Therapeutic Potential of the Marijuana-Derived Cannabinoids THC and CBD

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Learning Objectives

1. TO UNDERSTAND THE PHARMACOLOGY OF THC AND CBD
2. TO DISCUSS POTENTIAL ADVERSE EFFECTS AND DRUG INTERACTIONS
3. TO REVIEW THE CURRENT EVIDENCE SUPPORTING THERAPEUTIC USES OF THC AND CBD

Take home messages

- Cannabis (an hemp) are a mixture of compounds.
- The two primary cannabis constituents (THC and CBD) each have pharmacological effects
  - Recreational cannabis (marijuana) is generally high in THC, low in CBD
- CBD has better potential for therapeutic benefit
  - Does not produce dependence or euphoria
  - Clear benefits in seizure disorders
  - Low adverse effect profile
  - Promising early results in schizophrenia; addiction; anxiety
- THC
  - Best indication is in the treatment of pain

Disclosures

- Member of the Scientific Advisory Board of Phytecs, Inc.
- Received a research grant from Phytecs, Inc.
- Consultant for Beryl Therapeutics, Inc.

Outline

- Cannabis as a recreational drug
- THC: Mechanism of action and potential therapeutic roles
- CBD: Mechanism of action and potential therapeutic roles

Cannabis

- Annual herb; sexually dimorphic
- Botanical family includes hemp, cannabis indica and cannabis sativa
- Flowering tops contain “trichomes”; filled with terpenephenols
Family of terpenephenols found in the plants

- "Phytocannabinoids"
- 100 unique chemicals

Preparations of cannabis and hemp

- Recreational cannabis: Dried preparations or extracts of the plant, usually just the flowering tops
  - Very high cannabinoid contents; especially THC
  - Can be smoked, vaporized, placed into food, used as concentrates of oils (dabs)
- Hemp (seed) oil
  - Oil is pressed out of the seeds
  - Has very low amounts of both THC and CBD
- Hemp extract or hemp extract oil
  - Extract of the entire hemp plant; since CBD>THC, there is measurable but very low amounts of THC in these preparations
- CBD Oil
  - Can be a combination of hemp extract and hemp oil
  - Extracted from CBD rich, THC poor cannabis strains

Cannabis can be contaminated

1. Microbials: primarily bacteria and molds. Come from improper preparation of the material after harvest. Risk: fungal pneumonia
2. Heavy metals (Cadmium, arsenic and lead): cannabis is a bioaccumulating plant (hemp has been proposed for phytoremediation of contaminated soils).
3. Pesticides: 85% of legal cannabis in WA state contained pesticides, including proven carcinogens

Pharmacokinetic Profiles

- Neither THC nor CBD are well-absorbed orally (<10% bioavailability)
- THC is metabolized by CYP2C9, CYP2C19 and CYP3A4
- CBD is metabolized by CYP2C19 and CYP3A4
  - And a potent inhibitor of CYP2C19
- In vitro study suggests that CBD inhibits P-glycoprotein; could influence brain absorption of other drugs
- Some interactions of THC with multi-drug resistance proteins have been seen in vitro

THC

- THC IS MOST ABUNDANT CANNABINOID IN RECREATIONAL CANNABIS
- RESPONSIBLE FOR POSITIVE AND NEGATIVE EFFECTS OF CANNABIS USE FOR RECREATION; TO GET "HIGH"

Acute effects of smoked recreational cannabis

Effects on CNS function:
- Elevates mood
- Reduces anxiety
- Increases sociability
- Effects on posture; coordination of movement
- Alters sensory perception; time
- Alters short-term memory
- Changes in alertness; causes sleep
Effects outside of the CNS
- Effects on metabolism; fat storage
- Cardiovascular concerns
- Very little respiratory effects
Why do people use cannabis?

How does THC work?

- It is an agonist of a G protein coupled receptor (CB1R)
- CB1R is found throughout the brain; functions to regulate synaptic activity by inhibiting neurotransmitter release
- Endogenous ligands for CB1R: endocannabinoids—anandamide and 2-AG
- Endocannabinoids and the CB1R are called the “endocannabinoid signaling system”
- THC mimics the effects of the endocannabinoids at CB1R

CB1 receptor Expression Pattern

- All over the brain
- Regions involved in reward; mood; anxiety; memory; cognition; posture and movement regulation; autonomic function; regulation of stress hormones; regulation of blood pressure; pain
- Outside of the brain
- Pain sensing neurons
- Adipose tissue
- Sympathetic nervous system
- Liver
- Skeletal muscle
- Immune cells
- GI tract

Endocannabinoid (eCB) signaling ➔ homeostasis

- Promotes sleep
- Opposes neuronal and endocrine responses to stress
- Reduces perception of pain
- Maintain hedonia
- Reduce fear and anxiety
- Promote recovery following stress
- Reduces nausea
- Loss of this capacity could result in
  - Sleep disturbances
  - Hyperactive stress responses
  - Enhanced pain sensation
  - Depression and anhedonia
  - Anxiety disorders
  - PTSD
  - Cause nausea

Endocannabinoid Deficiency Syndrome

- Low endocannabinoid tone ➔ loss of homeostasis ➔ vulnerability to a variety of stress-related illnesses
- Including:
  - Depression
  - Anxiety
  - Post traumatic stress disorder
  - Functional Pain Disorders
  - Cyclic vomiting syndrome
  - Migraine headache
  - Sleep disturbances

Sequelae of chronic recreational cannabis use

- Cannabis use disorder (CUD)
  - Psychological and Physical Dependence
  - Pharmacokinetic tolerance
    - Increased metabolism
    - Tolerance: due to receptor down-regulation
    - Need more cannabis to produce the same effect
    - Endocannabinoid deficiency
  - Withdrawal upon cessation of use (50% of individuals)
    - Dysphoria (anxiety, irritability, depression, restlessness)
    - Disturbed sleep (with vivid dreams); GI symptoms; Decreased appetite
    - Reduced reactivity to dopamine
    - Diminishing of reward, increased negative emotionality
Other concerns with chronic cannabis

- **Cannabis hyperemesis syndrome**
  - Similar to cyclic vomiting syndrome
  - Alleviated by cessation; hot showers

- **Psychosis**
  - Cannabis-induced psychosis is associated with heavy use; sudden onset, often abates if cannabis is stopped
  - Shares many overlapping features with schizophrenia, may have more mood symptoms; visual hallucinations and paranoid ideation most common; and not always treated effectively with anti-psychotics
  - Acute cannabis intoxication can have a range of schizophrenia-type symptoms too

“Spice” and other synthetic cannabinoids

- Synthetic analogs of THC; often added to herbal preparations
- Like THC, they bind to CB1R and can produce all the same effects
- However, they are far more efficacious activators
- More severe and unpredictable effects (positive and negative)
  - Tachycardia, hypertension; hallucinations; hyperglycemia; agitation, anxiety
  - Suicidality, encephalopathy, stroke, coma, seizures
- Withdrawal symptoms are more severe

Therapeutic potential for CB1 agonists such as THC

- **Cannabis**
  - Dronabinol (Marinol): Form of THC; taken orally; bioavailability is about 6%, so not very effective
  - Sativex (nabiximols): mixture of THC, cannabidiol (CBD) (1/1) and other cannabinoids
  - THC-like compounds: nabilone (Cesemet)
- **Indications**: chemotherapy-induced nausea; spasticity associated with multiple sclerosis; pain

Therapeutic potential for CB1R agonists

- **To treat ”endocannabinoid deficiency”: yet untested**
  - Reverse or stop the negative effects of stress = a blockbuster!
  - How to diagnose endocannabinoid deficiency?
  - Because of tolerance development, will this work?
  - Many recreational cannabis users have figured out how to titrate the dose
  - Is there room for a pharmaceutical? Or is cannabis as good as it gets?
- **To treat pain**: Good evidence for modest efficacy
  - Neuropathic; functional pain disorders
  - Reduce spasticity; improve sleep in MS
  - Efficacy is more subjective than objective
- **Nabilone**: nightmares associated with PTSD

*Psychoneuroendocrinol 2015*
THC (i.e. cannabis) has failed to show efficacy in:
- Depression (Kotin et al. Arch Gen Psychiatry, 1973)
- Parkinson’s Disease (Carroll et al. Neurology, 2004)
- Worsens symptoms in schizophrenia (D’Souza et al. Biol Psychiatry, 2005)
- Neither safe nor effective in the treatment of anorexia nervosa (Gross et al. J Clin Psychopharmacol, 1983)

Cannabidiol (CBD)
- Found in the cannabis plant
- Enriched in some cannabis cultivars (not those typically used recreationally)
- Does not have psychoactive effects of THC

Theoretical mechanisms of action of CBD
- Activates cyclooxygenases; superoxide dismutase
- Free radical scavenger; reduces oxidative stress
- Inhibits CB receptors at high concentrations/doses

Preparations of CBD
- CBD oil
- Low THC/high CBD cannabis
- Epidiolex
  - A buccal spray containing only CBD (no THC) by GW Pharmaceuticals

Potential therapeutic effects of CBD
- Improve sleep quality
- Reduce anxiety
- Reduce nightmares
- Anti-psychotic
- Pro-cognitive
- Antidepressant
- Anti-craving
- Anti-inflammatory
- Anticonvulsant
- Antiemetic
- Neuroprotectant

Is there evidence?
CBD and seizure disorders

Lattanzi et al. Drugs, 2018

Adverse Events in Seizure Treatment Studies

Aminotransferase issue was primarily seen in patients also taking valproate

CBD and Psychosis

• Randomized to either CBD (n=20) or amisulpride (n=19)
• Dose escalation from 200 mg to 800 mg for both
• Previously untreated

CBD and Opiate Craving

Hurd et al., Neurotherapeutics 2015

Take home messages

• The two primary cannabinoids (THC and CBD) each have pharmacological effects
  ○ Recreational cannabis can contain both molecules; ratios are variable but most recreational cannabis is high in THC, low in CBD
• CBD has better potential for therapeutic benefit
  ○ Does not produce dependence or euphoria
  ○ Clear benefits in seizure disorders
  ○ Low adverse effect profile
  ○ Promising early results in schizophrenia; addiction; anxiety
• THC
  ○ Best indication is in the treatment of pain
• We need more high quality clinical trials

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