Pharmacologic Consideration for Cannabinoids

Wisconsin Society of Anesthesiologist Annual Meeting
September 7, 2019

Natalie Schmitz, MPA, PharmD, PhD
University of Wisconsin – Madison, School of Pharmacy

Endocannabinoid (eCB) System

- All vertebrate animals
- eCB has homeostatic roles in:
  - Hunger, feeding, and energy
  - Neural plasticity
  - Neuroprotection
  - Nociception, pain
  - Autonomic tone
  - Immune response
  - Connective tissue repair
  - Human behavior
- CB1 and CB2 receptors
Endogenous vs Exogenous Cannabinoids

**Endocannabinoids**
- Anandamide (AEA) and 2-arachidonoylglycerol (2-AG)
- Synthesized at or near the site of action
- Rapidly broken down at the site of action
- Signals are quick and localized

**Synthetic or Phytocannabinoids**
- THC and CBD
- Marinol, Nabilone, Sativex, Epidiolex
- Large volume of distribution
- Metabolized by the liver
- Sustained and global effect

Δ-9-tetrahydrocannabinol (THC)
- Discovered in 1964
- Psychoactive
- Anti-inflammatory
- Neuro-protective
- Anti-nausea
- Analgesic (neuropathic, chronic, and cancer pain)
- 11-OH-THC is estimated to be 4x more psychoactive than THC
Cannabidiol (CBD)

- Discovered in 1940
- Non-intoxicant
- No significant affinity to CB1 and CB2 receptors
- Blocks the formation of 11-OH-THC
- Mitigates side effects of THC while improving THC’s therapeutic activity
- Most common side effect is diarrhea

**CBD Targets and Action**

- Inhibits adenosine uptake
- Inhibits FAAH (increasing AEA)
- Inhibits release of proinflammatory cytokines (TNF-α, IL-6, IL-1β)
- Antioxidant and free radical scavenger

GPR55, TRPV1, TRPV2, TRPA1, PPARγ, 5-HT1A, α3 glycine
Proposed Pharmacologic Effects of Cannabinoids

<table>
<thead>
<tr>
<th>Analgesic</th>
<th>Anti-inflammatory</th>
<th>Anxiolytic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antispasmodic</td>
<td>Immunosuppressive</td>
<td>Antipsychotic</td>
</tr>
<tr>
<td>Anti-anorectic</td>
<td>Anti-host vs graft</td>
<td>Antidepressant</td>
</tr>
<tr>
<td>Antiemetic</td>
<td>Dermatologic</td>
<td>Vasorelaxant</td>
</tr>
<tr>
<td>Neuroprotectant</td>
<td>Anti-psoriatic</td>
<td>Anti-ischemic</td>
</tr>
<tr>
<td>Anti-cancer</td>
<td>Anti-eczema</td>
<td>Anticonvulsant</td>
</tr>
<tr>
<td>Antiproliferative</td>
<td>Anti-keratotic</td>
<td>↓ GI motility</td>
</tr>
<tr>
<td>Anti-metastatic</td>
<td>Anti-pruritic</td>
<td>↓ GI secretions</td>
</tr>
<tr>
<td>Anti-angiogenesis</td>
<td>UV light reducing</td>
<td>↓ Stomach acid</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>Bronchodilatory</td>
<td>↓ Acid reflux</td>
</tr>
<tr>
<td>Antibacterial</td>
<td>Anti-glaucoma</td>
<td>↓ Sleep induction</td>
</tr>
<tr>
<td>Antifungal</td>
<td>Anti-diabetic</td>
<td></td>
</tr>
<tr>
<td>Antiparasitic</td>
<td>Bone-stimulant</td>
<td></td>
</tr>
</tbody>
</table>

Formulations and Routes of Administration

- **Common modes of administration**
  - Inhalation (smoking, vaporization)
  - Oral
  - Oro-mucosal or Sublingual
  - Topical, Rectal

- **Common formulations**
  - Herbal cannabis, Resin
  - Chemically-extracted concentrates
  - Edibles, Tinctures
  - Lozenges, Lollipops, Nabiximols
  - Prescription cannabinoids (dronabinol, nabilone)
Cannabis Onset and Duration of Action

### Route of Administration: Inhalation

- 20-70% of THC reaches the lungs
- ~ 30% enters systemic circulation
- Shortest onset of action making dose titration possible

**Advantages**
- Simple
- Effective

**Disadvantages**
- Can contain irritants

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Action</th>
<th>Amenable to self-titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoked</td>
<td>5</td>
<td>2–4</td>
</tr>
<tr>
<td>Vaporized</td>
<td>5</td>
<td>2–4</td>
</tr>
<tr>
<td>Oral Botanical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooked</td>
<td>30–60</td>
<td>8–12</td>
</tr>
<tr>
<td>Oil</td>
<td>30–60</td>
<td>8–12</td>
</tr>
<tr>
<td>Tea</td>
<td>30–60</td>
<td>8–12</td>
</tr>
<tr>
<td>Nabilone</td>
<td>60–90</td>
<td>8–12</td>
</tr>
<tr>
<td>Dronabinol</td>
<td>30–60</td>
<td>4–6</td>
</tr>
<tr>
<td>Oromucosal (nabiximols)</td>
<td>15–40</td>
<td>2–4</td>
</tr>
</tbody>
</table>
Route of Administration: Oral

- Types
  - Oral solution
  - Capsules
  - “Edibles”
- Delayed onset of action
- Longer effect
  - Low and erratic gastrointestinal absorption

Route of Administration: Sublingual

- Types
  - Spray
  - Tincture
  - Lozenge
  - ODT
- Pharmacology
  - Mixed absorption, some drug passes through oral mucosa but other is ingested
Route of Administration: Topical

• Types
  • Creams
  • Ointments
  • Transdermal patch
• Pharmacology is poorly understood
• There is systemic absorption

Route of Administration: Rectal

• Stable and bioavailable suppositories have been formulated
• Onset of action ~ 10 minutes
**Drug Interactions: CYP540 Enzymes**

### Metabolism
- THC and CBD are metabolized by CYP3A4 and CYP2C9
- CBD is also metabolized by CYP2C19

### Induction
- THC is a CYP1A2 inducer
  - May reduce serum drug concentrations of clozapine, duloxetine, naproxen, cyclobenzaprine, olanzapine, haloperidol, and chlorpromazine

### Inhibition
- CYP3A4
  - May increase serum drug concentrations of macrolides, calcium channel blockers, benzodiazepines, cyclosporine, PDE5 inhibitors, antihistamines, haloperidol, antiretrovirals, and some statins
- CYP2D6
  - May increase serum drug concentrations of SSRIs, tricyclic antidepressants, antipsychotics, beta blockers and opioids


### Drug Interaction Studies

- **Warfarin**
  - THC and CBD increased warfarin levels
  - Frequent cannabis use is associated with increased INR
- **Alcohol**
  - Alcohol can increase THC levels
- **Theophylline**
  - Smoked cannabis can decrease theophylline levels
- **No effect on indinavir or nelfinavir**
- **Docetaxel or irinotecan**
  - No effect
- **Clobazam**
  - CBD increased clobazam active metabolite levels
  - No effect on valproate
- **CNS depressants**
  - Additive CNS depressant effects with alcohol, barbiturates, and benzodiazepines

Drug Safety

**Contraindications**
- Acute psychosis or unstable psychiatric condition
- Severe and unstable cardiopulmonary disease
- Pregnant or breastfeeding
- History of alcohol or substance abuse

**Precautions**
- Severe cardiovascular, immunological, liver, or kidney disease
- History of arrhythmias
- Personal history of psychiatric disorder
- Family history of schizophrenia
- Drug interactions
- Association with hyperemesis syndrome
- Pediatric and elderly patients

Potential Cannabis Contamination

- Fungal and bacterial pathogens
- Pesticides
- Heavy metals
Questions?