NABP 2009 SYMPOSIUM

- ***Cannabis in the Treatment of Chronic Pain***

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- Principal Investigator – **Characteristics of patients with chronic pain accessing treatment with medical cannabis in Washington State**

Lecture Outline

- Brief History
- Biology/Pharmacology of Marijuana (Cannabis)
- Clinical Trials
- Using Cannabinoids in this Setting

Historical Aspects

- Has been used medicinally, spiritually, and recreationally for thousands of years
- Was legal in USA until 1937 and was on the US Pharmacopoeia until 1942: this was done AGAINST the advice of the AMA (then known as the American Medical Society)
- Harry Anslinger – responsible for “Reefer Madness”: thus opiates became the pathway for pain management

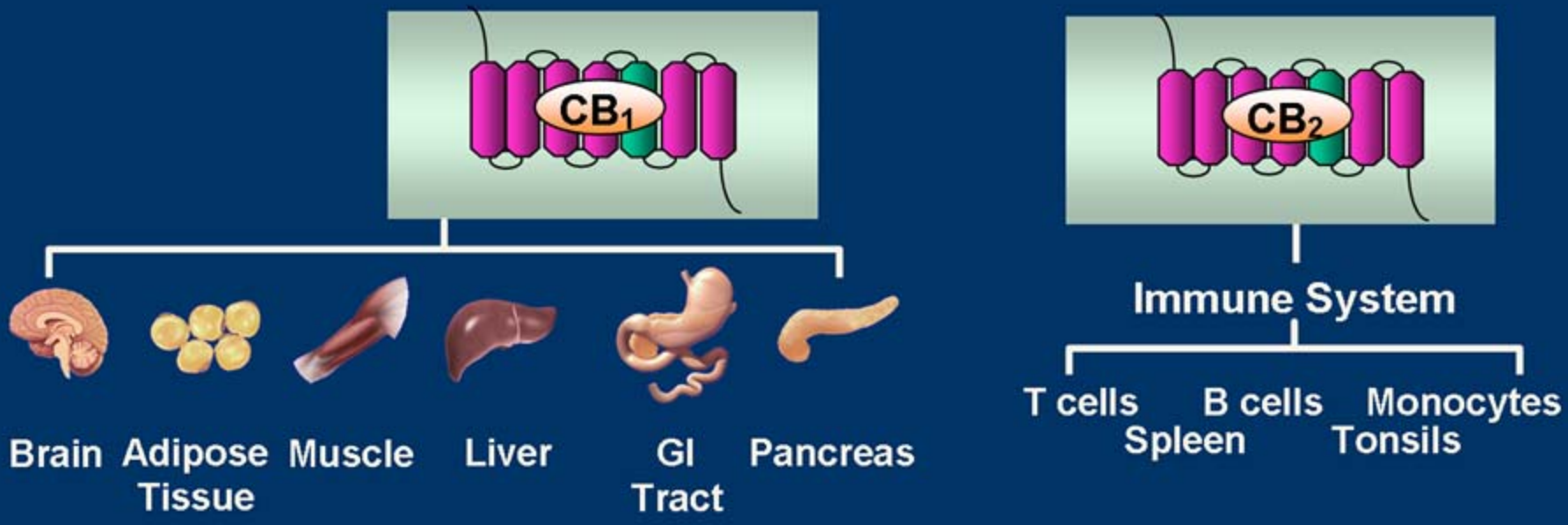
Biology of Cannabis

- Very complex: see papers
- Over 100 different cannabinoids
- Lipid soluble
- 21 carbon “terpenes”
- Cannabinoids very similar to flavinoids found in chocolate

Biology of Cannabinoids

- Endogenous System
- Receptor Based Mechanisms
- THC is most common AND most psychoactive (Marinol)
- Cannabidiol and Cannabinol are also very prevalent

Cannabinoid Receptors

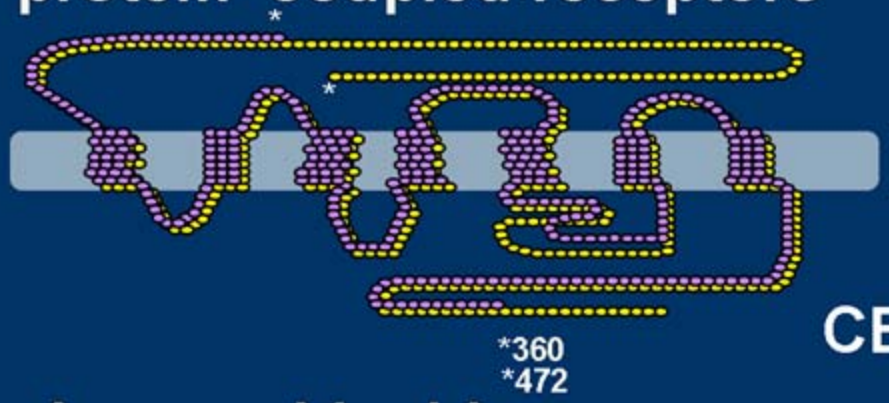


- G-protein–coupled receptors
- CB_1 receptors highly expressed in the brain
  - CB_1 receptors also found in adipose tissue, liver, muscle, the gastrointestinal tract, pancreas, as well as reproductive and cardiovascular tissues
- CB_2 receptors are expressed primarily in immune cells
  - CB_2 receptor expression in neurons is being studied

Devane WA et al. *Mol Pharmacol*. 1988;34:605-613.
Munro S et al. *Nature*. 1993;365:61-65.
Ameri A. *Prog Neurobiol*. 1999;58:315-348.
Osei-Hyiaman D, DePetrillo M, Pacher P, et al. *J Clin Invest*. 2005;115:1298-1305.
Cota D, Woods SC. *Curr Opin Endocrinol Diabetes*. 2005;12:338-351.

Key ECS Elements

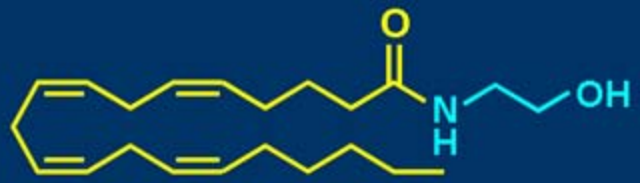
Cannabinoid receptors are G-protein–coupled receptors



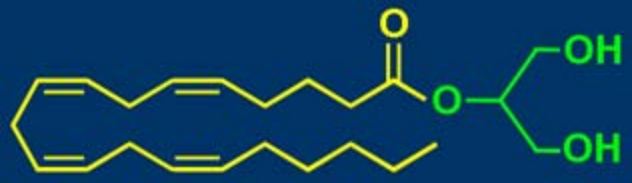
CB_1 receptor

- Central nervous system
  - Hippocampus
  - Basal ganglia
  - Cortex
  - Cerebellum
  - Hypothalamus
  - Limbic structures
  - Brainstem
- GI tract (myenteric neurons and epithelial cells)
- Liver (hepatocytes)
- Adipose tissue
- Muscle
- Pancreas (α-cells)

Endocannabinoids



Anandamide



2-Arachidonoyl-glycerol

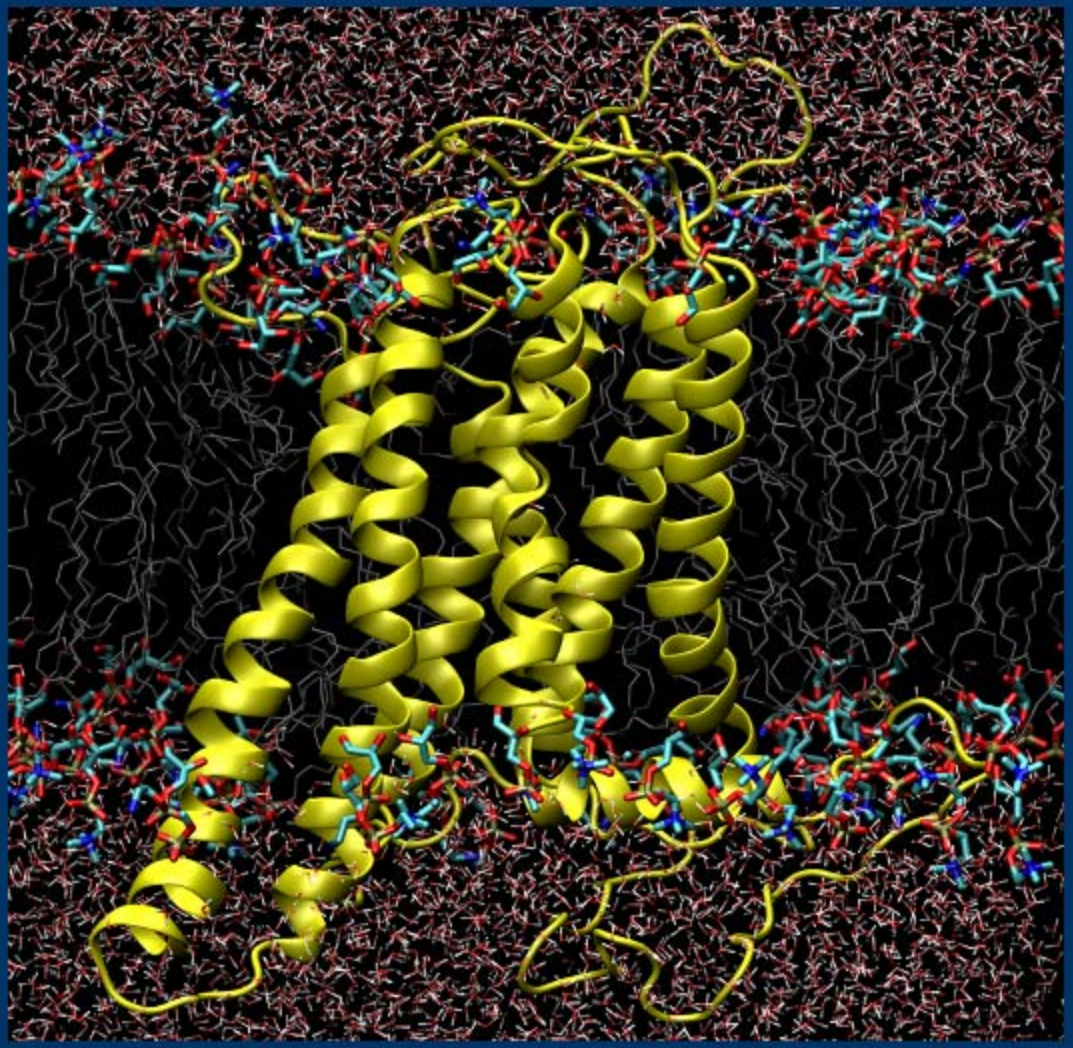
Endogenous, phospholipid-derived metabolites that bind to and activate cannabinoid receptors

CB_2 receptor

- Immune cells and tissues
  - T cells, B cells
  - Macrophages
  - Dendritic cells
  - Spleen, tonsils
  - Adipose tissue

De Petrocellis et al. *Br J Pharmacol*. 2004;;141:765-774.
Pertwee et al. *Pharmacol Ther*. 1997;74:129-180.
Roche R et al. *Histochem Cell Biol*. 2006;126(2):177-187.

The CB_1 Receptor



The CB_1 receptor consists of 7 transmembrane helices

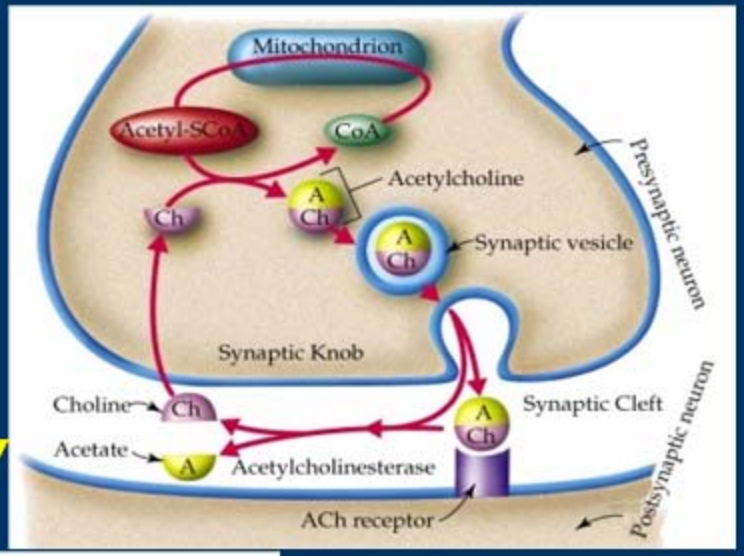
Courtesy of Patricia Reggio, PhD

Difference Between Classical and Retrograde Neurotransmission

Classical neurotransmitter

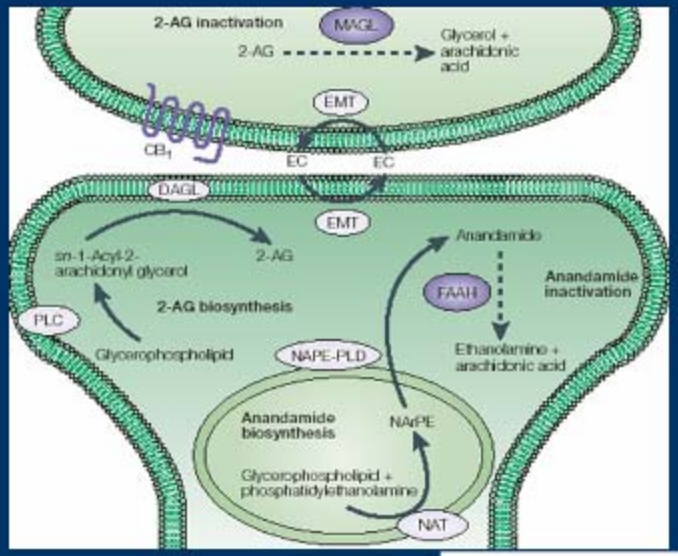
Retrograde neurotransmitter

Presynaptic



Postsynaptic

Presynaptic



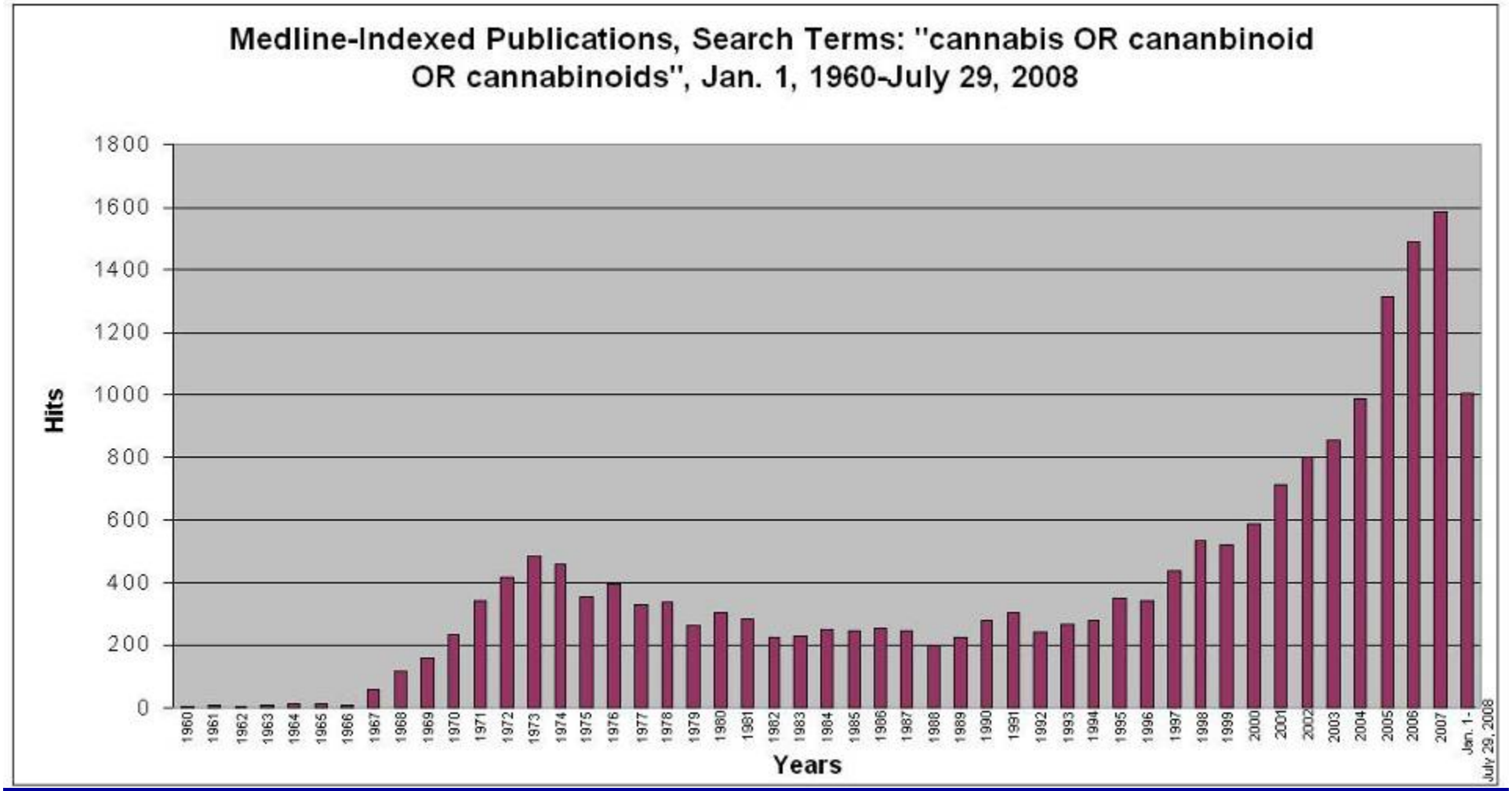
Postsynaptic

Di Marzo V, Matias I. *Nat Neurosci*. 2005;8:585-589.
Di Marzo Vet al. *Nat Rev Drug Discov*. 2004;3:771-784.
Wilson RI, Nicoll RA. *Nature*. 2001;410:588-592.
Vaughan CW, Christie MJ. 2005:367-383.

Physiological Effects of Endocannabinoids

- Endocannabinoids are often produced as an adaptive response to cellular stress, aimed at reestablishing cell homeostasis
- Endocannabinoids affect a large number of physiologic processes including
  - –Feeding behavior
  - –Energy balance, metabolism, and GI function
  - –Pain perception
  - –Motor control and posture
  - – Learning, memory, and emotions
  - – Immune and inflammatory responses
  - – Cardiovascular function
  - – Reproduction
  - – Bone formation

Cota D, Woods S. *Curr Opin Endocrinol Diabetes*. 2005;12:338-351; De Petrocellis L et al. *Br J Pharmacol*. 2004;141:765-774; Pagotto Uet al. *Endocr Rev*. 2006;27:73-100; Ameri A. *Prog Neurobiol*. 1999;58:315-348; Cota Det al. *J Clin Invest*. 2003;112:423-431; Di Marzo V, Matias I. *Nat Neurosci*. 2005;8:585-589; Kershaw EE, Flier JS. *J Clin Endocrinol Metab*. 2004;89:2548-2556; Correa F et al. *Mini Rev Med Chem*. 2005;5:671-675; van der Stelt M et al. *Embo J*. 2005;24:3026-3037; Wang H et al. *Endocr Rev*. 2006;27:427-448; Idris AI et al. *Nat Med*. 2005;11:774-779; de Oliveira Alvares L et al. *Brain Res*. 2006;1075:60-67; Arenos JD et al. *Eur J Pharmacol*. 2006;539:177-183; Mikics E et al. *Behav Pharmacol*. 2006;17:223-230; Guindon J et al. *Pain*. 2006;121:85-93.



~15,000 articles on chemistry and pharmacology of cannabis and cannabinoids

2,000+ articles on endocannabinoids

10 + RCTs with cannabis published in the US in the last 7.5 yrs

American Cannabinoid Medicines in Perfectly Legal Use:

Chemicals, Extracts, Botanicals

Photo from epocrates.com

Dronabinol
(Marinol™)

Photo from pharmer.org

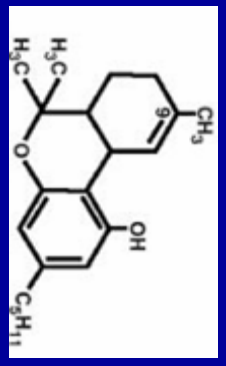
Nabilone
(Cesamet™)

Photo from nida.org

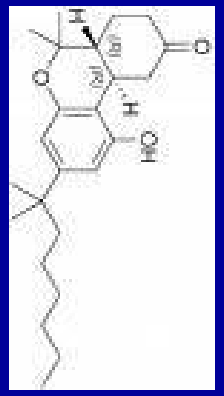
Cannabis Sativa L.
Extracts (Sativex™)


Photo from Russo et al. 2002

Cannabis Sativa L.
Cigarettes



Since
1985



Since
1985

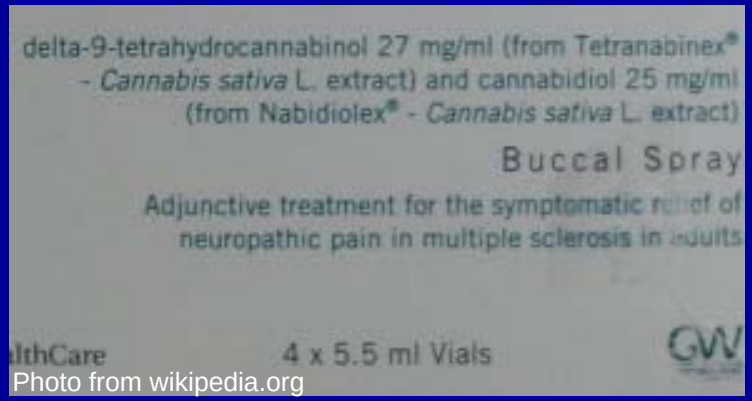


Photo from wikipedia.org

Since
2006

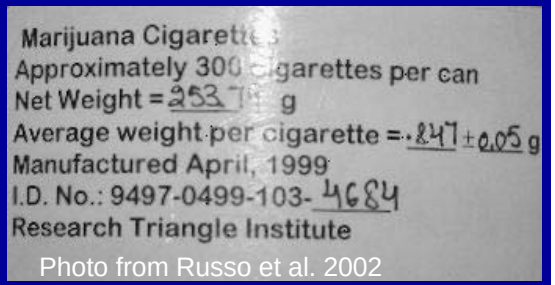


Photo from Russo et al. 2002

Since
1976

Biology of Cannabis

- Percent of different cannabinoids depends on plant strain and how it is grown
- THC effects are modulated by other cannabinoids
- Endogenous cannabinoids: Anandamide
- May be responsible for “runner’s high”

Clinical Pharmacology

- Receptors mainly in hippocampus, cerebellum, and peripheral nerves
- Brainstem receptors inhibit nausea, NOT respiration
- Pharmacology greatly affected by bioavailability
- Smoking/Vaporization versus ingestion

Clinical Pharmacology

- Analgesia: different mechanism than opiates, some synergy though.
- Spasticity: likely GABA mediated
- Appetite enhancement: hippocampal?
- Anti-emetic: cerebellar?

Clinical Pharmacology

- Adverse effects: mainly seen in new users
- Euphoria versus paranoia
- Short term memory impairment
- Balance, incoordination
- These are reversible, short lived effects (3-4 hours max)
- Serious adverse effects NOT seen in chronic users

Metabolism

- Hepatic Cytochrome P450 system
- Quickly deactivated but slowly metabolized and cleared
- Excreted in urine and feces
- In high doses may compete with P450 system with other drugs

Clinical Trials

- Hampered by government regulations
- Must use federally produced cannabis
- Mixed Results
- Methodological problems

Clinical Trials

- Works for neuropathic pain (Abrams, et al)
- Mixed results for spasticity (Wade, Zajicek, et al)
- Appetite improved by THC
- Generally very well-tolerated; minimal drug-drug interactions; minimal adverse effects (Ware, et al)

Using Cannabis

- Chronic Pain
- Palliative care
- Complementing other drugs or therapies
- Unique delivery may be an advantage: inhalation

Central and Peripheral Mechanisms of Cannabis

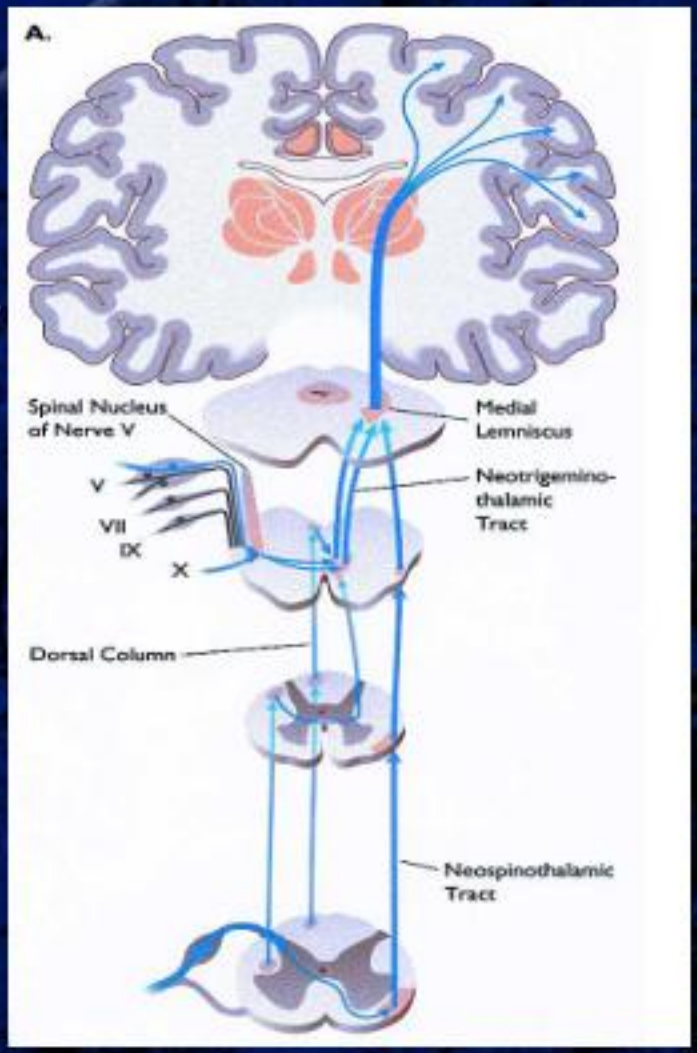
What symptoms may respond in this setting?

What is the benefit of central effects?

Pain-Sensing System Malfunction in Chronic Pain

Pain Sensing

In chronic pain, pain signals are generated without physiologic significance

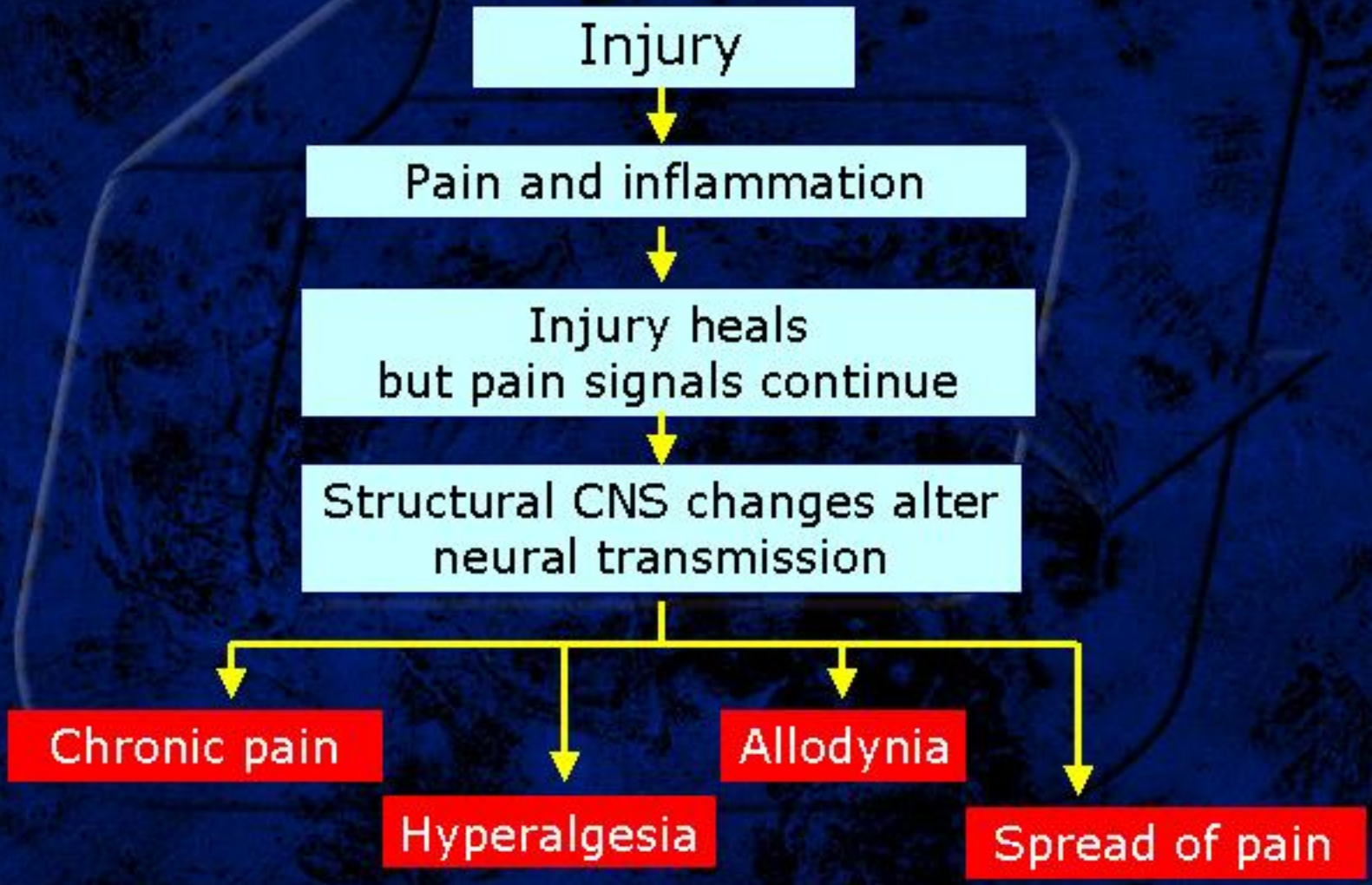


Normal pain:
Pain-sensing signals are initiated in response to a stimulus
- They elicit a pain-relieving response

Chronic pain:
Pain signals are generated for no reason and may be intensified
- Pain-relieving mechanisms may be defective or deactivated

(1. Brookoff, 2000, Illustration by Seward Hung; 2. Besson, 1999)

Pathogenesis of Chronic Pain



(Adapted from Marcus, 2000)

Components of Pain That May Respond to Cannabis

- Neuropathic – burning, lancinating
- Mechanical: dull, aching
- Inflammatory: acute, sharp
- Our data show that patients use cannabis to treat multiple pain syndromes

Pros/Cons/Risks/Benefits

- Good analgesia
- High dosing ceiling vs toxicity
- Risk for psychological addiction
- Minimal physical dependence
- Little drug-drug interactions

Pros/Cons/Risks/Benefits

- Tolerance may develop
- Long term users may need higher doses
- Patient/family will have to buy it
- Marinol NOT as effective – only has THC
- Has street value but NOT as much as opioids!

Other Uses of Cannabis in This Setting

- Spasticity
- Appetite (may offset narcotic or chemotherapy induced anorexia or nausea)
- Mood enhancement
- Animal studies show cannabinoids have a neuroprotective and anti-tumor effect
- No respiratory suppression!

Cannabis Helps Patients with Many Forms of Chronic Pain

- Myofascial Pain Syndrome (MPS)
- Diabetic Neuropathy (DN)
- Neuropathic Pain Syndrome (NPS)
- Central Pain Syndrome (CPS)
- Phantom Pain (PP)
- Spinal Cord Injury (SCI)
- Fibromyalgia Syndrome (FMS)
- Osteoarthritis (OA)
- Rheumatoid Arthritis (RA)
- Discogenic Back Pain (DP)
- HIV Neuropathy (HIV)
- Malignant Pain (MP)

Patient Snapshots

- **Patient #101**: “He has been using marijuana on his own, as he feels [it] gives him the best pain relief of anything that he has used.” 2-3 inhalations on a MJ cigarette 2-3[x]/day, & this improves his pain levels drastically w/o incapacitating him.

- **Patient #7**: “using MJ successfully on a daily basis; pain from 8-9/10—>2-3/10; needs only ~2-3 inhalations from a MJ cigarette to get pain relief”

Patient Snapshots

- **Patient #38**: “marijuana daily with no SE; only thing she is now currently using for pain”;

- **Patient #67**: “She has been using cannabis in the past and has had excellent results with respect to her migraine headaches.” Using <1/4 oz/week

Patient Snapshots

- **Patient #126**: “states openly that he has used marijuana in the past and it has helped his pain substantially. Tolerates it much better than opiates and his use of marijuana has substantially decreased his dependence on opiates”
- **Patient #133**: “he is using MC to control his pain with good luck with that. He also uses oxycodone and oxyContin, but he tries to limit this.”

Our Data

- Stereotypes and myths about MC must be dispelled
- Our data should help deconstruct myths about the kinds of patients accessing MC treatment:
- Our randomly picked study patients were 1) not young males; 2) not malingers; 3) not feigning disease to access cannabis
- Our data, both subjective and objective diagnostic data, shows that MC patients are middle aged women and men, with complex medical problems

The Role of the Pharmacist in Medicinal Cannabis…

- Pharmacists NEED to be involved: Help educate patients in proper use - counsel the patient and family
- Pharmacists could be involved in the compounding of cannabis tinctures, ointments, salves, inhalers, and capsules
- Pharmacists can help regulate the dosing and help ensure that patients are using high quality medicinal cannabis to improve efficacy
- Pharmacists can help in formulating delivery routes that maximizes benefits and minimizes side effects

How Do We Move Forward? EDUCATION and COLLABORATION

- Need physicians and pharmacists to be knowledgeable and organized
- Pharmacies should be the source of medical cannabis: NO “street deals”
- Growing and cultivation are other areas for opportunity

Myths, et al

- Efforts to influence public opinion about MC are made by federal law enforcement spokespersons, as seen in the following two illustrations
- “Dr. Pot” and “Dr. Pat” appear on a Drug Enforcement Administration (DEA) prevention Web site targeted toward adolescent education entitled “Rx pot: a prescription for disaster.”

Finally…

- Cannabis is effective and safe but IS a medication: Pharmacists MUST be involved
- Physicians need to remember the four “A’s”:- Analgesia (symptom relief);-ADLs; Adverse Effects; Aberrant Usage
- Follow the law and use proper documentation
- Use science and logic to guide the way medicinal cannabis is regulated, not propaganda and politics

Thanks for attending

- For questions we can be contacted by e-mail:
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