Cannabis

History
- Cannabis use began in Asia.
- Our “founding fathers” were hemp farmers.
- U.S. introduced to recreational Cannabis by immigrants.
- Original Cannabis plant identified was Cannabis sativa.
- Are there 3 species? Or 1 species with 3 varieties?

Over 400 different compounds in Cannabis.
- 60+ are unique (“cannabinoids”)
  - Principle psychoactive compound is delta-9-tetrahydrocannabinol (THC).
  - 2 other psychoactive compounds:
    - cannabinol
    - cannabidiol
Two common Cannabis preparations

- Hashish
  - Concentrated resin.
  - ~15% THC
- Marijuana
  - Dried leaves and flowers.
  - ~5% THC

Acute Effects of Cannabis Intoxication

- Relaxation, feelings of contentment.
- Mind expanding effects.
  - Increases in insight, creativity?
    - Hard to document.
  - Senses are more acute?
    - Not likely.
  - Emotion is intensified.

Cannabis Intoxication continued...

- Cognitive Impairments
  - Impaired Attention
  - Impaired Short-term Memory
    - Altered time perception.
- Weak Analgesia
- Appetite Stimulant
- Sympathomimetic Effects
Pharmacokinetics of THC

• Absorbed most effectively by inhalation.

• Oral absorption leads to:
  • First pass metabolism.
  • Slow onset.
  • Poor dose control.
  • Fewer psychoactive compounds?

• THC is available as an oral medication:
  • Dronabinol (*Marinol*)

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Pharmacokinetics of THC continued...

• 2 important distribution characteristics.
  • High affinity for blood proteins.
  • Very lipid soluble.

• Functional half-life of 1-2 hours.
  • Elimination half-life of 20-30 hours.

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Pharmacokinetics of THC continued...

• Metabolism
  • Mostly by liver.
  • Partially in lungs.
  • More than 30 different metabolites, many of which are also psychoactive.
Pharmacodynamics - Cannabinoid receptors in many brain areas.
- Hippocampus - memory.
- Cortex - cognition and perception.
- Hypothalamus - motivation, hunger.
- Cerebellum – Motor control.
- Basal Ganglia – Decreased spasticity.
- Spinal cord - analgesia.
- PNS - sympathomimetic effects.

Several endocannabinoids have been identified.
- Anandamide.
- Anandamide doesn’t behave like “normal” neurotransmitters.
  - Not stored in vesicles.
  - Shown to act as a neuromodulator of a variety of other NTs via axoaxonic synapse.

Endocannabinoids may act as retrograde messengers.
Depolarization Induced Suppression of Inhibition
1. Excitatory NT binds to endocannabinoid neuron.
2. Endocannabinoids are released, which diffuse to a presynaptic neuron.
3. NT release from presynaptic neuron is inhibited.
A cannabinoid antagonist has been shown effective for treatment of nicotine addiction and obesity.

- Rimonobant (*Acomplia*)

**Tolerance**

- Reverse tolerance for initial exposures.
  - Learning how to smoke and recognize effects?
  - Fatty buildup?
  - Placebo effects?
- For high doses, normal tolerance can develop later.

**Addiction**

- Moderate risk of psychological dependence.
  - Inability to quit.
  - Drug seeking behavior.
  - Problems associated with use.
- THC increases DA levels in nucleus accumbens.
- Low risk of physical dependence.
  - Withdrawal syndrome usually only from high use.
Acute Toxicity

- Never an overdose death.
- T.I. of 10000.
- Other risks include panic reaction and behavioral toxicity.

Chronic Toxicity

- Lung Irritation
- Potential as a carcinogen is unclear.
- Cannabis contains carcinogens… … but cannabinoids can suppress tumor growth!
- Reproductive hormones affected.
- Consequences?
- Inhibition of the immune system.
- Consequences?
- No apparent cardiovascular toxicity.

Evidence for nervous system toxicity is mixed.

- Low to moderate levels of THC kills cultured neurons.
- Rats chronically exposed to VERY high levels show long-term behavioral or brain changes in some studies (e.g., Fehr et al., 1976).
- Moderate chronic levels caused no changes in monkeys (Silkker et al., 1992).
- Very little CAUSATIVE evidence of lasting cognitive deficits in humans… However… early marijuana use is CORRELATED with higher rates of mental illness.
Medical uses of marijuana.

• Dronabinol (*Marinol*) approved as:
  • an appetite stimulant
  • treatment for chemotherapy induced nausea.
• Medicinal marijuana legal in 9 states, but not in federal laws.
• Federal enforcement concentrates on supply and distribution.