Cannabis and Schizophrenia

Team AxOn AxOff

Topics of Interest

Endocannabinoid **Signaling** - Cody

A **Timeline** of Endocannabinoid Effects - Megumi

Schizophrenia **Overview** - Nataly

Schizophrenia and the **Dopamine** Hypothesis - Boya

Schizophrenia and **Metabolic Dysregulation** - Lorraine
Background Knowledge

Overall Cannabis use is *decreasing*

- Article published in 2010

Cannabis use in younger people is *increasing*

- So street weed at an early age = Scizo? Other Drugs?

**THC ** Concentrations:

- Marijuana (Grass) - 4% THC
- Resin (Hash) - 4% THC
- Sinsemilla (Skunk) - **16-20% THC**
Endocannabinoid (eCB) Signaling Terminology

-Ligands:
- Tetrahydrocannabinol (THC)
- Anandamide (AEA)
- 2-Arachidonoyl-Glycerol (2-AG)

-Cannabinoid Receptor 1 and 2 (CB1, CB2)

-Neurotransmitters:
- Dopamine (DA), GABA, Glutamate (Glu)

eCB Ligands

THC - Exogenous Ligand
- Active Ingredient in “Weed”

AEA - First Endogenous Ligand
- Postsynaptically -> Retrograde
- Discovered first, but irrelevant?

2-AG - More Abundant than the latter
- Presynaptically -> Auto/Paracrine
- Decrease Ionic Traffic and AC

eCB Receptors

CB1 - One of the most abundant G-Protein-Coupled Receptors in the brain

CB2 - Thought to be more associated with the immune system

Fig. 1. The endocannabinoids “fine-tune” synaptic signalling. GABA and glutamate modulate the excitability of midbrain dopamine neurons and prefrontal cortical pyramidal cells. These are influenced by endocannabinoids via CB₁ receptors. THC is a CB₁ agonist and appears to switch off inhibitory inputs to dopamine neurons.
Endocannabinoid signaling induces synaptic depression at excitatory synapses

1. Action Potential Generated and Glutamate Release
2. Glutamate Receptors Activated
3. Depolarization and eCB Biosynthesis
4. eCB Retrograde Transport and CB1R Activation
5. Target Signaling Pathways and Reduce Glutamate Release

**Diagram Notes:***
- AC = adenyl cyclase
- AEA = anandamide
- CB1R = cannabinoid type 1 receptor
- COX-2 = cyclooxygenase 2
- ERK = extracellular signal-regulated kinase
- FAAH = fatty acid amide hydrolase
- Glutamate receptors = AMPAR or mGluR1/5
- NAPE = N-arachidonoyl phosphatidyl ethanolamine

**Pathways:***
- CB1R activation leads to activation of AC, cAMP, and PKA
- eCB retrograde transport reduces glutamate release
- eCB biosynthesis and transport pathways are involved

**Key Molecules:***
- 2-arachidonylethanolamine (AEA)
- Cannabinoid type 1 receptor (CB1R)
- Diacylglycerol lipase
- Phospholipase D
- N-arachidonoyl phosphatidyl ethanolamine (NAPE)
Schizophrenia

★ What is it?

- A chronic brain disorder that impacts about 1 percent of the population. It’s a brain disorder that can impact people’s lives and is completely unforgiving.
- It affects both men and women pretty evenly, though men tend to have an earlier onset.
- No cure as of present day, but there is treatment available to help with treating of the symptoms.
Normal vs. a Schizophrenic Brain
What causes Schizophrenia?

- Many factors
  - Genetics
  - Environment
  - Drug use
  - Brain chemistry
  - Prenatal Viral Infections and birth trauma

Ultimately, science still hasn’t given us the direct answers to what exactly causes it, but as of right now we know it’s a combination of multiple factors.
Subtypes of Schizophrenia

- Paranoid
- Catatonic
- Disorganized
- Undifferentiated
- Residual
Symptoms of a Schizophrenic

Positive psychotic symptoms
❖ This has to do with the symptoms gained not normally seen in people
➢ Hallucinations
➢ Delusions

Cognitive symptoms
❖ This has to do with cognitive issues. Things that are normally impaired are:
➢ Memory
➢ Attention
➢ Planning
➢ Decision making

Negative Symptoms
❖ This has to do with symptoms associated with disruption of normal behavioral and emotional responses.
➢ Alogia, affective flattening, avolition, anhedonia, asociality
Treatments available

- Treatments
  - Hospitalization
  - Medication
  - Psychotherapeutic Treatment
  - Illness management skills
  - Integrated treatment for co-occurring substance abuse
  - Rehabilitation
  - Individual Psychotherapy
  - Cognitive behavioral therapy
  - Family Education
  - Self-Help Groups
Who does it affect?

- Schizophrenia doesn’t just affect the individual, it impacts both them, their families and loved ones, and society too.
- Schizophrenics struggle finding jobs as the illness impacts their cognitive function
  - Often times family members have to help the individual
- Emotionally it can be stressful as no one wants to see a loved one going through this.
- According to a research done, in 2013 it cost the US approximately spend $155.7 billion.
Schizophrenia affects approximately 2.4 million adult Americans.

**DID YOU KNOW?**

Schizophrenia is a treatable mental illness. Access to timely treatments and supports can help people live full and healthy lives, including paid or volunteer work, fulfilling relationships and good mental health. When people have challenges accessing the care they need, or experience stigma, their risks for poor mental health increase:

- **4x** more likely to be victims of violent crimes.
- **20%** shorter lifespan.
- Often report hostility, fearful attitudes, stereotypes and insensitivity from others.
- **15%** are employed in Canada, often paid less and hold fewer full-time positions.
Some good news!
Famous People With Schizophrenia

John Nash – Nobel Prize winner
Syd Barrett – guitarist for Pink Floyd
Mary Todd Lincoln – wife of Abraham Lincoln
“Studying” Cannabis
Cognitive effects

- Learning and memory deficits
- Reduced attention
- Reduced ability to process and regulate emotion
- Lower resting global, prefrontal, and anterior cingulate cortex blood flow
  (Martin-Santos et al. 2010)
- When administered w/ THC: increased prefrontal, insular, and anterior cingulated activity during rest and cognitive tasks
Structural effects

- Reduced amygdala and hippocampal volumes (Arnone et al. 2008; Rais et al. 2008; Yucel et al. 2008)
- More pronounced grey matter loss with lateral and third ventricle enlargement
- Gyrification abnormalities in cortex (Mata et al. 2010)
- Increase in diffusivity of white matter in corpus callosum
Adverse Effects of Cannabis

- Influence the onset of psychosis (Arseneault et. al 2002, Henquet et. al 2005a, and Di Forti et. al 2009)
- Predisposition to higher rates of depression & anxiety (Patton et al 2002)
- Reduction of expected years of completed education (Van Ours and Williams, 2007; Pudney, 2004; Van Ours and Williams, 2009)
Cannabis Use and Schizophrenia

Main factors:

- Degree of exposure
  - Dose-response relationship
- Age of exposure
- Genetic predisposition
- Environmental risk factors

“There’s no risk to smoking weed”

“ThErE’S No RiSk tO sMoKinG WeEd”
Degree of Exposure

- Dose-response relationship: higher dose, higher risk
- 2x risk than non-users; 3% developed Schizophrenia (Andreasson et al. 1987)
- Heavy users 6x more likely than non-users (Zammit et al. 2002)
- 3x more likely to develop psychotic symptoms (Van Os et al 2002)
- Cannabis users in first psychotic episode more likely to have been using cannabis longer and everyday than general population (Di Forti et al. 2009)
Age of exposure

- Higher cumulative exposure to cannabis → excessive activation of CB receptors
- Increased vulnerability to THC during critical phases of brain maturation
  - Glutamate, catecholamine, serotonergic systems
  - Elements of dopaminergic system increase in adolescence
- Use by 12:
  - Strong assoc. with top 10% score of psychotic experiences (Schubart et al. 2010)
- Use by 15:
  - 2x likely to develop non-affective psychosis (McGrath et al. 2010)
  - Sig. increase risk of schizophreniform disorder (Arsenault et al. 2002)
- Use by 18:
  - 2x risk of psychotic symptoms if cannabis dependent (Fergusson et al. 2003)
Genetic predisposition

- **COMT**: key enzyme that encodes catechol-O-methyltransferase & involved in prefrontal cortex metabolism of dopamine released into synapses
  - mutation → valine (Val) to methionine (Met) substitution → less enzymatic activity & slower break down of dopamine
- **Val/Val genotype more likely to develop THC-induced psychotic symptoms and schizophreniform disorder** (Caspi et al. 2005; Henquet et al. 2006)
- **AKT1**: serine/threonine kinase
  - Genetic variation may mediate effects on psychosis expression assoc. w/ cannabis use
  - Cannabinoids act on CB1 and CB2 → activate AKT1 → signal downstream of dopamine D2 receptor
Environmental risk factors

- Joint presence of childhood trauma and cannabis use → increase likelihood of psychotic symptoms (Harley et al. 2010)
“[Don’t] smoke weed everyday.”

-Snoop Dogg
Schizophrenia and the Dopamine Hypothesis
Chlorpromazine

- Developed as a presurgical sedative
- Unexpected Antipsychotic effects
- Finding in schizophrenic population was reproduced in more than ten clinical studies in three years.
Chlorpromazine & Haloperidol

- In mouse brain
  - Increase the concentration of dopamine metabolites
  - *Without* altering the dopamine concentration
  - *Block* monoaminergic receptors in brain
- Propose:
  - Blockade of dopamine neurotransmission relieves psychotic symptoms
  - *Excessive* dopamine transmission → Schizophrenia
Amphetamine

- High doses can produce acute psychosis in normal people
- Symptoms
  - Indistinguishable from the paranoid subtype of schizophrenia
  - Immediately mediated by antipsychotic treatment
- A powerful dopamine releaser in brain
Hyper-dopamine

Hyperactivity of dopamine transmission is responsible for schizophrenia.
Positive Symptoms and D2 Receptors

- Efficacy of antipsychotic drugs & Potency to block D2 receptors
- Subcortical Region
  - Striatum
  - Nucleus Accumbens
- Predominant occupancy of DA terminals and D2 receptor
Negative Symptoms and Cognitive Symptoms

- Enduring negative symptoms and cognitive deficits
- Resistance to D2 receptor antagonists
- Card sorting task performance:
  - Similar to patients with frontal lobe damage
  - Primary Locus → Prefrontal Cortex
- Functional brain imaging
  - Prefrontal Cortex → “Characteristic low level of activity”
D1 receptor - main receptor in neocortex

Prefrontal DA transmission at D1 receptors $\rightarrow$ Optimal PFC performance

Hypoactivity $\rightarrow$ Hypofrontality

Deficits $\rightarrow$ Negative symptoms & Cognitive impairments
Schizophrenia & Imbalanced DA activity

**Hyperactive** mesolimbic DA projections

→ **Hyperstimulation** of D2 receptors

→ **Positive** symptoms

**Hypoactive** mesocortical DA projections to the PFC

→ **Hypostimulation** of D1 receptors,

→ **Negative** symptoms & **Cognitive** deficits
Further thoughts

- Prefrontal DA activity vs Subcortical DA activity
  
  Inhibitory effect ?

  Deficiency $\rightarrow$ Disinhibition ?

- Glutamatergic Pathway ?
- GABAergic Pathway ?
Links Between Schizo & Metabolic Dysregulation

No Weed Beyond This Point.
Let's take it back to WEEK 1
Highlighting a Couple Things

Association between metabolic disturbances and neuropsychiatric disorders:

Bidirectional association!

Psychiatric disorders

Neurodegenerative diseases

Schizophrenia
Bipolar disorder
Depression

Associated with T2D & obesity

Schizophrenia
Bipolar disorder
Depression

CO-occur with diabetes, obesity

60% higher risk of T2D

Associated with T2D & obesity

Alzheimer's Disease
Vascular Dementia
Parkinson's Disease
Huntington's Disease

T2D is an independent risk factor for dementia!

UM. WHOA.
A Bidirectional Association Indeed

Let’s take a look at the following:

- Antipsychotics induce metabolic dysregulation
- Metabolic dysregulation induces schizophrenia
Antipsychotics Induce Metabolic Dysregulation Background

- Antipsychotics is only 1 risk factor
- Typical vs **Atypical** antipsychotics
- Metabolic dysregulations:
  - Obesity, type 2 diabetes, hyperglycemia

- Risperdal (risperidone)
- Abilify (aripiprazole)
- Clozaril (clozapine)
- Seroquel (quetiapine)
- Zyprexa (olanzapine)
- Geodon (ziprasidone)
- Invega (paliperidone)
- Latuda (lurasidone)
Antipsychotics Induce Metabolic Dysregulation

- Antagonistic effects on H1, 5-HT2C, & adrenergic alpha 2, 5-HT1 alpha, and M3.
- Increased leptin $\rightarrow$ leptin resistance
- Inhibit glucose transport
- Increased insulin $\rightarrow$ insulin resistance
Metabolic Dysregulation Induces Schizo.

- Maternal Obesity (indirect, but still interesting!)
  - Preeclampsia
  - Maternal high fat diet (mHFD)
    - Exposure to inflammatory cytokines
    - Increase of Mu Opioid Receptor
Main Take Away

- Antipsychotics used to treat schizo. can play a role in inducing metabolic dysregulation via hormones and receptors in the pancreas and brain.
  - Monitoring
- Schizophrenia can be induced prenatally via metabolic dysregulation of the mother
  - Think of the children.
Additional Fun Factoids
The Overlap Between Alzheimer’s and Schizo

- Genetic gene susceptibility
- Depression
- Metabolic dysregulation
- Neural Atrophy
- Prenatal Infection?
- Increased central KYNA
- Increase in osteoporosis
- Melatonin Production
- Central Mu Opioid Receptor
- Treatments??

**Please refer to: Metabolic Syndrome, Alzheimer Disease, Schizophrenia, and Depression: Role For Leptin, Melatonin, Kynurenine Pathways, And Neuropeptides**
In Sum

1. Cannabinoids exert their effect either via retrograde signaling or through exogenous sources; both leading to the decrease in synaptic activity.

2. Main factors of cannabis use and Schizophrenia: degree of exposure, age of exposure, genetic predisposition, and environmental risk factors

3. Schizophrenia is a serious chronic mental illness that affects about 1% of the world's population.

4. Abnormal DA activity in the prefrontal and subcortical area is the main cause of Schizophrenia

5. Schizophrenia and metabolic disruptions both may induce each other.
Sources

http://www.healthcommunities.com/schizophrenia/schizophrenia-overview.shtml
https://www.nami.org/learn-more/mental-health-conditions/schizophrenia
https://www.psychiatry.org/patients-families/schizophrenia/what-is-schizophrenia
https://www.psychologytoday.com/us/conditions/schizophrenia
https://www.webmd.com/schizophrenia/ss/slideshow-schizophrenia-famous-names
http://www.apa.org/helpcenter/recognizing-schizophrenia.aspx
http://schizophrenia.com/?p=336
https://www.gene.com/stories/from-compassion-to-action
https://www.everydayhealth.com/schizophrenia/guide/treatment/
Sources

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4619177/

http://clinical.diabetesjournals.org/content/24/1/18


https://www.schizophreniaforum.org/forums/dopamine-hypothesis-schizophrenia
