Article paru dans « Nature » et Pubmed

Published: ***20 march 2012***

https://www.nature.com/articles/tp201215.

Résumé de l'article

Discussion

Nos résultats prouvent que le cannabidiol, constituant non cannabimimétique de la marijuana, exerce des effets antipsychotiques cliniquement pertinents qui sont associés à une tolérance et une sécurité marquées, par rapport aux médicaments actuels. Bien qu'une pléthore de mécanismes pharmacologiques aient récemment été suggérés comme étant pertinents pour l'effet antipsychotique du cannabidiol(31), le principal mécanisme pharmacologique par lequel le cannabidiol exerce cet effet antipsychotique chez l'homme n'est pas clair à l'heure actuelle. Cependant, l'association significative observée chez les patients traités par le cannabidiol entre l'amélioration des symptômes cliniques et les taux sériques d'anandamide suggère que la capacité du cannabidiol à inhiber l'activité de la FAAH et à améliorer la signalisation intrinsèque de l'anandamide pourrait être un élément fonctionnellement pertinent de ses propriétés antipsychotiques. Bien que seuls les taux sériques d'anandamide aient été évalués dans cette étude par comparaison avec des échantillons de liquide céphalorachidien(13, 32), l'effet systémique du cannabidiol sur l'inhibition des FAAH est très probablement reflété dans ce compartiment. En outre, si les valeurs sériques des endocannabinoïdes se sont révélées moins utiles dans les premiers stades de la schizophrénie, elles ont été signalées comme précieuses dans les cas plus chroniques(33, 34.) Premièrement, dans une cohorte relativement importante de patients schizophrènes n'ayant jamais reçu d'antipsychotiques (n=47), on a constaté que les taux d'anandamide cérébro-spinal étaient inversement corrélés aux symptômes psychotiques(13). Deuxièmement, les sujets à haut risque de

psychose(35) qui présentaient des taux d'anandamide cérébro-spinal plus faibles ont également montré un risque plus élevé de transiter vers une psychose franche(32.) Comme c'est souvent le cas dans ce type d'étude, nous ne pouvons pas exclure que le cannabidiol puisse réduire les symptômes psychotiques par des mécanismes complémentaires ou même alternatifs à l'inhibition des FAAH, y compris les interactions avec les récepteurs de la sérotonine 5-HT1A36 , les récepteurs GPR5537 et les récepteurs vanilloïdes-1 potentiels transitoires (19.)

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Discussion

Our results provide evidence that the non-cannabimimetic constituent of marijuana, cannabidiol, exerts clinically relevant antipsychotic effects that are associated with marked tolerability and safety, when compared with current medications. Although a plethora of pharmacological mechanisms have recently been suggested relevant for the antipsychotic effect of cannabidiol[31] the primary pharmacological mechanism through which cannabidiol exerts this antipsychotic effect in humans is unclear at present. However, the significant association observed in cannabidiol-treated patients between improvement of clinical symptoms and serum anandamide levels suggests that the ability of cannabidiol to inhibit the FAAH activity and enhance intrinsic anandamide signaling might be a functionally relevant component of its antipsychotic properties. Although only serum levels of anandamide were assessed in this study in

comparison with cerebrospinal fluid samples,[13, 32] the systemic effect of cannabidiol on FAAH inhibition is highly likely to be reflected in this compartment. In addition, while serum values of endocannabinoids have been found less useful in early stages of schizophrenia, they have been reported valuable in more chronic cases.[33, 34] Our interpretation is supported by two sets of clinical data. First, in a relatively large cohort of antipsychotic-naïve schizophrenic patients (*n*=47), cerebrospinal anandamide levels were found to be inversely correlated with psychotic symptoms.[13] Second, high-risk subjects for psychosis[35] who exhibited lower cerebrospinal levels of anandamide also showed a higher risk for transiting to frank psychosis.[32] As is often the case in this type of study, we cannot exclude that cannabidiol may reduce psychotic symptoms through complementary or even alternative mechanisms to FAAH inhibition, including interactions with serotonin 5-HT_{1A} receptors,[36] GPR55 receptors[37] and transient receptor potential vanilloid-1 receptors.[19] Nevertheless, our results do provide a rationale for additional clinical testing of selective FAAH inhibitors in schizophrenia.

References

1. 1

   Rogers DP, Goldsmith CA . Treatment of schizophrenia in the 21st century: beyond the neurotransmitter hypothesis. *Expert Rev Neurother* 2009; **9**: 47–54.

   Article PubMed Google Scholar

2. 2

   Piomelli D . The molecular logic of endocannabinoid signalling. *Nat Rev Neurosci* 2003; **4**: 873–884.

   CAS Article PubMed Google Scholar

3. 3

Leweke FM, Schneider U, Thies M, Münte TF, Emrich HM . Effects of synthetic Δ^9-tetrahydrocannabinol on binocular depth inversion of natural and artificial objects in man. *Psychopharmacology* 1999; **142**: 230–235.

CAS Article PubMed Google Scholar

4. 4

D'Souza CD, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu Y-T *et al*. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology* 2004; **29**: 1558–1572.

Article PubMed Google Scholar

5. 5

Morrison PD, Nottage J, Stone JM, Bhattacharyya S, Tunstall N, Brenneisen R *et al*. Disruption of frontal theta coherence by Delta(9)-tetrahydrocannabinol is associated with positive psychotic symptoms. *Neuropsychopharmacology* 2011; **36**: 827–836.

CAS Article PubMed Google Scholar

6. 6

D'Souza DC, Abi-Saab WM, Madonick S, Forselius-Bielen K, Doersch A, Braley G *et al*. Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biol Psychiatry* 2005; **57**: 594–608.

Article PubMed Google Scholar

7. 7

Henquet C, van Os J, Kuepper R, Delespaul P, Smits M, Campo JA *et al*. Psychosis reactivity to cannabis use in daily life: an experience sampling study. *Br J Psychiatry* 2010; **196**: 447–453.

Article PubMed Google Scholar

8. 8

Scatton B, Sanger DJ . Pharmacological and molecular targets in the search for novel antipsychotics. *Behav Pharmacol* 2000; **11**: 243–256.

CAS Article PubMed Google Scholar

9. 9

Eggan SM, Hashimoto T, Lewis DA . Reduced cortical cannabinoid 1 receptor messenger RNA and protein expression in schizophrenia. *Arch Gen Psychiatry* 2008; **65**: 772–784.

Article PubMed PubMed Central Google Scholar

10.10

Meltzer HY, Arvanitis L, Bauer D, Rein W . Placebo-controlled evaluation of four novel compounds for the treatment of schizophrenia and schizoaffective disorder. *Am J Psychiatry* 2004; **161**: 975–984.

Article PubMed Google Scholar

11.11

Sanofi-Aventis. Efficacy and safety of AVE1625 as a co-treatment with antipsychotic therapy in schizophrenia (CONNECT). ClinicalTrials gov, May 11 2010; edn, vol. NCT00439634. US National Institute of Health, 2010.

12.12

Leweke FM, Giuffrida A, Wurster U, Emrich HM, Piomelli D . Elevated endogenous cannabinoids in schizophrenia. *Neuroreport* 1999; **10**: 1665–1669.

CAS Article Google Scholar

13.13

Giuffrida A, Leweke FM, Gerth CW, Schreiber D, Koethe D, Faulhaber J *et al*. Cerebrospinal anandamide levels are elevated in acute schizophrenia and are inversely correlated with psychotic symptoms. *Neuropsychopharmacology* 2004; **29**: 2108–2114.

CAS Article PubMed Google Scholar

14.14

Di Marzo V, Petrosino S . Endocannabinoids and the regulation of their levels in health and disease. *Curr Opin Lipidol* 2007; **18**: 129–140.

CAS Article PubMed Google Scholar

15.15

Beltramo M, de Fonseca FR, Navarro M, Calignano A, Gorriti MA, Grammatikopoulos G *et al*. Reversal of dopamine D(2) receptor responses by an anandamide transport inhibitor. *J Neurosci* 2000; **20**: 3401–3407.

CAS Article PubMed Google Scholar

16.16

Seillier A, Advani T, Cassano T, Hensler JG, Giuffrida A . Inhibition of fatty-acid amide hydrolase and CB1 receptor antagonism differentially affect behavioural responses in normal and PCP-treated rats. *Int J Neuropsychopharmacol* 2010; **13**: 373–386.

CAS Article PubMed Google Scholar

17.17

Petitet F, Jeantaud B, Reibaud M, Imperato A, Dubroeucq M-C . Complex pharmacology of natural cannabinoids: evidence for partial agonist activity of delta-9-tetrahydrocannabinol and antagonist activity of cannabidiol on rat brain cannabinoid receptors. *Life Sci* 1998; **63**: PL1–PL6.

CAS Article PubMed Google Scholar

18.18

Thomas A, Baillie GL, Phillips AM, Razdan RK, Ross RA, Pertwee RG . Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists *in vitro*. *Br J Pharmacol* 2007; **150**: 613–623.

CAS Article PubMed PubMed Central Google Scholar

19.19

Bisogno T, Hanus L, De Petrocellis L, Tchilibon S, Ponde DE, Brandi I *et al*. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br J Pharmacol* 2001; **134**: 845–852.

CAS Article PubMed PubMed Central Google Scholar

20.20

Zuardi AW, Morais SL, Guimarães FS, Mechoulam R . Antipsychotic effect of cannabidiol. *J Clin Psychiatry* 1995; **56**: 485–486.

CAS PubMed Google Scholar

21.21

Zuardi AW, Hallak JE, Dursun SM, Morais SL, Faria Sanches R, Musty RE *et al*. Cannabidiol monotherapy for treatment-resistant schizophrenia. *J Psychopharmacol* 2006; **20**: 683–686.

CAS Article PubMed Google Scholar

22.22

Leweke FM, Schneider U, Radwan M, Schmidt E, Emrich HM . Different effects of nabilone and cannabidiol on binocular depth inversion in man. *Pharmacol Biochem Behav* 2000; **66**: 175–181.

CAS Article PubMed Google Scholar

23.23

Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T *et al*. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology* 2010; **35**: 764–774.

CAS Article Google Scholar

24.24

Schreiber D, Harlfinger S, Nolden BM, Gerth CW, Schömig E, Klosterkötter J *et al*. Determination of anandamide and other fatty acylethanolamides in human serum by electrospray tandem mass spectrometry. *Anal Biochem* 2007; **361**: 162–168.

CAS Article PubMed Google Scholar

25.25

Giuffrida A, Rodriguez de Fonseca F, Piomelli D . Quantification of bioactive acylethanolamides in rat plasma by electrospray mass spectrometry. *Anal Biochem* 2000; **280**: 87–93.

CAS Article PubMed Google Scholar

26.26

Danion JM, Rein W, Fleurot O . Improvement of schizophrenic patients with primary negative symptoms treated with amisulpride. Amisulpride Study Group. *Am J Psychiatry* 1999; **156**: 610–616.

CAS PubMed Google Scholar

27.27

Hauschke D, Kieser M . Multiple testing to establish noninferiority of k treatments with a reference based on the ratio of two means. *Drug Inf J* 2001; **35**: 1247–1251.

Article Google Scholar

28.28

van Os J, Burns T, Cavallaro R, Leucht S, Peuskens J, Helldin L *et al*. Standardized remission criteria in schizophrenia. *Acta Psychiatr Scand* 2006; **113**: 91–95.

CAS Article PubMed Google Scholar

29.29

Committee for proprietary medicinal products (CPMP). Note for guidance on the clinical investigation of medicinal products in the treatment of schizophrenia. February 26 1998; CPMP/EWP/559/95, The European Agency for the Evaluation of Medicinal Products, London, 1998.

30.30

Leucht S, Pitschel-Walz G, Engel RR, Kissling W . Amisulpride, an unusual ‘atypical’ antipsychotic: a meta-analysis of randomized controlled trials. *Am J Psychiatry* 2002; **159**: 180–190.

Article PubMed Google Scholar

31.31

Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R . Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends Pharmacol Sci* 2009; **30**: 515–527.

CAS Article PubMed Google Scholar

32.32

Koethe D, Giuffrida A, Schreiber D, Hellmich M, Schultze-Lutter F, Ruhrmann S *et al*. Anandamide elevation in cerebrospinal fluid in initial prodromal states of psychosis. *Br J Psychiatry* 2009; **194**: 371–372.

Article PubMed Google Scholar

33.33

Potvin S, Kouassi E, Lipp O, Bouchard RH, Roy MA, Demers MF *et al*. Endogenous cannabinoids in patients with schizophrenia and substance use disorder during quetiapine therapy. *J Psychopharmacol* 2008; **22**: 262–269.

CAS Article PubMed Google Scholar

34.34

De Marchi N, De Petrocellis L, Orlando P, Daniele F, Fezza F, Di Marzo V . Endocannabinoid signalling in the blood of patients with schizophrenia. *Lipids Health Dis* 2003; **2**: 5–13.

Article PubMed PubMed Central Google Scholar

35.35

Ruhrmann S, Schultze-Lutter F, Salokangas RK, Heinimaa M, Linszen D, Dingemans P *et al*. Prediction of psychosis in adolescents and young adults at high risk: results from the prospective European prediction of psychosis study. *Arch Gen Psychiatry* 2010; **67**: 241–251.

Article PubMed Google Scholar

36.36

Russo E, Burnett A, Hall B, Parker K . Agonistic properties of cannabidiol at 5-HT1a receptors. *Neurochem Res* 2005; **30**: 1037–1043.

CAS Article PubMed Google Scholar

37.37

Ryberg E, Larsson N, Sjogren S, Hjorth S, Hermansson NO, Leonova J *et al*. The orphan receptor GPR55 is a novel cannabinoid receptor. *Br J Pharmacol* 2007; **152**: 1092–1101.

CAS Article PubMed PubMed Central Google Scholar

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Acknowledgements

This study was supported by grants from the Stanley Medical Research Institute (FML) and the National Institute on Drug Abuse (DP). The funding sources had no influence on the design of the study or the analysis and interpretation of the results. We acknowledge the contribution of Drs

Frauke Schultze-Lutter and Stephan Ruhrmann to the protocol and design and of Drs Christian Mauss, Brit M Nolden, Tobias Buzello, Miriam A Neatby and Anita Haensel to the execution of the clinical part of this study. We are also grateful to Prof Andrea Giuffrida for his fruitful input during the course of this study.

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Ethics declarations

Competing interests

The authors declare no conflict of interest.