The Endocannabinoid System and Psychoses

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The endocannabinoid system and its physiological role

- multifaceted modulating system
- major homeostatic system:
  in particular active, if processes fall out of balance after external and/or internal "stress" or impact
Optimal activity of the endocannabinoid system for maintenance of homeostasis

Dysregulated endocannabinoid system: new allostatic set-point → pathology

- e.g. GI disease, allergy, schizophrenia, affective disorders, anxiety, epilepsy
- e.g. adiposity, addiction, atherosclerosis

Region-specific ECS activity
Cannabis use as a risk factor in psychiatry

$\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC)
Cannabis use as a risk factor in psychiatry

Cannabis use in adolescence and risk for development of psychosis at age 26 (Dunedin Cohort, Arseneault et al. 2002)

Estimated risk ratio of psychosis by level of cannabis use in original studies (Marconi et al. 2016)
The endocannabinoid system in schizophrenia

Effects of exogenous cannabinoids

- Early and excessive cannabis use as one risk factor in vulnerable persons
- $\Delta^9$-THC acutely induces psychotic symptoms in healthy volunteers
  (Koethe et al. 2009, Sherif et al. 2016)
Influence of $\Delta^9$-THC on psychopathology

- $\Delta^9$-THC induced psychopathological symptoms resembled those of IPS
- Sub-cluster of thought disturbance: HC treated with $\Delta^9$-THC showed comparable score as IPS and SZ patients

HC: Healthy volunteers, HC-THC: Healthy volunteers, 15 mg $\Delta^9$-THC p.o., IPS: Initial prodromal states/At Risk Mental Health Individuals, SZ: Antipsychotic-naïve acute paranoid schizophrenia – (N=16 each) BPRS: Brief Psychiatric Rating Scale

Koethe et al. 2006
The endocannabinoid system in schizophrenia

Effects of exogenous cannabinoids

- Early and excessive cannabis use as one risk factor in vulnerable persons
- Highly psychosis-prone individuals experience more pronounced psychotic-like symptoms after acute cannabis use than healthy controls (Mason et al. 2009)
- $\Delta^9$-THC exacerbates symptoms in schizophrenics (D’Souza et al. 2005)
The endocannabinoid system in schizophrenia

Anandamide in CSF

Risk for IPS patients to transit into psychosis based on CSF anandamide

CB₁-receptor availability in acute schizophrenia in vivo

C: Controls (84) • S-N: Paranoid schizophrenia - Antipsychotic-naïve (47) • S-AT: Schizophrenia – treated with 5HT₂A-D₂-antagonists (34) • S-CT: Schizophrenia – treated with D₂-antagonists (37) • D: Dementia (13) • AD: Affective Disorders (22) • IPS: Initial Prodromal States of psychosis (27)

Schizophrenia - Antipsychotic-naïve
Correlation of CSF anandamide to symptoms (PANSS)

Ceccarini et al. NeuroImage (2013)
The endocannabinoid system in schizophrenia

Model of the antipsychotic action of anandamide

Dopamine

D_{2}-R

Anandamide

Psychotic symptoms

G_{i}CB_{1}-R

Giuffrida et al., 2004
Optimal activity of the endocannabinoid system for maintenance of homeostasis

- GI disease, allergy, schizophrenia, affective disorders, anxiety, epilepsy
- e.g. adiposity, addiction, atherosclerosis

Pathology | normal Physiology | Pathology
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region specific ECS activity
Optimal activity of the endocannabinoid system for maintenance of homeostasis

Stimulation or inhibition of the endocannabinoid system may alleviate the pathology

Courtesy of Beat Lutz
Phytocannabinoids – Potential antipsychotics?

Modulation of endocannabinoid functions
(Bisogno et al. 2001)

Δ⁹-Tetrahydrocannabinol

Cannabidiol
Phytocannabinoids – Potential antipsychotics?

Modulation of endocannabinoid functions
(Bisogno et al. 2001)
Amisulpride vs. cannabidiol in schizophrenia

A proof-of-concept randomized controlled clinical trial in 42 acute schizophrenia patients

Screening up to 7 days

Titration Day 1 to 7

Maintainance - 3 weeks

Cannabidiol
600 to 800 mg/d

+ Lorazepam up to 7.5 mg/d

Amisulpride
600 to 800 mg/d

Switch to Amisulpride

Leweke FM et al., Transl Psychiatry (2012)
Amisulpride vs. cannabidiol in schizophrenia

Changes from baseline determined using Mixed-Effect Model Repeated Measure (MMRM) analysis (N=42)

Side-effect profile

Psychotic Symptoms (PANSS total)

Extrapyramidal symptoms

Weight gain (kg)

Prolactin (µg/l)

Effects of cannabidiol and amisulpride on eicosanoids in serum in schizophrenia

Blockade of the Fatty acid amide hydrolase (FAAH) enzyme

Data show predicted means and standard errors at each week. Statistical significance is calculated between groups († p≤0.05, †† p≤0.01, ††† p≤0.001) and vs. baseline (i.e. 0; * CBD, # AMI; ***/### p≤0.05, **/## p≤0.01, */# p≤0.001).

Leweke FM et al., Transl Psychiatry (2012)
Cannabidiol vs. placebo in schizophrenia

A placebo-controlled randomized cross-over clinical trial
on the antipsychotic properties of cannabidiol

ClinicalTrials.gov Identifier:

NCT00309413
Cannabidiol as adjunctive therapy in schizophrenia or related disorders

A double-blind, randomised, placebo-controlled, parallel group trial of cannabidiol (CBD)

ClinicalTrials.gov Identifier:

NCT02006628

Conclusions

1. Excessive and early use of cannabis or $\Delta^9$-THC in particular is associated with an increased risk to suffer psychosis

2. The endocannabinoid system is deeply involved in the pathophysiology of schizophrenia

3. Cannabinoid receptors and the endocannabinoid anandamide play an important role in controlling and preventing psychotic symptoms

4. Modulation and strengthening of endocannabinoid functioning may result in antipsychotic effects through a completely new mechanism of action
Thank you!

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