Cannabinoids: Respiratory Effects

ROBERT KAUFMANN, MD
MEDICAL CONSULTANT
RESEARCH DIRECTOR
CBD AMERICAN SHAMAN

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Hemp vs. Marijuana
Hemp vs. Marijuana

Tetrahydrocannabinol (THC)

Cannabidiol (CBD)
# Is CBD Marijuana?

<table>
<thead>
<tr>
<th>CBD</th>
<th>Marijuana</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabis Sativa</td>
<td>Cannabis Sativa</td>
</tr>
<tr>
<td>Hemp Plant</td>
<td>Marijuana Plant</td>
</tr>
<tr>
<td>Tall plant w/ thin leaves</td>
<td>Short plant with broad leaves</td>
</tr>
<tr>
<td>Has small seed head</td>
<td>Has large seed head</td>
</tr>
<tr>
<td>Cannabidiol (CBD)</td>
<td>Tetrahydrocannabinol (THC)</td>
</tr>
<tr>
<td>No psychotropic effect</td>
<td>Used for psychotrophic effect</td>
</tr>
<tr>
<td>Minimal (No) physical impairment</td>
<td>Significant Physical Impairment</td>
</tr>
<tr>
<td>Medicinal properties</td>
<td>Medicinal properties</td>
</tr>
<tr>
<td>Binds to CB1 and CB2</td>
<td>Binds to CB1</td>
</tr>
<tr>
<td>Binds to other Receptors</td>
<td>Low affinity to other Receptors</td>
</tr>
</tbody>
</table>
THC vs CBD
Toxicity

- THC has neural toxicity
- THC interferes with decision making
- THC inhibits mechanical responsiveness
- THC can lead to overdose and death

- CBD does none of the above
- One cannot overdose on CBD
## Is CBD the same as CBD-enriched Hemp Oil?

<table>
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<tr>
<th>CBD</th>
<th>CBD-enriched HEMP OIL</th>
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<td>Cannabis Sativa</td>
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<tr>
<td>Hemp Plant</td>
<td>Hemp Plant</td>
</tr>
<tr>
<td>CBD is the only Cannabinoid</td>
<td>CBD is main Cannabinoid</td>
</tr>
<tr>
<td>No Terpenes (aromatic oils)</td>
<td>Over 150 Terpenes</td>
</tr>
<tr>
<td>No THC</td>
<td>Contains some THC</td>
</tr>
<tr>
<td>No Flavonoids (color, taste)</td>
<td>About 20 Flavonoids</td>
</tr>
<tr>
<td>No other cannabinoids</td>
<td>80-100 other cannabinoids</td>
</tr>
<tr>
<td>No entourage effect</td>
<td>Important entourage effect</td>
</tr>
<tr>
<td>Has some medicinal properties</td>
<td>Has lots of medicinal properties</td>
</tr>
</tbody>
</table>
The Endocannabinoid System

- Anandamide
  - First, naturally occurring endogenous cannabinoid (endocannabinoid)
  - 1992
  - Phytocannabinoid: THC

- 2-arachidonoylglycerol (2-AG)
  - Second, naturally occurring endogenous cannabinoid
  - Phytocannabinoid: CBD
Endocannabinoid System
What does it do?

- Regulate a variety of physiological and cognitive processes including:
  - Fertility
  - Pregnancy
  - Pre and postnatal development
  - Motor learning
  - Appetite
  - Pain sensation
  - Mood
  - Memory
Endocannabinoid System
What does it do?

- Voluntary physical exercise
  - Man, take a load off
  - Let’s go running
- Exercise-induced euphoria
  - Oh, I am exhausted
  - Man, wasn’t that great
- Modulating locomotor activity
  - Fumbling/lack of balance
  - Physical dexterity
- Motivational Salience for rewards
  - Laid back--I don’t care
  - Let’s get ‘er done!!—Speed!!
Endocannabinoid Receptors
CB1

- Brain and spinal cord and autonomic nervous system
- Pituitary, thyroid and adrenal gland
- Fat cells, Muscle cells, liver cells
- Digestive tract, Lungs, Kidney
- Testes (Leydig cells and sperm)
- Ovaries, oviducts, myometrium, decidua, and placenta

**Mechanism of action**
- Decreases intracellular cAMP concentration
- Increases intracellular cAMP concentration
Endocannabinoid Receptors

CB2

- Immune System
- Brain
- Peripheral Nerves
- Lungs
- Gastrointestinal

**Mechanism of action**
- Inhibits the activity of adenylyl cyclase
- Coupled to the MAPK-ERK pathway
  - results in changes in cell migration
  - implicated in neuroplasticity
  - Long term memory formation
- Activity depends on what compounds binds to the receptor
TCH vs Anandamide
CBD vs 2-AG
Endocannabinoid Receptors
Other Receptors

- Other receptors
  - 5HT1A
  - Vanilloid
- Orphan receptor
  - GPR18
  - GPR55
  - GPR119
- Other heterodimer receptors
  - CB1-OX1
The Entourage Effect

...the biological activity of 2-Ara-Gl can be increased by related, endogenous 2-acyl-glycerols, which alone show no significant activity in any of the tests employed.


The biological activity of a cannabinoid can be modified by other related compounds found in the hemp plant which alone show no significant similar bioactivity.
Effects of the whole plant can be very different than a single compound from that plant.

- THC by itself can have different effects than marijuana
- CBD by itself can have different effects than hemp oil
Classic Receptor Binding

Receptor site

Ligand bound to Receptor site

Cell Membrane

Activation site (inactive)

Activation site (activated)
Stereotypic Receptor Binding

A. Receptor site
   - Ligand 1
   - Ligand 2
   - Ligand 3

B. Ligand bound to Receptor site
   - Ligand 1

C. Ligand bound to Receptor site
   - Ligand 2

D. Ligand cannot bind to Receptor site
   - Ligand 3

Activation site (inactive)

Activation site (activated)

Activation site (inactive)
Allosteric Receptor Binding

A
- Receptor site
- Ligand 1
- Activation site (inactive)

B
- Ligand bound to Receptor site
- Activation site (activated)

C
- Ligand bound to Allosteric site
- Activation site (inactive)

D
- Ligand bound to Receptor site
- Activation site (active, but different)
Method of ingestion

- Absorption: Rate and Percentage absorbed (Exact values unknown—can only be estimated by clinical efficacy)

- Smoking: Rate: Fast  Pct: high (~15-27%)
- Sublingual: Rate: Fast  Pct: lower (~6-15%)
- Oral (Standard Oil): Rate: Slow  Pct: low (~3-6%)
- Oral (Nano technology): Rate: Fast  Pct: high (~18-45%)

- Smoking Cannabinoids has respiratory effects different from ingesting cannabinoids secondary to the smoke.
Respiratory Effects of Smoking Cannabis

- Increased Sputum (acute and chronic)
- Cough (acute and chronic)
- Wheeze (acute and chronic)
- No SOB increase

- Acute Bronchitis: Acute Inflammatory response secondary to inhalant injury
- Chronic Bronchitis: Chronic inflammation

- All of the above symptoms and pathology are reversible after quitting cannabis smoking

- Ribeiro L, Ind PW. Marijuana and the lung: hysteria or cause for concern? Breathe 2018;14:196-205.
Chronic Cannabis Smoking
PFT Changes

- Cross Sectional Study: 339 patients
  - Non-smokers (81)
  - Cannabis only (75)
  - Cannabis and Cigarette (91)
  - Cigarette only (92)

- PFT: Dose Response relationship between marijuana smoking and non-smokers:
  - Increase in FVC and TLC
  - No change in FEV1
  - Decrease in FEV1/FVC ratio
  - Decrease in airway conductance

Chronic Cannabis Smoking
Emphysematous Changes

- Same Study

- Hi-Res Computerized Tomography
  - Increase in macroscopic emphysema in cigarette smokers/non-smokers
  - No increase in emphysema in cannabis-only smokers/non-smokers
  - Increase in Low-density lung regions in cannabis smokers

- LDL regions interpreted as hyperinflation and not macroscopic emphysema

Chronic Cannabis Smoking
Emphysematous Changes

- Cross Sectional Study: 500 Patients
  - Tobacco only (248)
  - Tobacco and cannabis (marijuana and resin) (252)
- Cannabis smoking adds to tobacco smoking COPD risks
  - 1 joint-year 0.3% increase in prevalence of COPD
- Tobacco and Cannabis worsens (% change/joint-yr)
  - FEV1/FVC <0.7 (0.3%)
  - Dyspnea (0.2%)
  - Coughing (0.3%)
  - Phlegm (0.4%)
  - Wheezing (0.2%)
  - Wheezing without infection (0.2%)

Chronic Cannabis Smoking
Bullous Lung Disease

- Accepted as a complication of marijuana smoking
- 57 cases are described (2018)
- Majority of patients
  - Heavy marijuana users (up to 149 joint-years)
  - Upper lobe Involved
  - Peripheral emphysema
  - Presented with pneumothorax (presumably bullous rupture)
Chronic Cannabis Smoking
Summary Pathological changes

- increase in TLC
- Increase in FVC
- No change in FEV1
- Decrease in FEV1/FVC ratio
- Airflow Obstruction (large bronchi secondary to inflammation)
- Bullous formation
- Hyperinflation

- Different than COPD (Dec. FVC and FEV1/FVC ratio)
- Reversible in non-cigarette smokers
- Increases COPD risk in cigarette smokers

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Cannabis Smoking Lung Cancer Risks

- Cannabis contains carcinogens similar to those in cigarettes
- Cannabis causes premalignant bronchial changes (pathology)
- Cannabis does not increase lung cancer six (6 case-control studies)
Cannabis Smoking
Pneumonia Risks

- Cannabis has immunosuppressive effect on alveolar macrophages
- Cannabis causes loss of ciliated bronchial epithelium
- No increase in incidence of bacterial pneumonia in healthy adults
- May increase the risk of pneumonia in immunocompromised pts.
- Cannabis with aspergillus may cause aspergillosis and Acute BronchoPulmonary Aspergillosis (ABPA)
Chronic Cannabis Smoking
Summary

- Cannabis only Smoking
  - Increase in TLC
  - Increase in FVC
  - No change in FEV1
  - Increase airway obstruction
  - Increase bronchial inflammation
  - All the above are reversible with quitting

- Cannabis and Tobacco Smoking
  - Worsens COPD PFT changes
  - Worsens COPD Symptoms

- Pneumonia
  - No increase in normal patients
  - Increased in immuno-compromised pts
  - ABPA increased

- Risk of cancer
  - Confusing
Why doesn’t Cannabis smoking increase Lung Cancer?

- Cannabinoids (CBD) are:
  - Anti-angiogenic:
  - Inhibit lung cancer cell invasion
  - Anti-metastatic
  - Increase apoptosis of lung cancer cells
  - Increase autophagy of lung cancer cells
  - Increase cell cycle arrest in lung cancer cells
  - Inhibit epithelial-to-mesenchymal transition
  - Enhance tumor immune surveillance
  - Support chemotherapeutics’ effects on drug-resistant cancer cells
Cannabinoids for Asthma
Non-inhaled Cannabinoids

- THC and CBD can cause bronchodilation and decrease pulmonary inflammation
- THC, CBD and CBN inhibit serum levels of IL-4, IL-5, IL-13, IL-6, and TNF-α to inhaled allergens (decreases inflammatory response)
- CBD Inhibits bronchial constriction to inhaled allergens
- CBN and THC reduce bronchial IgE production to inhaled allergens
- CBN and THC reduce mucus production to inhaled allergens
- CB2 receptor agonist prevents bronchoconstriction and airway edema in GERD model

Can Cannabidiol (CBD) be Rx for Inflammatory Lung Disease

- Decreases total lung resistance and elastance
- Decreases leukocyte migration into the lungs
- Decreases myeloperoxidase activity in the lung tissue
- Decreases protein concentration and production of pro-inflammatory cytokines (TNF and IL-6) and chemokines (MCP-1 and MIP-2) in the bronchoalveolar lavage supernatant.

Cannabidiol (CBD) in RSV & Systemic Sclerosis

- CB2 receptor agonist (CBD) decreases RSV symptoms in mice and humans.
- CB2 receptor blockade increases RSV pathology and symptoms in mice and humans.
- CBD prevents fibrosis in lungs in systemic sclerosis model via CB2 and PPARgamma receptors.

Great CBD Anecdotal Responses
Why No FDA Approval

- Pain Relief
- Anxiety
- Lung Cancer
- Epilepsy
- Parkinson’s Disease
- Psoriasis
- Atopic Dermatitis
- Asthma
- Diabetes (BS, Pain, & Neuropath.)
- Autoimmune diseases
- Alzheimer’s Disease
- Dementia
- Attention-Deficit Hyperactive Disorder
- Post Traumatic Stress Disorder
- Allergic Rhinitis
- Inflammatory Diseases
- Bipolar Disease
- Schizophrenia
- Vomiting
- Eating Disorders
- Tourette’s Syndrome
Antecdotal Success vs. Research Findings

Why the discrepancy?

- In US: Monopoly on the supply of to researchers
- Companies cannot use their own product raised and/or made in the USA in studies of marijuana, THC, or CBD. They must use government supplied drug.
- Marijuana, THC, and CBD supplied by the government cannot be tested by the researchers in any manner, including for quality, purity, contamination, pesticides, etc.
- When researchers have tested the products supplied by the government, the products tested have failed every single test for quality, purity, contamination (fungus, other compounds), pesticides and heavy metals.
Antecdotal Success vs. Research Findings
Why the discrepancy?

- Patients are using products that are completely different from those having to be used by researchers in the US.
- The FDA will not consider as significant evidence any studies performed outside the USA and such studies must be reproduced in the US.
- However, the marijuana, THC, or CBD being used must be supplied by the government.
- Catch-22 for research on marijuana, THC, or CBD here in the US.