Neurobiological Consequences of Adolescent Cannabinoid Use

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Increased Availability of Cannabis

Legal Recreational Use
8 States + DC

Medical Use:
28 States

Full Prohibition:
5 States

Unforeseen Consequences of this Unprecedented Experiment?
Marijuana Effects on Reward Circuit Development

Adolescence:
A Critical Period of Cognitive and Neural Circuit Development

Does Cannabis Alter Brain Circuit Development, Increasing Risk of Psychiatric Disorders?
Early Cannabis Use is Linked to Negative Outcomes in Humans

Cognitive, Memory Deficits
Schizophrenia (not violence though)
Use of “Harder Drugs” (Gateway Effect)

But Correlation is $\neq$ Causation!
Do Cannabinoid Drugs, Given to Adolescent Animals, Persistently Alter Disease Risk?

Cognitive, Memory Deficits
Changes in Emotional Behavior
Changes in Motivated Behavior

Chadwick, Miller, & Hurd 2013, Front Psychiatry
Adolescent Cannabinoid Drug

Daily throughout Adolescence (14d)
PD30-44

14d Washout
PD45-59

Adolescent Cannabinoid
Adolescent Vehicle

Cannabinoid-Induced Behavioral Changes?
**Adolescent Cannabinoid Drug Affects Palatable Food Intake**

**Stable Liquid Sucrose/Water Intake**

- **Ctrl**
- **Adol**
- **WIN**

**Acute Hunger**

- **Ctrl**
- **Adol**
- **WIN**

**Acute Satiety**

- **Water**
- **Sucrose**

**Binge-like Food Consumption**

- **Adol-Veh**
- **Adol-WIN**

**Pre-Test Fast or Feast**
Adolescent Cannabinoid Drug Alters Responses to Novelty

Vulnerability to Addiction?

Adolescent THC Increases Heroin Intake

Schoch et al
Psychopharmacology 2018

Belin et al
Neuropsychopharmacology 2011

Ellgren et al
Neuropsychopharmacology 2007

Familiar Environment  Novel Environment

Novelty Preference

Adol-Veh  Adol-WIN

Percent Time on Novel Side

0 20 40 60 80 100

Number of responses on the active lever

0 10 20 30 40 50 60 70 80

Heroin dose (µg/kg/min)

7.5 15 30 60 100

Heroin intake (mg)

0.0 0.2 0.4 0.6 0.8 1.0 1.2

Heroin dose (µg/kg/min)

7.5 15 30 60 100
Cannabinoid Drugs, Given to Adolescent Animals, Permanently Alter Behavior

Cognitive, Memory Deficits
Changes in Emotional Behavior
Changes in Motivated Behavior
e.g. Increased Heroin Intake

But...
...is this relevant to humans?
Are Current Animal Models Relevant to Humans?

Drug Being Used
- Mostly Synthetic Cannabinoid Receptor Agonists
- Some use THC, but THC is not Cannabis
- Nearly Always Injected

Treatment Duration and Timing
- Typically Daily
- Typically Starts Prior to Puberty

Drug Dosage
- Rewarding? Aversive?
Step 1: Administer Rewarding, not Aversive Doses

“Microdose” of Synthetic Agonist WIN55, 212-2 (WINµ)

WINµ in Adolescents: is Not Anxiogenic, is Rewarding
Step 2: Administer THC, not Synthetic Drugs

WIN55, 212-2 “Microdose”
Step 2: Administer THC/Cannabis by Inhalation
Results so Far:
Changes in *Endogenous Cannabinoids*
Endogenous Cannabinoids: “The Brakes” On Neurotransmission
Endocannabinoids in Adolescent Neural Circuit Development

Brenhouse & Anderson, 2011

Chadwick, Miller, Hurd 2013

Casey & Jones 2010
Adolescent Cannabinoid Exposure Persistently Alters Dopamine and Endocannabinoid Systems into Adulthood

Dopamine (DA) System:
- NAc D2 Gene Expression (Hurd et al. 2014, Neuropharm)
- VTA DA Cell Density (Behan et al. 2012, Neuropsychopharm)
- Spontaneous DA Activity (Renard et al. 2017, Cereb Cortex)
- Drug-Induced DA Neuron Firing (Pistis et al. 2004, Biol Psychiatry)

Endocannabinoid (ECB) System:
- CB1R binding in PFC (Rubino et al. 2015, Neurobio of Dis)
- Disrupted ECB-long term depression (Lovelace et al. 2015, Neuropharm)
- Anandamide in NAc and PFC (Ellgren et al. 2008, European NPP; Rubino et al. 2015, Neurobio of Dis)

Does Adolescent Cannabinoid Exposure Increase Vulnerability to a “Second Hit” Later in Life?
Adolescent Development of Motivation Circuits: Impact of Exogenous Cannabinoid Receptor Stimulation

Vulnerability to Addiction-Related Behaviors?

Risk Increased

Does a Challenge in Adulthood Reveal Changes in Reward Circuits or Behavior?

Chadwick, Miller, & Hurd 2013, Front Psychiatry

Does a Challenge in Adulthood Reveal Changes in Reward Circuits or Behavior?
Our Early Results

Potentiated Reward Seeking Behavior

Especially When Dopamine Neurons are Highly Recruited

Potentiated Neural Activity in Reward Circuits

Deficits in Endogenous Cannabinoid “Brakes” on Reward Circuits
Adolescent WIN Microdose Potentiates Dopamine-Stimulated Behavior and mPFC Activity

Moral: It is clear there are reasons for concern, but systematic study, and improved animal models are required!!