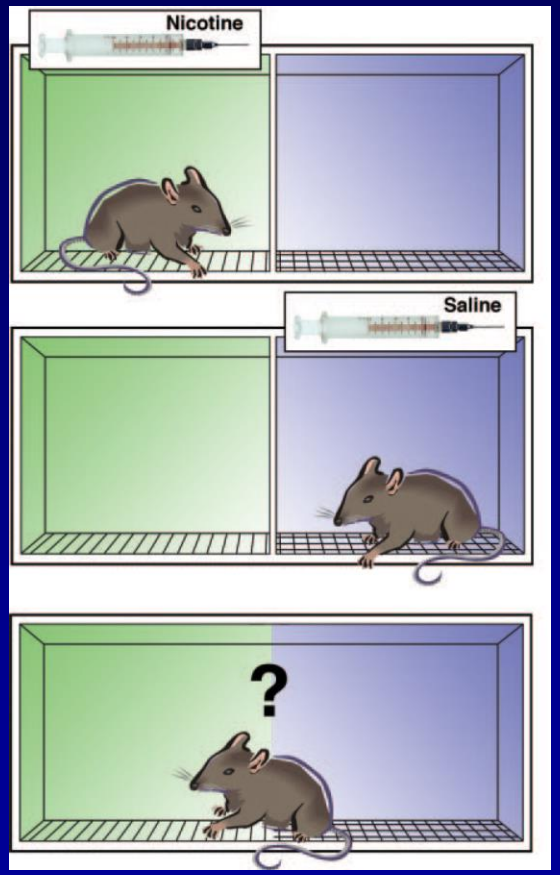
## Toxic

- Xerostomia,Hypohydrosis, Hypertension,Tachycardia
- Conjunctival Irritation
- Bronchopulmonary Irritation
- Endocrine changes
- ↓Immunomodulation
- LD 50% in rats > 1200 mg/kg

# Are canabinoids like other drugs of abuse?

**Clinical data: ?**

- Tolerance rapid on/off
- Withdrawal syndrome: atypical, mild
- Dependence: 9% of those who ever used




*Le Foll & Goldberg 2005*

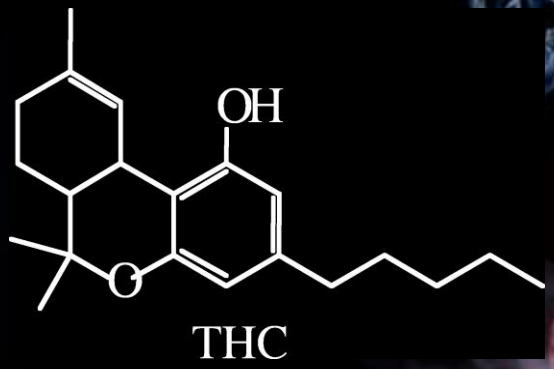
**Preclinical data: YES**

- ✓ Is **self administered**
- ✓ **THC seeking** can be **reinstated** over delay
- ✓ **↑CRF & BSR (“brain stimulation reward”)**
- ✓ **Dopamine**
- ✓ Produces **Conditioned Place Preference (CPP)**

# Chemical constituents of Cannabis

**Chemical classes**

Cannabinoids (66)
Nitrogenous compounds (27)
Amino acids(18)
Proteins/ enzymes (11)
Sugars (34)
Hydrocarbons (50)
Simple alcohols (7)
Simple aldehydes (12)
Simple ketones (13)
Simple acids (21)
Fatty acids (22)
Simple esters/lactones (13)
Steroids (11)
Terpenes (20)
Non-cannabinoid phenols (25)
Flavoroids (21)
Vitamins (1)
Pigments (2)
Elements (9)
**Total known compounds** (483)

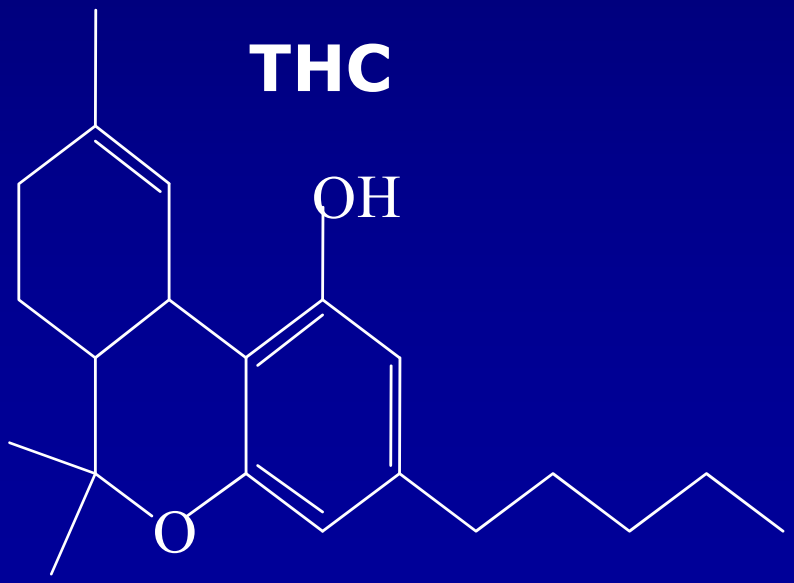



**Delta-9-tetrahydrocannabinol (THC) is the active ingredient of marijuana**

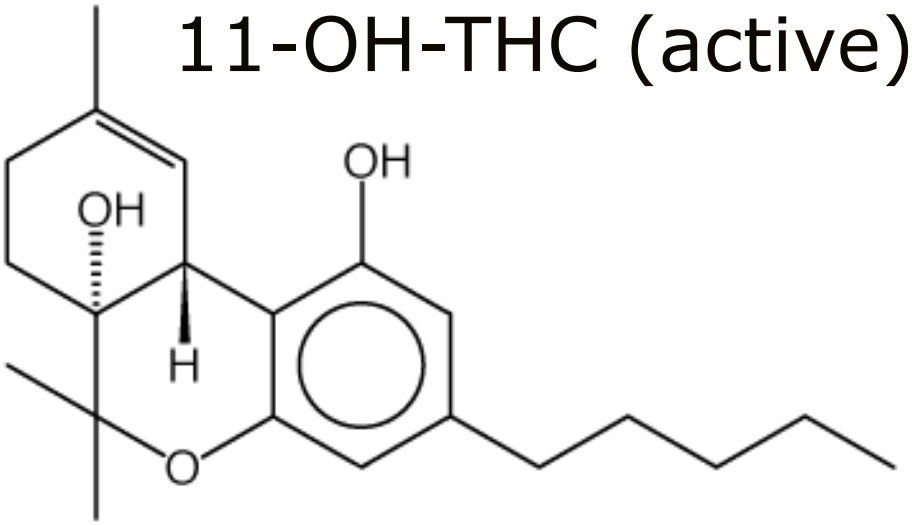
**major metabolites OH-THC** (11-delta-9-THC) **and THC-COOH** (11-nor-delta-9-THC-carboxylic acid, inactive)

**Levo is the more active isomer**

**THC**




11-OH-THC (active)



# Epidemiology: *The Demand*

- Most common illicit psychoactive drug worldwide

94 million Americans (40 %) over 12 have tried marijuana (National Survey on Drug Use and Health, 2003)

http://www.marijuana-info.org

# THC Content in street preparations

## > 4% Marijuana

## 30% Hashish



**$10 billion spent in the US in 2000**

**$70 to $1,200 per pound, $600 to $4,000 for sin-semilla**

# The Supply

- All 50 States, Puerto Rico and Guam reported cannabis cultivation
- Indoor hydroponic operations in every State and Puerto Rico
- Major foreign sources: Mexico (7900 metric tons), Canada, Colombia, and Jamaica (200 metric tons)

# Absorption, Metabolism & Elimination

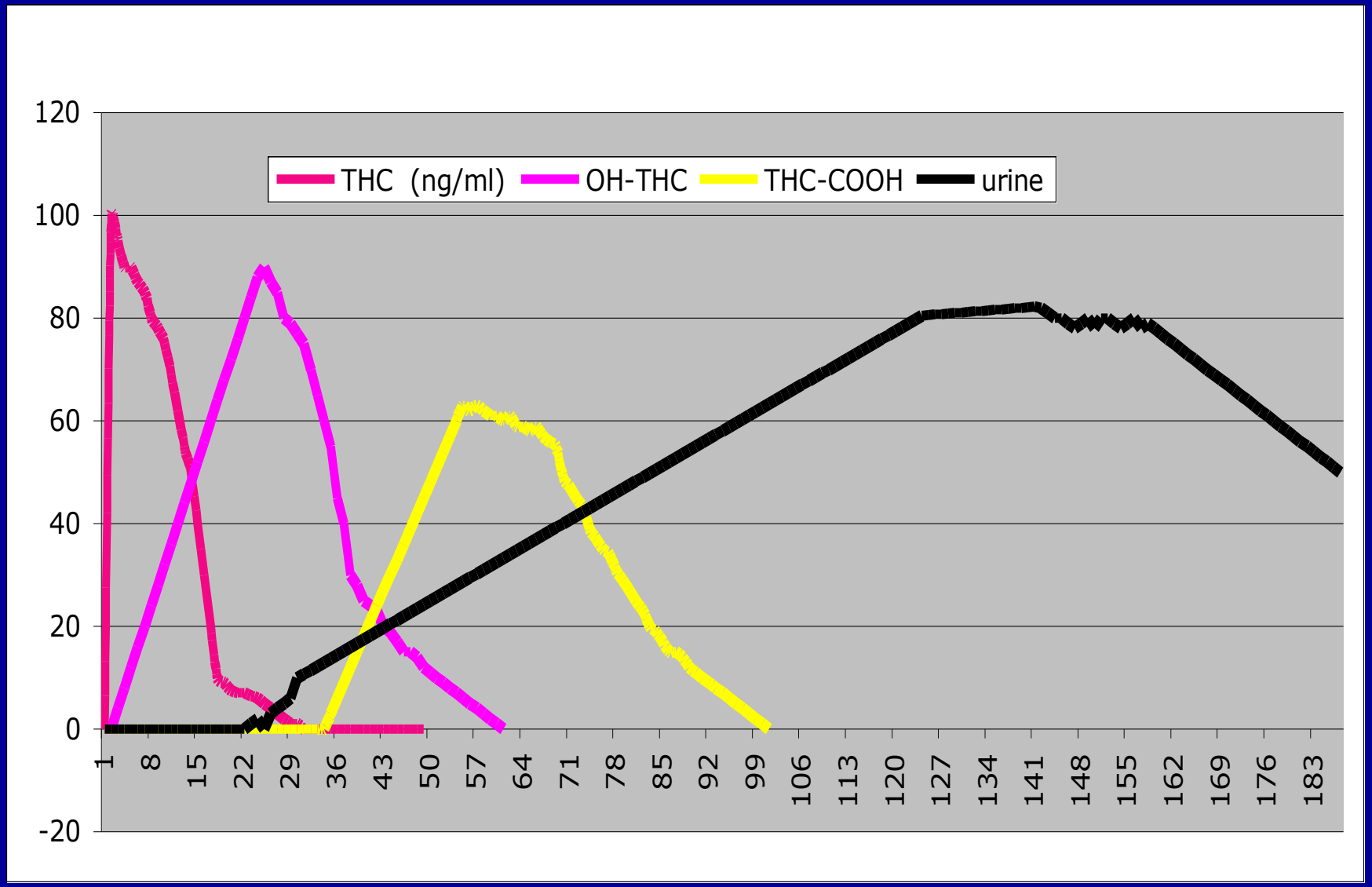
- Psychotropic threshold > 25 ng/ml
- Peak plasma levels > 100 ng/ml drop to < 2 ng/ml in 4 hours
- Psychotropic effects lag the plasma level after inhalation
- Peak effect (inhaled) <10 min
  Peak effect (ingested) 2.5+ hrs (first pass yields OH-THC)
- Liver - CYT P450
- Lipophilic: redistributed in fatty tissues and could be released back into circulation
- Elimination: 35% urine, 65% feces

# Detection

- **Screening - Immunoassay in urine: sensitivity threshold is 50 ng/ml, does not discriminate THC from the metabolites**
- **Confirmation - Gas chromatography and other specific methods**
- **Single joint can lead to a positive urine test for 8-96 hrs**
- **Plasma but not urine samples are correlated with time and amount used**

**MMWR Weekly September 16, 1983 / 32(36);469-71**
**NHTSA Fact sheet 2002**

# THC and metabolites in plasma and urine



1930: American Cannabis USP
“narcotic,analgesic,sedative…”
Parke, Davis and Co

2006: Sativex™

oral and spray

GW pharmaceuticals
(UK/Canada)

# May I prescribe you a joint?

11 states legalized medicinal use with medical recommendation: AK AZ CA CO HI ME NV OR RI VT WA

35 states allow use by prescription

**BUT**

**Schedule I substance under the Controlled Substances Act**: *high potential for abuse, no currently accepted medical use and a lack of accepted safety* = illegal, except FDA - approved research programs

so

# Synthetic Cannabinoid Agonists

- **Dronabinol (Marinol): Synthetic THC**
  FDA-approved for **nausea associated with chemotherapy** and for **AIDS-related wasting**

- **Nabilone (Cesamet): THC analogue**
  **Same indications as Marinol (UK)**

- **HU-210: x100 to 800 more potent than THC**
- **WIN-55,212-2: Binds to CB2 > CB1**

# Cannabinoid Receptors

**G protein-coupled, with seven transmembrane regions**

- ***CB1***

**Brain**, fat cells, liver, duodenum, muscle

- ***CB2***

**lymphocytes**>macrophages>cytokines

# Endocannabinoids: *Bind CB1 > CB 2*

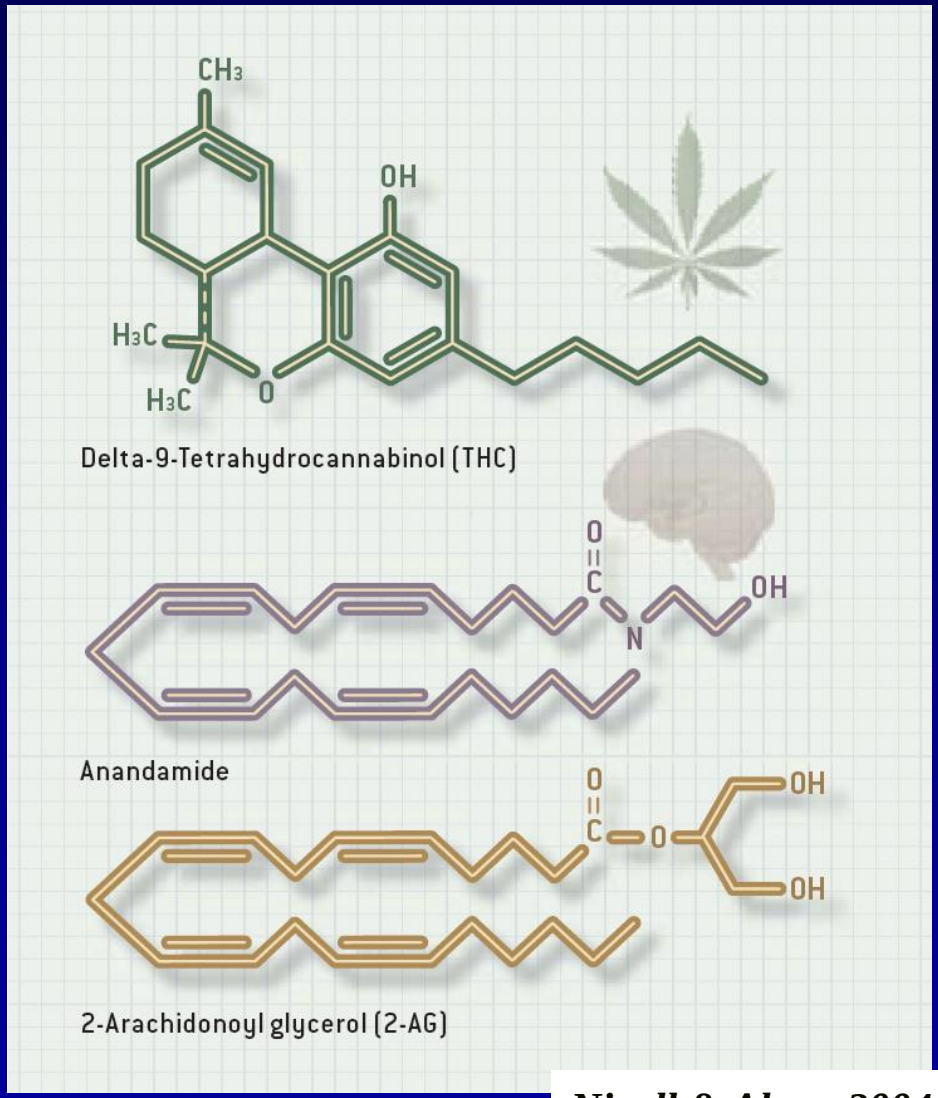
*structure, related to prostaglandins*

- **Annandamide**

(arachidonyl-ethanolamid)

- **2-Arachidonoyl - glycerol (2-AG)**

more abundant, less potent

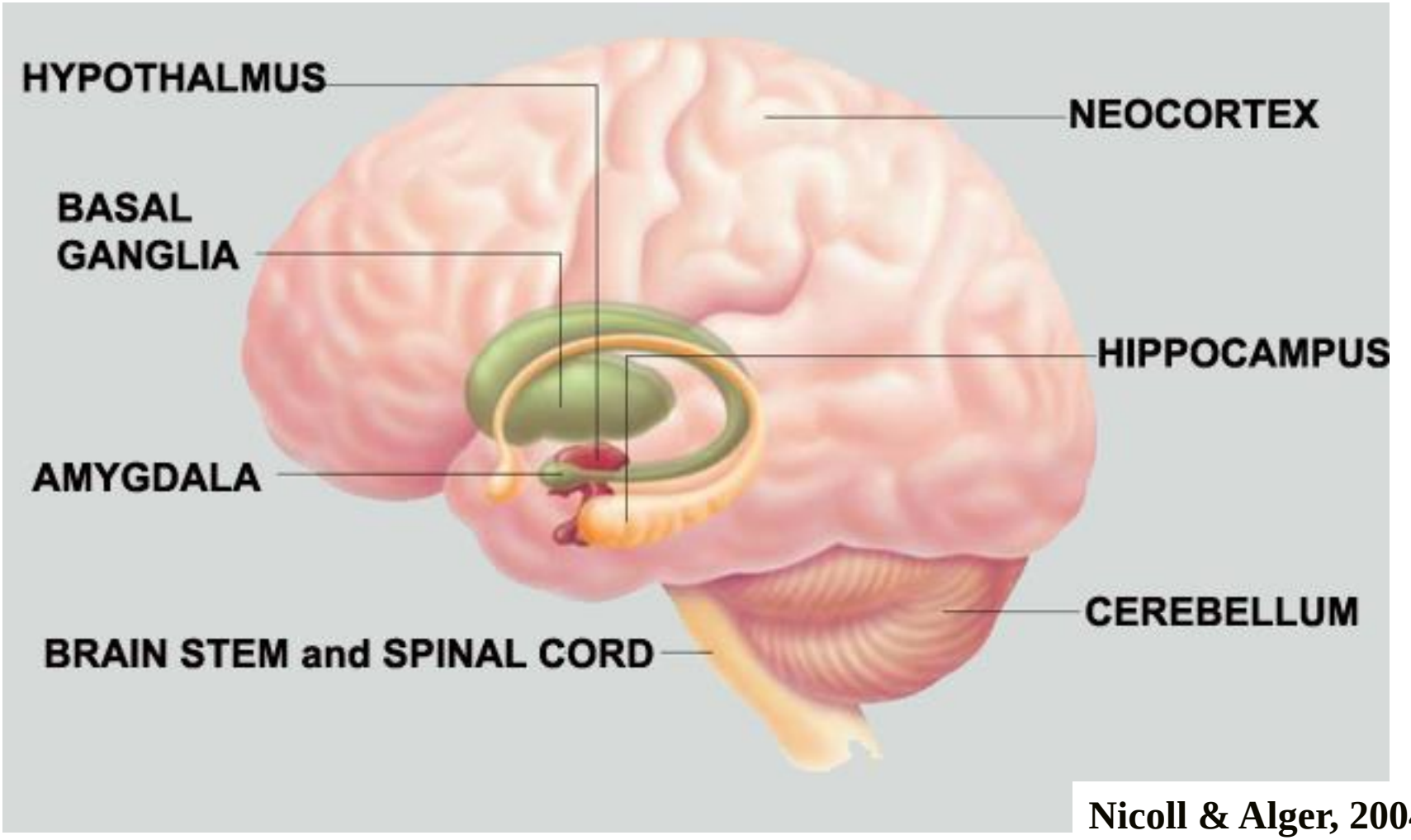



*Nicoll & Alger, 2004*

# CB1 receptors in the brain

**Dense**:Basal Ganglia, Cerebellum, Hippocampus, NAcc, Middle Prefrontal and Parietal Cortex

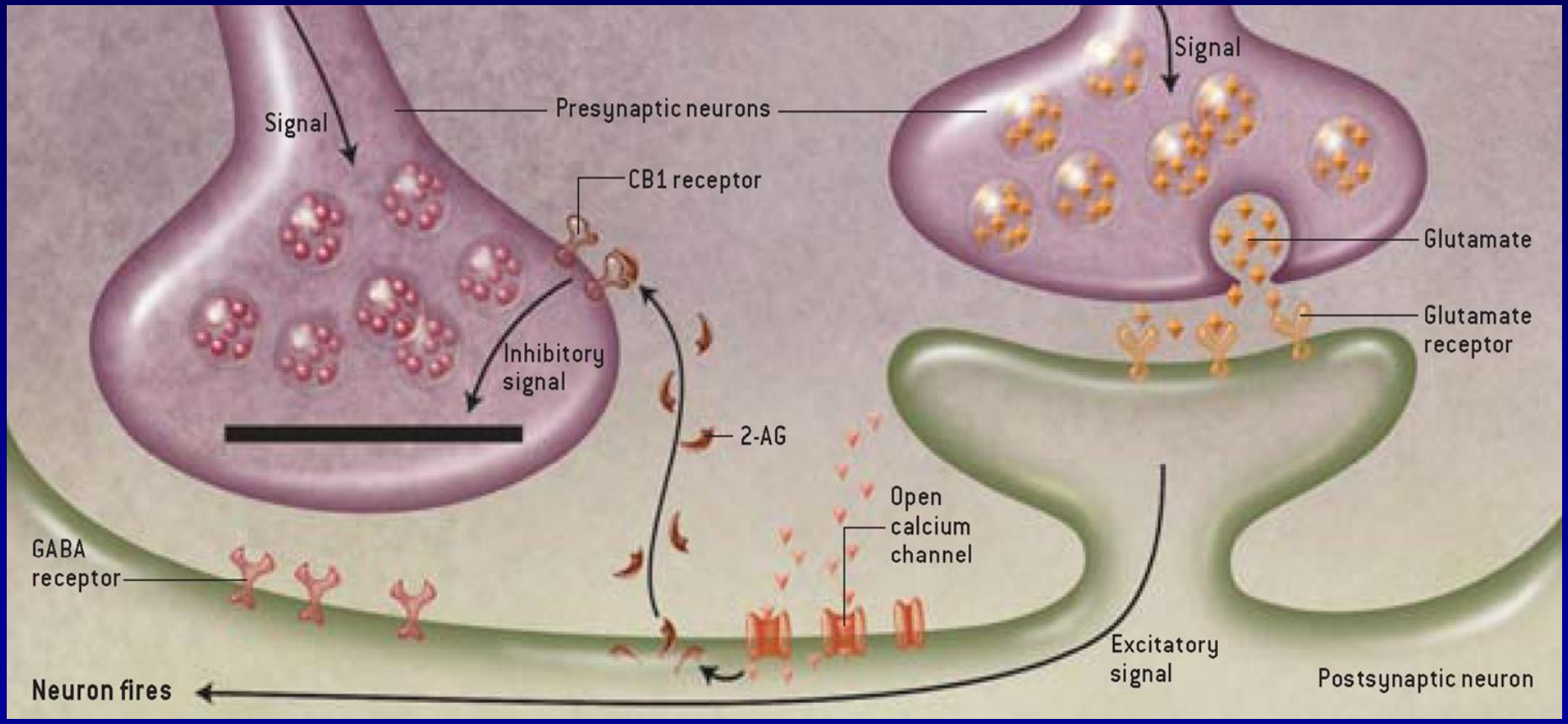
**Moderate**: Amygdala, Spinal Cord, Brainstem




Nicoll & Alger, 2004

# Depolarization-induced suppression of inhibition

**POSTSYNAPTIC endocannabinoid release inhibits PRESYNAPTIC GABA and glutamate release**



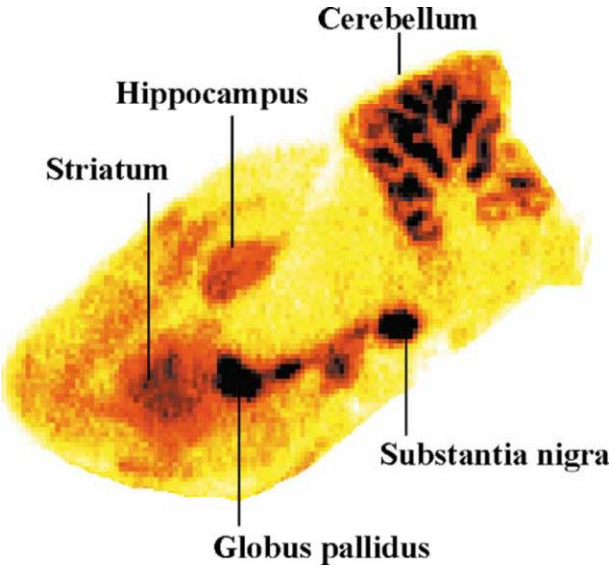

Nicoll & Alger, 2004

# Synthetic Cannabinoid Antagonists

**SR 141716A (RIMONABANT, Phase 3 trials)**

AM 281, AM 251 = CB1

SR 144528 = CB2




# CB1 antagonists

Rimonabant

SPECT ligand

*Volkow 2004*

# Obesity = Hyperactive endocannabinoid system?

Endocannabinoids and cannabis

- Induce appetite (orexigenesis)
- Reduce satiety
- Stimulate lipogenesis
- Reduce energy expenditure
- Increase hedonic reward value of palatable food

*A CB1 antagonist should have opposite effects…*

# Treatment for Cannabis Dependence

- The demand for treatment at substance use disorder programs doubled between 1992 and 1998 in the United States.
- The percentage of illicit drug abuse treatment admissions for marijuana (23%) has approximated that for cocaine (27%) and heroin (23%) (1178).

# Therapeutic potential of CB1 antagonists for substance abuse indications

Blocks the direct reinforcing effects of some drugs of abuse and food

Blocks the motivational effects (relapse prevention) of most drugs of abuse

Preclinical: SR141716 blocked conditioned place preference and reinstatement of drug seeking behavior to heroin and nicotine but not cocaine (De Vries et al 2001)

Clinical: Rimonabant doubled smoking quit rates

# Conclusions

- Marijuana delivery system (the “joint”) is more harmful that the substance itself (1999 IoM report)
- Relative to other illicit and legal psychoactive substances, the abuse and addictive potential of cannabinoids is modest
- Once separated from marijuana, **cannabinoid agonists** are a promising new class of compounds for a variety of non-psychiatric indications
- **Cannabinoid antagonists** are a potentially important new class of compounds for the treatment of the disorders of motivation and reward system that include drug addiction, drug abuse

**Selected references:**


- Substance Abuse and Mental Health Services Administration. *Results from the 2003 National Survey on Drug Use and Health: National Findings*. NSDUH Series H-25. DHHS Pub. No. (SMA) 04-3964. Rockville, MD: SAMHSA, 2004.
- Arendt, M., R. Rosenberg, et al. (2005). "Cannabis-induced psychosis and subsequent schizophrenia-spectrum disorders: follow-up study of 535 incident cases." Br J Psychiatry 187: 510-5.
- Bolla, K. I., K. Brown, et al. (2002). "Dose-related neurocognitive effects of marijuana use." Neurology 59(9): 1337-43.
- Di Marzo, V. and I. Matias (2005). "Endocannabinoid control of food intake and energy balance." Nat Neurosci 8(5): 585-9.
- Marx, J. (2006). "Drug development. Drugs inspired by a drug." Science 311(5759): 322-5.
- di Tomaso, E., M. Beltramo, et al. (1996). "Brain cannabinoids in chocolate." Nature 382(6593): 677-8.
- Fernandez, J. R. and D. B. Allison (2004). "Rimonabant Sanofi-Synthelabo." Curr Opin Investig Drugs 5(4): 430-5.
- Marx, J. (2006). "Drug development. Drugs inspired by a drug." Science 311(5759): 322-5.
- Mechoulam, R. (1970). "Marihuana chemistry." Science 168(936): 1159-66.
- Monteleone, P., I. Matias, et al. (2005). "Blood levels of the endocannabinoid anandamide are increased in anorexia nervosa and in binge-eating disorder, but not in bulimia nervosa." Neuropsychopharmacology 30(6): 1216-21.
- Piomelli, D. (2004). "The endogenous cannabinoid system and the treatment of marijuana dependence." Neuropharmacology 47 Suppl 1: 359-67.
- Di Marzo V, Petrocellis LD. Plant, synthetic, and endogenous cannabinoids in medicine. Annu Rev Med. 2006;57:553-74.
- Piomelli, D. (2005). "The endocannabinoid system: a drug discovery perspective." Curr Opin Investig Drugs 6(7): 672-9.
- Thornton-Jones, Z. D., S. P. Vickers, et al. (2005). "The cannabinoid CB1 receptor antagonist SR141716A reduces appetitive and consummatory responses for food." Psychopharmacology (Berl) 179(2): 452-60.
- Marsicano G, Wotjak CT, Azad SC, et al. The endogenous cannabinoid system controls extinction of aversive memories. Nature. 2002 Aug 1;418(6897):530-4.
- van der Stelt, M. and V. Di Marzo (2003). "The endocannabinoid system in the basal ganglia and in the mesolimbic reward system: implications for neurological and psychiatric disorders." Eur J Pharmacol 480(1-3): 133-50.

# Post-Lecture Exam

1. Cannabis use can lead to all except:
    a. Euphoria
    b. Impaired memory
    c. Weight gain
    d. Altered perception
    e. Anxiolysis

# Post-Lecture Exam

2. Cannabis has been used as a therapeutic agent for the following conditions:
    a. Extreme nausea
    b. Increased intraocular pressure
    c. Inflammation
    d. AIDS-related wasting
    e. All of the above

# Post-Lecture Exam

3. Which of the following is/are not true:
   a. About 40% of Americans over the age of 12 have tried marijuana
   b. A single joint can lead to a positive urine test for 8-96 hours
   c. It is absolutely legal to prescribe marijuana in some states, but not in others
   d. Marijuana is Schedule 1 substance under the Controlled Substance Act E
   e. All of the above statements are false

# Post-Lecture Exam

4. Which statement about cannabinoids is/are true:
   a. Cannabinoid agonists can be used for the treatment of obesity
   b. Cannabinoid antagonists can be used to treat nausea associated with chemotherapy
   c. Cannabinoid CB1 receptos can be found in the basal ganglia, cerebellum, hippocampus, and cortex D
   d. All of the above are true

# Post-Lecture Exam

5. Which is true about schizophrenia and cannabis:
   a. The risk for developing schizophrenia is higher for those using cannabis at an early age versus those starting in late adolescence
   b. The risk for developing schizophrenia is highest for those who use cannabis at an early age and who have the MET-MET COMT genotype
   c. The risk for developing schizophrenia is higher for those who being using alcohol at an early age versus those starting in late adolescence.
   d. All of the above are true

# Answers to Pre and Post Lecture Exams

1. C
2. E
3. C
4. C
5. A