Cannabis

The Effect of THC on Our Endogenous Cannabinoid Neural System

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CSAM Addiction Review Course
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I have no financial relationship with any entity discussed in this talk except those private patients who pay me to treat their addictive disease.
I. Basic Science

Overview
Shifting Your Perspective

“We also have urns, if you want to think outside the box.”
The Magic is in the Brain, Not in the Herb

The Mystery: Why Does Cannabis, and Not Alfalfa, Get Us High?
Retracing the Endorphin Story

- From Psychoactive Plants (Poppy/Cannabis)
- To Their Botanical Essence (Opiates/THC)
- To Receptor Sites
- To Naturally Occurring Brain Molecules (Endorphin Neurotransmitters/ Endocannabinoid Neuromodulators)
Exogenous Cannabinoid
Mechoulam - 1964

\[ \Delta^9-THC \]
Distribution of Receptor Sites
Radiolabeled CP-55,940

- CB1 Receptors - 1988
  - Hippocampus – Memory and Learning
  - Amygdala – Novelty, Emotion, Appetites
  - Basal Ganglia – Motor
  - Cerebellum – Real Time Coordination, Selective Attention and Time Sense
  - Nucleus Accumbens - Reward Mechanism (Addiction)
  - Cortex (Anterior > Posterior) – Frontal Lobe Executive Functions

- CB2 Receptors - 1993
  - Macrophages
  - Spleen, Intestines
Endogenous Cannabinoid
Mechoulam - 1992

Anandamide
Endogenous Cannabinoids

- Anandamide (arachidonolyethanolamide, AEA, or AnNH)
- 2-AG (2-arachidonylglycerol)
- 2-AGE (Noladin ether, or 2-arachidonyl glycercyl ether)

NOT stored in Synaptic Vesicles – but rather produced from cellular membranes as needed
- Anandamide and receptor sites are present in all mammals

- Anandamide and receptor sites are also present in birds, amphibians, fish, sea urchins, leeches, mussels, and even the most primitive animal with a nerve network, the Hydra, where it is involved in the “feeding mechanism”
1.) The role of our endocannabinoid system is largely to regulate activity of other neurotransmitters

2.) "There is barely a physiological system in which endocannabinoids are not involved. Hence its importance is far beyond that of THC and marihuana….” - Mechoulam
Hippocampal Cannabinoid Receptors
The Role of Cannabinoids in the Hippocampus

Modulating Working Memory
Hippocampal Effects of Marijuana

- Memory and Learning
- Acute Short-term Memory Effect
- Social Recognition Research
Cannabinoids and Social Recognition

- Adult mice/rats investigating juveniles
- Effect of THC
- Cannabinoid antagonist SR141716A
- SR141716A effect on aged mice/rats
- Cannabinoids inhibit the Hippocampus
- Cannabinoid blockers reverse the inhibition

Terranova et al: “Improvement of memory in rodents by the selective CB1 cannabinoid receptor antagonist, SR141617A,” *Psychopharmacology Ser. (Berl)* 126:165-172
Mechanism of Cannabinoid Effect on the Hippocampus

Cannabinoids reduce GABA release in the hippocampus, inhibiting the LTP and LTD required to trigger the synaptic changes that underlie memory formation.

The Amygdala
Cannabinoids in the Amygdala

- Registration of Novelty
- Determination of Emotional Relevance
- Forgetting of Aversive Memories
- Regulation of Appetites
- Regulation of Pain Threshold
- Regulation of Anxiety/Fear
- Global Characteristics of Consciousness
Virtual Novelty

The Impact of THC on the Amygdala

- Sensory Effects – Dishabituation
- Attentional Effects – Increased Field Size
- Numinosity – The Sense of Awe
Chronic exposure to delta-9-THC (5 days) decreases the specific binding of CB1 receptors from ~20-60%, depending on the specific brain area measured.

J Romera, “Effect of chronic exposure to delta9-tetrahydrocannabinoloin cannabinoid receptor binding and mRNA levels in several rat brain regions,” *Brain Res Mol Brain Res* 1997 Jun;46(1-2):100-8

Result: Roller Coaster Dynamic
Cannabinoid Modulation of the Extinction of Conditioned Fear

- SR141716A (a cannabinoid antagonist) produces dose-dependent decreases in extinction of fear-potentiated startle

- AM404 (an inhibitor of eCB breakdown and reuptake) produces dose-dependent enhancements of extinction

- SR141716A blocks the effect of AM404

Amygdalar Endocannabinoid Effects on Appetite and Bonding

- Cannabinoid stimulation increases appetite and blockers decrease appetite

- Clinical trial of 20 mg of the CB1 antagonist rimonabant (Acomplia, from Sanofi-Synthelabo) showed an average 20 pound weight loss (and a positive impact on smoking cessation)

- The cannabinoid blocker SR141716A given to rat pups within 24 hours of birth stops suckling and causes death in 4-8 days

Motor Effects of Cannabinoids

- Cannabinoid Agonists
  - Reduce spontaneous activity – catalepsy (Basal Ganglia)
  - Incoordination

- Cerebellar “Flow” (Related to Distortions in Time Sense?)

- Driving Research

- Flight Simulator Research
  
Endocannabinoids in the Nucleus Accumbens

- Cannabinoid agonists increase the efflux of dopamine seen with other drugs of addiction
- NA plasticity in response to endocannabinoid induced dopamine increase
- Infusion of cannabinoid blocker leads to withdrawal symptoms after 8 days of THC administration
- Increase in dopamine levels is blocked by naloxone
Naloxone Effect on THC’s Stimulation of Dopamine in NA

Tanda et al., “Cannabinoid and heroin activation of mesolimbic transmission by a common mu1 opioid receptor mechanism,” *Science*, 1997 Jun 27;276(5321):2048-50
CB1 Knockouts

- CB1 knockout mice appeared healthy and fertile, but they have a significantly increased mortality

- Increased memory and decreased forgetting of aversive memories

- Hypomotility, especially in exploration

- Failure to self-administer morphine
Marijuana’s Impact on the Frontal and Prefrontal Cortex

- Decreased Blood Flow and Glucose Metabolism
- Decreased EEG Energy
- Neuropsychological Impairment
  - Diminished Executive Functions
  - Temporal Disorganization (Altered Perception of Time)
  - Impaired Planning
  - Altered Self-Awareness
Functions Regulated by Tonic Endocannabinoid Activity

- Modulating size of working memory and aversive memory
- Modulating pain threshold
- Modulating threshold of novelty/familiarity
- Modulating attentional scope (narrow Vs. widened focus)
- Modulating level of spontaneous motor activity
- Modulating fear, anxiety and stress responses
- Modulating appetite(s)/bonding
- Modulating global characteristics of consciousness
II. Use, Abuse and Addiction
Marijuana Use in U.S.
Nat’l Household Survey on Drug Use - 2005

- **Lifetime Prevalence**
  - 17.4% of 12-17
  - 52.4% of 18-25
  - 41.1% 26+

- **Previous year**
  - 13.3% of 12-27
  - 28.0% of 18-25
  - 6.9% of 26+

- **Previous month**
  - 6.8% of 12-17
  - 16.6% of 18-25
  - 4.1% of 26+
Trends - Monitoring the Future

Use
% who used in last twelve months

Year

Twelfth Grade
Tenth Grade
Eighth Grade

'75 '77 '79 '81 '83 '85 '87 '89 '91 '93 '95 '97 '99 '01 '03 '05
Valued Experiences from Marijuana

- Relax – “Chill”
- Loosening of associations
- Intensification of ordinary experience
- Heightening of humor
- Pleasant imaginative reverie
- All of which provides a welcome relief from the tedium of everyday life


“Hashish... gives the power of imagination and takes away the ability to profit from it.”

Charles Baudelaire (1860) *Les Paradis Artificiel*
Criteria for Addiction

- Tolerance/Withdrawal
- Preoccupation
- Loss of Control
- Continued Use in the Face of Adverse Consequences
- Cognitive Distortions/Denial
Andrew Weil’s Definition of a Bad Relationship with a Drug

- Ignorance that the substance is a drug and of what it does to your body
- Loss of the desired effect with increasing frequency of use
- Difficulty separating from the drug
- Impairment of health or social functioning
The Question of Marijuana Addiction

“There is no question marijuana can be addictive; that argument is over. The most important thing right now is to understand the vulnerability of young, developing brains to these increased concentrations of cannabis”

Dr. Nora Volkow, NIDA Director, Los Angelos Times, 4/26/04
Rates of Cannabis Dependence

- 10% for anyone 18 years and older who ever experiments
- 3 times more likely to lead to dependency for those who first smoke before 18 years old
Early Reactions to Cannabis Predict Later Dependence

- Positive Subjective Responses:
  - Got Really High
  - Felt Happy
  - Felt Relaxed
  - Did Silly Things
  - Laughed a Lot

- 5 Positive responses to initial marijuana use increased odds of later dependence by 28.5 times

- Negative responses were unrelated to later dependence:
  - Felt ill, dizzy
  - Felt Frightened
  - Passed Out

Proposed Cannabis Withdrawal Syndrome Criteria
(Common Symptoms)

- Anger or Aggression
- Decreased Appetite / Wt. Loss
- Irritability
- Nervousness / Anxiety
- Restlessness
- Sleep Difficulties / Strange Dreams

Time Course of Withdrawal

Cannabis Withdrawal in the United States

N=2613 (1119 cannabis only)

- 59% of frequent cannabis users report experiencing 1 or more symptoms, 44% report 2 or more and 34% report 3 or more

- 2 homogeneous sets of symptoms
  - *Weakness* (weakness, hypersomnia, psychomotor retardation, yawning)
  - *Anxiety/Depression* (anxiety, depression, sweating, nausea, muscle aches, restlessness, tremors, insomnia)

- Significant relationship found between use of a substance to relieve/reduce both sets of withdrawal symptoms
Special Risks for Adolescents

Seduction vs. Addiction

- Marijuana as self medication (esp. with ADHD)
- Marijuana as a vehicle for independence and affiliation
- Marijuana as an antidote to boredom
- Marijuana as a palliative to the demands of adolescent development
- Immature brain and paucity of experience
Hindering Final Brain Maturation

Cannabis users display lower activation (fMRI) in the Prefrontal Cortex

Educational Achievement

- Early use more damaging than later onset of use

- Lower GPA’s, negative attitudes toward, and reduced satisfaction with school, increased absenteeism, expulsions, suspensions, dropouts and unemployment

- Those who have smoked more than 100 times:
  - Rates of leaving school - 5.8 times higher
  - Rates of entering college - 3.3 times lower
  - Rates of college degree - 4.5 time lower

Treatment

Trends across this literature suggest that the types of treatments effective with other substances are likely to be effective with marijuana dependence.

Treatment / Recovery
1999 - 220,000 (14%) Admissions
Reasons for Admission

- Loss of control of use
- Cognitive and Motivational Impairment, with Impact on Occupational and Academic Performance
- Decreased self-esteem
- Depression
- Complaint of a partner
Cognitive functioning of long-term heavy cannabis users seeking treatment

On 9 standard neuropsychological tests that assessed attention, memory, and executive functioning

- Impaired Learning
- Impaired Retention
- Impaired Retrieval

Impairments endure beyond the period of intoxication and are worse with increasing years of regular cannabis use

Treatment / Recovery

Characteristic Descriptions of Improvement

- Clarity, Clarity, Clarity - Lifting of the fog that they had not known was present
- Recognition of Past Denial
- Freedom (An Internal Sense)
- Improved Relationships
Robust Interactions between Cannabinoids and Other Drugs of Abuse
Cannabinoids and Alcohol

- Rats bred to voluntarily ingest alcohol reduce consumption when given the cannabinoid blocker SR141716A
- Cannabinoid agonists increase alcohol consumption by these rats
- Chronic alcohol consumption downregulates CB1 receptors and increases production of anandamide
Cannabinoids and Cocaine

- The synthetic cannabinoid agonist, HU210, provokes relapse to cocaine seeking after prolonged withdrawal periods.

- Furthermore, the selective CB1 receptor antagonist, SR141716A, attenuates relapse induced by re-exposure to cocaine-associated cues or cocaine itself.

- De Vries, T. J., et al., “A cannabinoid mechanism in relapse to cocaine seeking.”
Cannabinoids and Opiates

- Morphine does not induce dopamine increase in NA in CB(1) Knockouts

- SR141716A, a selective central cannabinoid CB1 receptor antagonist, blocked heroin self-administration in rats.

- Morphine-dependent animals injected with SR141716A exhibited a partial opiate-like withdrawal syndrome

- Opiate dependence produces an upregulation of CB(1) receptors

The Take-away: Our Endocannabinoid and Endorphin Neural Systems are independent, but highly interactive systems
III. Medical Cannabis
Rationale for Potential Cannabinoid Medications

- Pain
- Motor disorders - Spasticity
- Appetite(s)/N&V/bonding disorders
- Memory disorders
- Fear and anxiety disorders
- Mood disorders
- Novelty/familiarity and Attentional disorders - Boredom (?)
Cannabinoids and Opiates
A Special Relationship for Pain Relief

Brain researchers now see the endogenous opioid and cannabinoid systems in the CNS as two independent but parallel and overlapping physiological regulatory systems. Both are involved in controlling our sensitivity to pain, and both may be involved in some way in the reward mechanisms of the brain.
AM1241
A Novel Cannabinoid

- CB2 agonist only
- Provides pain relief equal to opioids in rat studies of neuropathic and inflammatory pain
- No sedative effects


Rimonabant (Acomplia)
CB1 Endocannabinoid Receptor Antagonist

- 20 pound weight loss after 2 years treatment
  (Those switched to placebo during year two regained their weight)

- Smoking cessation aid (36% vs 20% 10 week success rate) with less weight gain (subjects who successfully quit smoking without rimonabant gained 84% more weight)

- 1 in 8 stopped due to side effects: nausea, diarrhea, depression, dizziness, anxiety, and amnesia
THC Effect on MS

Marijuana for Harm Reduction

- **Pro:**
  - Heroin substitution for pot in Vietnam
    [References in Dan Baum’s *Smoke and Mirrors*]

- **Con:**
  - 34% of alcohol, cocaine and heroin relapsers used marijuana post-treatment, while only 7% of nonrelapsers did
  - “…alcohol and marijuana are economic complements, not substitutes…. Policies that increase the price of alcohol, such as increases in beer tax, decrease the quantity of marijuana consumed by at least as much as alcohol consumption in percentage terms.”
Potential Side Effects
Impact of Marijuana Smoke on the Respiratory System

Each inhalation
- 2/3 larger
- Inhaled 1/3 deeper
- Held 4 times longer
- 50% higher in tar

- Acute and Chronic Bronchitis
- Local Immunological Impairment
- Precancerous Changes

# Marijuana vs. Tobacco

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Marijuana</th>
<th>Tobacco</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>22.7 mg</td>
<td>39.0 mg</td>
</tr>
<tr>
<td>THC</td>
<td>820.0 mic</td>
<td>-----</td>
</tr>
<tr>
<td>Nicotine</td>
<td>-----</td>
<td>2850.0 mic</td>
</tr>
<tr>
<td>Phenol</td>
<td>76.8 mic</td>
<td>138.5 mic</td>
</tr>
<tr>
<td>Naphthalene</td>
<td>3.0 mic</td>
<td>1.2 mic</td>
</tr>
<tr>
<td>Benzanthracene</td>
<td>75.0 ng</td>
<td>43.0 ng</td>
</tr>
<tr>
<td>Benzpyrene</td>
<td>31.0 ng</td>
<td>21.1 ng</td>
</tr>
</tbody>
</table>
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<tr>
<th>Chemical</th>
<th>Marijuana</th>
<th>Tobacco</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon Monoxide</td>
<td>17.6 mg</td>
<td>20.2 mg</td>
</tr>
<tr>
<td>Ammonia</td>
<td>0.3 mg</td>
<td>0.2 mg</td>
</tr>
<tr>
<td>Hydrogen Cyanide</td>
<td>532.0 mic</td>
<td>498.0 mic</td>
</tr>
<tr>
<td>Acetaldehyde</td>
<td>1200.0 mic</td>
<td>980.0 mic</td>
</tr>
<tr>
<td>Acetone</td>
<td>443.0 mic</td>
<td>578.0 mic</td>
</tr>
<tr>
<td>Benzene</td>
<td>76.0 mic</td>
<td>67.0 mic</td>
</tr>
<tr>
<td>Toluene</td>
<td>112.0 mic</td>
<td>108.0 mic</td>
</tr>
</tbody>
</table>
“The weight of the available evidence suggests that long-term heavy use of cannabis does not produce any severe or grossly debilitating impairment of cognitive function.”

Effects of **Chronic** Stimulation by Exogenous Cannabinoids - 1995

- The ability to focus attention and filter out irrelevant information, measured by frontal processing negativity to irrelevant stimuli, was impaired progressively with number of years of use.

- The speed of information processing, measured by the latency of parietal P300, was delayed with increasing frequency of use.

Solowij, Michie and Fox: “Differential Impairments of Selective Attention Due to Frequency and Duration of Cannabis Use,” *Biological Psychiatry*, Vol 37 #10, 731-9, May 15, 1995
Cannabis and Psychosis

- Cannabis use is associated with a dose dependent increased risk of developing schizophrenia ($\sim x 2$)

- There is a strong association between use of cannabis and earlier age at first psychotic episode in male schizophrenics.
  Castle and Murray, Ed. *Marijuana and Madness, Cambridge Univ. Press, 2004*
Recent Cautionary Data

- Schizophrenics using cannabis lose more brain volume over 5 years than those who abstain.

- Long term cannabis use (at least twice monthly for an average of 19 years) produced 6-12% reductions in volume of hippocampus and amygdala.

- Rodents have a 44% decrease in hippocampal synapses 7 months after last exposure to THC
Recent Cautionary Data, Cont.

- A sample of 140 Multiple Sclerosis patients found 10 currently using smoked cannabis – statistically younger than the group as a whole

- Matched with comparables from the group who were not cannabis users, scores on the Symbol Digit Modalities Test were poorer for cannabis users:
  - Slower performance
  - Altered patterns of response

High Risk Populations

- Children and Adolescents
- The Fetus
- Pre-existing Chemical Dependence and Family History (+) for CD
- Pre-existing or latent Psychiatric Illness
There is no known safe dose of cannabis during pregnancy. Smoking marijuana causes the same problems as smoking tobacco (prematurity and low birth weight).
Motor Coordination

Patients should be strongly advised against operating hazardous machinery, including automobiles, until they are reasonably certain the effects of marijuana have worn off. Judgment of motor abilities can be affected.
Standards of Medical Practice

California requires that medications, especially those with a potential for abuse or damaging side effects, be prescribed (or recommended) by your physician only within the following context:
Standards of Medical Practice
(Cont.)

- A good faith History and Physical
- A Treatment Plan, with Diagnosis/Goals
- Informed Consent
- Periodic Reviews of Effectiveness
- Proper Records

We encourage patients to cooperate with your doctor’s adherence to these important standards.
“Easy???” . . . As It *Should* Be!!

IT’S THE LAW!

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Psychological (Side) Effects

- Alterations in Mood
- Cognitive Impairment
- Sedation and Drowsiness
- Perceptual Alterations/Sensory Intensification
- Distinct Alterations in Consciousness

Warning: Marijuana is a mood altering drug capable of producing dependence