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Title

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Publication Date

2023

Data Availability

The data associated with this publication are not available for this reason: N/A

A Proposed Mechanism to Adolescent Cannabis Induced Psychosis

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Abstract

As the rate of cannabis induced psychosis increases in many parts of the world, it is important to understand the pathophysiology of this disorder. In this review we will attempt to connect cannabis induced physiological changes with new PET data on CB1 receptors in patients with schizophrenia to provide a theoretical mechanisms of cannabis-induced psychosis in adolescence. We propose that adolescent cannabis induced psychosis is possibly induced by chronic usage of cannabis during an important neurodevelopmental timeframe. This induces CB1 receptor down regulation due to tolerance, a similar pathophysiological state seen in patients with schizophrenia. The risk of developing cannabis induced psychosis is proposed to be a combination of when cannabis use is first initiated, potency of cannabis, frequency of use and genetic predisposition. After reviewing these steadily increasing data, we propose future studies and policy changes to further understand this mechanism and decrease the incidence of adolescent cannabis induced psychosis.

Cannabis Physiology, Usage and Epidemiology

Cannabis is one of my most commonly consumed recreational drugs in the world. It's major psychoactive effects are through Δ^9 -tetrahydrocannabinol (THC).

Usage:

- In the US, 42 million people have tried cannabis at least once.¹
- High school usage: 37% of students have used at least once.²
- Daily usage per grade:
 - 8th : 1.1 %
 - 10th : 4.4 %
 - 12th : 6.9 %
- Adolescents are **4 to 7 times** more likely to develop a cannabis use disorder if marijuana use is started before the age of 18 when compared to adults.⁴

Potency:

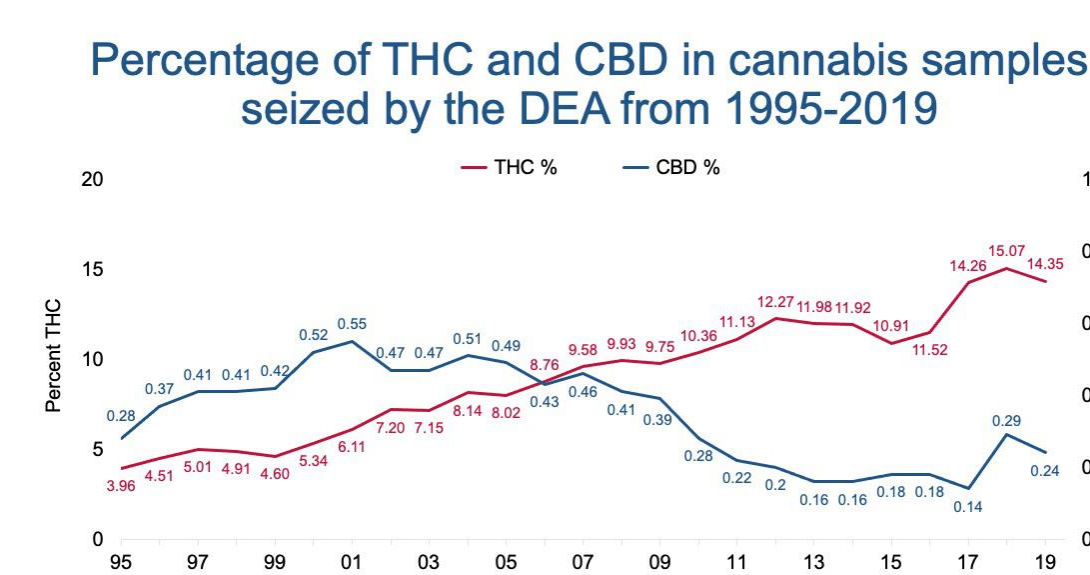
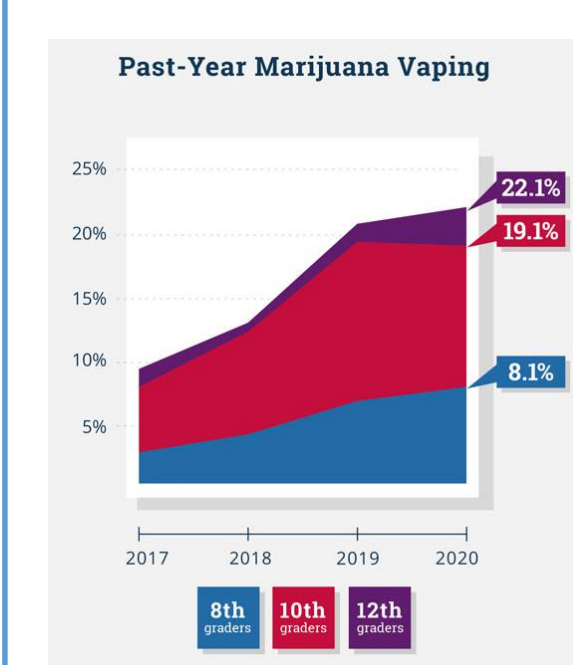


Figure 1: Graph shows data of seized cannabis samples by the DEA from 1995 to 2019.⁵

- 70+ % of cannabis advertised online is 15+ % THC⁶
- Average THC content of cannabis found online⁶:
 - Recreational: **21.5% ± 6.0**
 - Medical: **19.2% ± 6.2**

Forms of Consumption:



The quantity of adolescences trying cannabis through vaping is increasing.

Figure 2: Demonstrates the percentage of students that have consumed cannabis through vaping by grade from 2017 to 2020.⁷

Endocannabinoid System

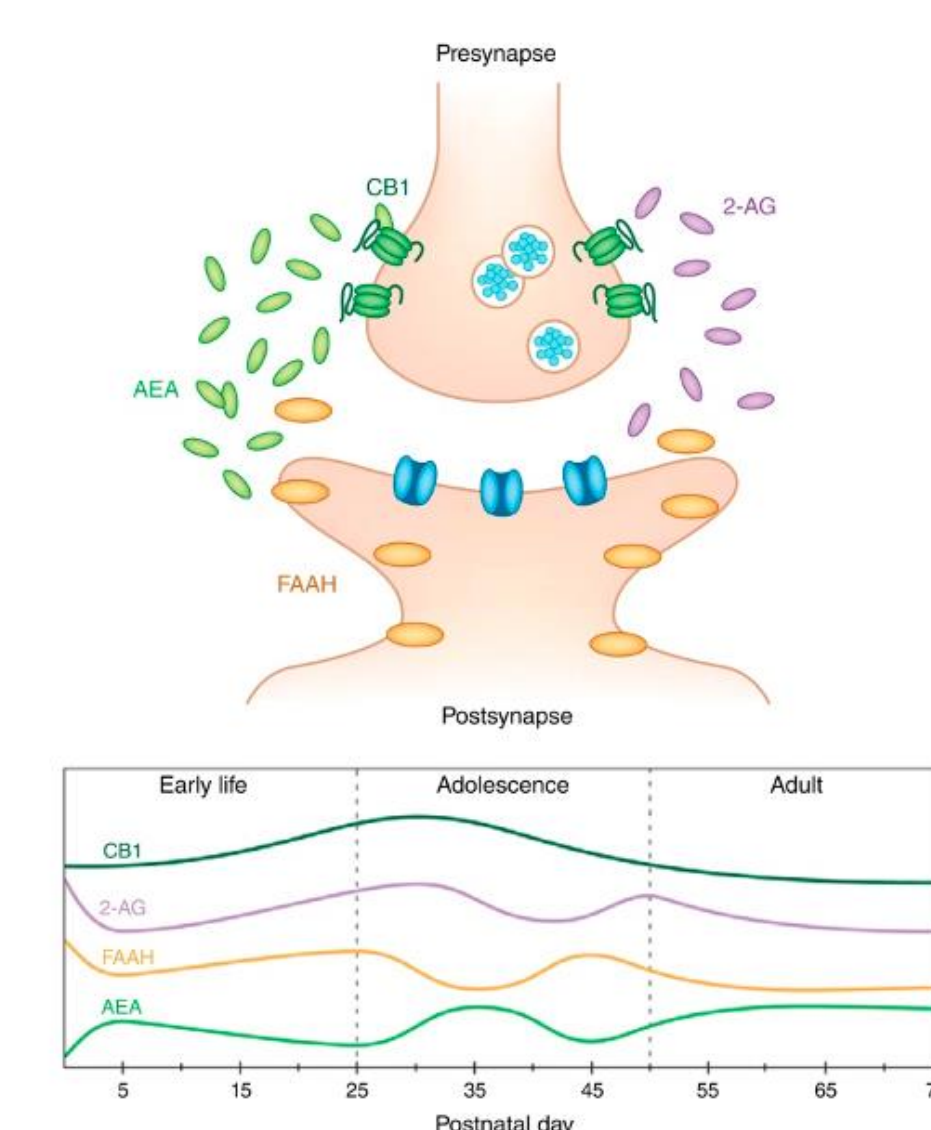


Figure 3: Illustrates the CB₁ receptor on the presynaptic terminal. Around it are AEA (arachidonoylethanolamide) and 2-AG (2-arachidonylglycerol) the normal physiological ligand of the CB₁ receptor. The bottom chart presents the quantity of enzymes and ligands through development.⁸

Endocannabinoid system is a group of ligands and receptors involved with many different processes such as neuronal development, regulation of neuronal transmission, mood, memory formation, etc⁹. The major receptors in the endocannabinoid system are the CB₁ and CB₂ receptor.

The **CB₁ receptor** is a presynaptic, **inhibitory G-protein receptor**. It is most concentrated in the PFC where it refines **excitatory glutamatergic**¹⁰ and **inhibitory GABAergic**¹¹ signaling during adolescences.

CB₁ Receptors in Schizophrenia

Author	Year	Radioligand	Patients with Schizophrenia	Controls	Outcomes
Wong et al. ¹²	2010	[¹¹ C]OMAR	9	10	↑ CB ₁ R : pons
Ceccarini et al. ¹⁴	2013	[¹⁸ F]MK-9470	67	12	↑ CB ₁ R : nucleus accumbens, insula, cingulate cortex, inferior frontal cortex, parietal and mediotemporal lobe
Ranganathan et al. ¹⁵	2016	[¹¹ C]OMAR	25	18	↓ CB ₁ R : amygdala, caudate, posterior cingulate cortex, hippocampus, hypothalamus, and insula
Borgan et al. ¹⁶	2019	[¹¹ C]MePPEP	40	20	↓ CB ₁ R : anterior cingulate cortex, hippocampus, striatum, and thalamus

Table 1: An overview of PET studies in humans looking into CB₁R in patients with Schizophrenia.

In this study we looked into CB₁ receptor levels in humans using PET. The results are shown above (Table 1).

Though the results are mixed, a few articles have been written to explain the mixed results.

Multiple authors have stated that there could be discrepancies in these study outcomes including symptom severity, sex, age, PET tracers, statistical analysis methods, or comorbid nicotine usage¹⁷

The current consensus is that the CB₁ Receptor is decreased in patients with schizophrenia.

Proposed Mechanism

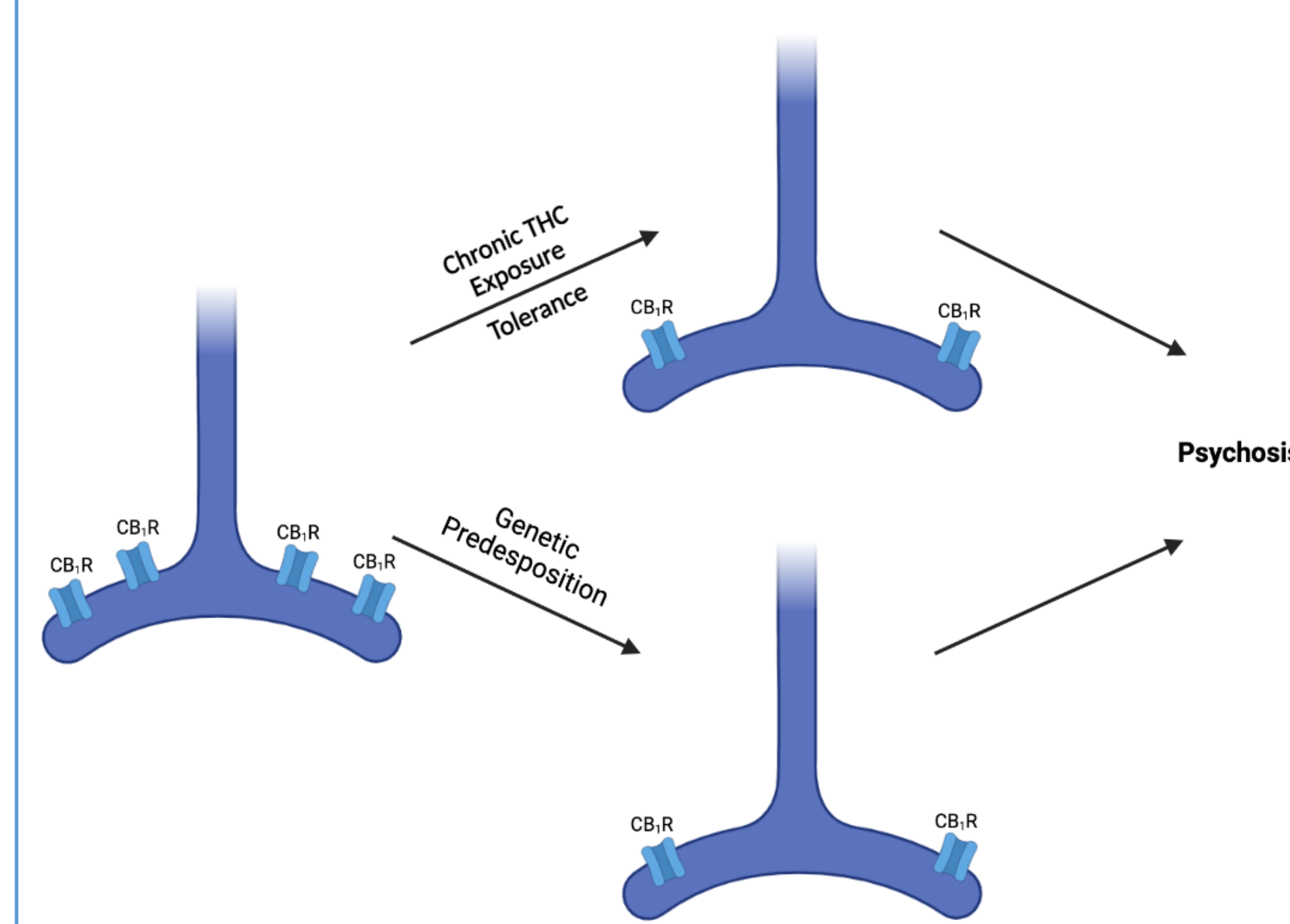


Figure 4: Two mechanisms of Psychosis: The figure above demonstrates how both chronic THC exposure and genetic factors induce similar CB₁R pathophysiological states, which both result in psychosis. Chronic THC exposure results in a downregulation of CB₁R due to tolerance.

The proposed mechanism is that both schizophrenia and chronic cannabis usage create a similar pathophysiological state:

- **Schizophrenia:** Genetic and environmental factors decrease CB₁ receptor availability
- **Chronic cannabis usage:** Tolerance induced by partial cannabinoid THC in cannabis causes a down regulation of the CB₁ receptor.

Both mechanisms induce a disruption in proper neurodevelopment during adolescences which results in a lack/decrease of refining by the CB₁ receptor during adolescence. The lack of refinement induces psychosis.

Why doesn't everyone who smokes cannabis during adolescence develop psychosis?

We propose there are 4 factors:

1. Age of onset
2. Consistency of use
3. Potency of Cannabis
4. Genetic predisposition

Age of onset is important because it seem there is a specific window of susceptibility where THC can induce neuro dysfunction in adolescence unlike in adulthood.

Consistency of usage determines how much tolerance is seen with the CB₁ receptor. The more usage the greater the effect.

Potency of Cannabis influences the effect of tolerance. Higher levels of THC leads to a great down regulation.

Genetic predisposition makes certain populations more susceptible to cannabis induced psychosis. Genetic variations in COMT¹⁹ and AKT1²⁰ have both demonstrated increased risk of cannabis induced psychosis.

Summary: Future Research

Proposed Future research:

- How do **high potent cannabis** products effect neurodevelopment and risk of developing psychosis?
- What are the **pathophysiological mechanisms of CB₁ receptor dysfunction** which possibly lead to cannabis induced psychosis?
- Use **PET to analyze CB₁ receptor availability** within adolescence during **cannabis usage and after cessation**.
- Determine the **neurodevelopmental timeline** where adolescences are most susceptible.
- Continue to look into **genetic variations** which can increase cannabis induced psychosis.

Policy Proposal:

- **Increase education** of students as early as **middle school** on the affects of cannabis on the brain.
- Promote **Cannabis screening** among pediatrician and family medicine physicians.
- **Identify** cannabis use disorder and refer patients to appropriate treatment: Cognitive behavioral therapy

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Acknowledgements

I would like to thank Dr. Cameron Carter and Dr. Tyler Lesh for their input and mentorship with this project. I would like to thank Dr. Saul Schaefer and Holly Ly for their support in the MD/PhD program and research selective. I would like to thank UC Davis School of Medicine for their support through this research selective.