The serotonergic hallucinogen 5-Methoxy-N,N-dimethyltriptamine (5-MeO-DMT) disrupts cortical function. Reversal by antipsychotic drugs.

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INTRODUCTION

5-MeO-DMT (component of *Ayahuasca*, an Amazonian beverage) is a natural indoleamine hallucinogen with non-selective serotonin 5-HT_{1A}/5-HT_{2A} receptor agonist properties. Its ability to cause physiological and behavioural changes such as hallucinations can be used to study the neurobiological basis of psychotic symptoms in schizophrenia. We previously reported that other psychotomimetic agents (the non-competitive NMDA-R antagonist phencyclidine –PCP- and the 5-$HT_{2A/2C}$ agonist –DOI-) markedly reduce low frequency cortical oscillations (LFCO; <4Hz) in rodent prefrontal cortex (PFC), an effect reversed by antipsychotic drugs (1,2,3). Likewise, behavioural studies showed that the effect of 5-MeO-DMT on locomotor activity depends on the activation of 5-HT_{1A} receptors (4,5). Here we examined the effect of 5-MeO-DMT on cortical activity in rodents and the potential reversal of its action by antipsychotic drugs.

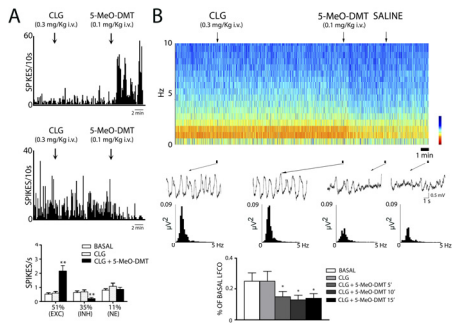
AIMS

- To examine the effect of the hallucinogen 5-MeO-DMT on mPFC activity (Low frequency cortical oscillations –LFCO- and pyramidal discharge).
- To examine the 5-HT receptors potentially involved (5-HT_{1A} and 5-HT_{2A}) in 5-MeO-DMT effects using selective antagonists and 5-HT_{2A} receptor knockout mice (KO2A).
- To examine the action of 5-MeO-DMT on monoamine release (DA and 5-HT) in mPFC in WT and KO2A mice in parallel to behavior changes.
- To examine the potential reversal of 5-MeO-DMT by marketed antipsychotic drugs (*Haloperidol*, non-selective D_2-R antagonist; *Risperidone* non-selective 5-HT_{2A} > D_2-R antagonist; *Clozapine,* non-selective 5-HT_{2A} antagonist) and by the mGlu2/3 receptor agonist (LY379268)
- To examine brain areas involved using blood-oxygen level dependent (BOLD) functional magnetic resonance (fMRI).
- To examine the effect of 5-MeO-DMT in cortical areas potentially involved in hallucinations (somatosensory, auditory and visual primary cortices; S1, Au1 and V1 respectively)

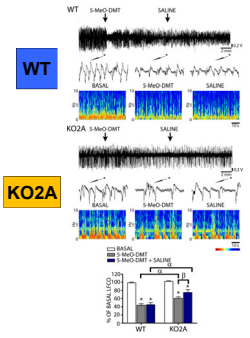
RESULTS

How does 5-MeO-DMT act?

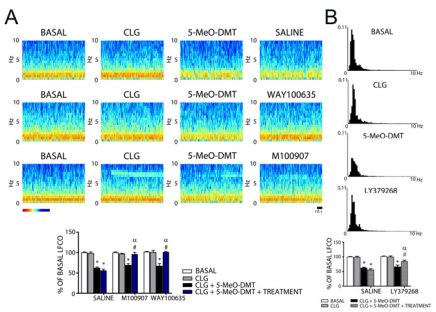
5-MeO-DMT, in combination with clorgyline, reduces LFCO and altered pyramidal discarge producing and overall activation of rat mPFC



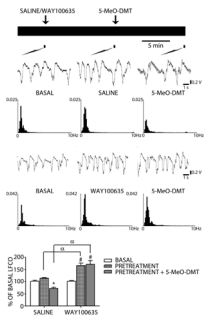
5-MeO-DMT reduces LFCO in mPFC differently in WT and KO2A mice



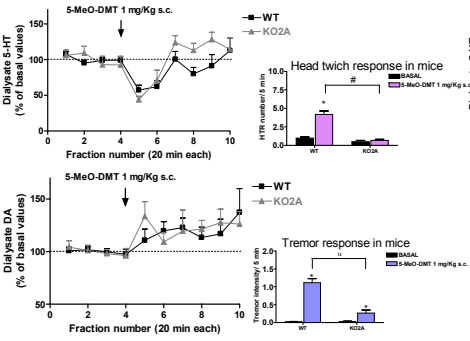
Reversal by selective serotonin receptor antagonists and the mGlu2/3 receptor agonist LY379268 in rat



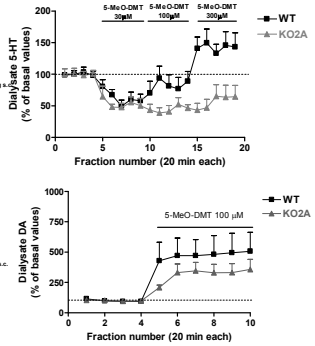
Antagonism by WAY100635 in KO2A mice



5-MeO-DMT ↑ DA and ↓ 5-HT release in mPFC via 5-HT_{1A}-R. In parallel, 5-MeO-DMT induces stereotypes in WT and but not (or less) in KO2A mice

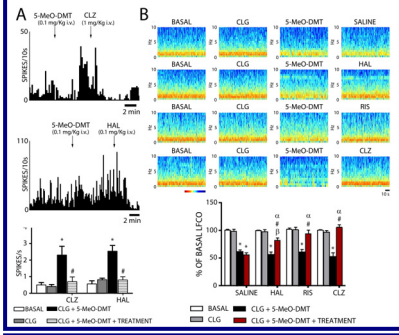


Local perfusion of 5-MeO-DMT alters mPFC 5-HT release via 5-$HT_{1A/2A}$–R and DA release via 5-HT_{1A}-R

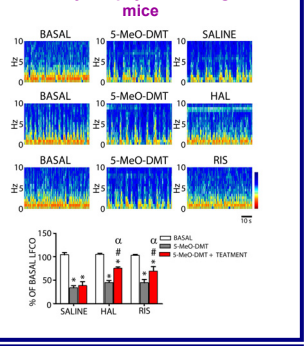


5-MeO-DMT disrupts LFCO in mPFC

Reversal by antipsychotic drugs in rat

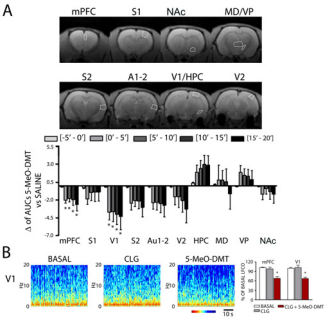


Reversal by antipsychotic drugs in WT mice

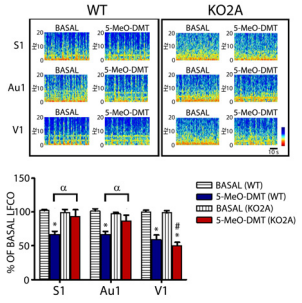


Where does 5-MeO-DMT act?

5-MeO-DMT, in combination with clorgyline, alters BOLD responses in rat mPFC and primary visual cortex



5-MeO-DMT alters LFCO in S1, Au1 and V1 in WT and in V1 only in KO2A mice



Materials and Methods

Animals: Male albino Wistar rats (250-300 g) and male C57BL/6 WT and KO2A mice (9-15 weeks).

Anesthesia: Chloral hydrate: 400 mg/kg i.p, Perfusion pump: 50-70 mg/Kg/h i.p (Electrophysiology and fMRI); Pentobarbital Sodium: 40 mg/Kg i.p. (Intracerebral microdialysis *in vivo*)

Electrophysiological recordings: *Single unit extracellular recording of pyramidal neurons* in mPFC identified by antidromic estimulation from ventral tegmental area; *Local field potential (LFP)* in mPFC and *Epidural Electrocorticogram (ECoG)* in S1, Au1 and V1.

fMRI: were conducted on the IDIBAPS Experimental MRI Unit; 7.0 T BioSpec 70/30 horizontal animal scanner (Bruker BioSpin, Ettlingen, Germany), equipped with a 12 cm inner diameter actively shielded gradient system (400 mT/m). TurboRARE images covering the whole brain were continuosly acquired during 50 min (20 min before and 30 min after drug administration).

Intracerebral microdialysis *in vivo*: Implant of probes in mPFC in anesthetized mice and 24 h later evaluation of 5-HT and DA release in freely moving mice.

Behaviour: Stereotypes associated to 5-HT_{1A}/5-HT_{2A} receptor activation (tremor and head twich response –HTR- , respectively), recorded during microdialysis experiments involving 5-MeO-DMT administration.

Drugs: Drugs were administered i.v. (Electrophysiology and fMRI in rats); s.c. (Electrophysiology and Microdialysis in mice) or locally (intra-mPFC; Microdialysis in mice): 5-MeO-DMT (0.1 or 1 mg/Kg and 30-100-300 µM in LCR+Citalopram 1µM for 5-HT and LCR+Nomifensine 10 µM for DA); Clorgyline (CLG, MAO-A inhibitor; 0.3 mg/Kg); Haloperidol (HAL, 0.1-0.2 or 0.6 mg/Kg); Risperidone (RIS, 0.2 or 1 mg/Kg); Clozapine (1 mg/Kg) WAY100635 (50-100 µg/Kg or 0.5 mg/Kg); M100907 (0.3 mg/Kg); LY379268 (LY, 0.5-1.5 mg/Kg)

Analysis: Firing rate (spikes/second) and LFCO (power spectra; values from 0.15-4Hz); fMRI (Δ of AUCs between 5-MeO-DMT and SALINE); Microdialysis (HPLC with electrochemical detection); Stereotypes (HTR: counts5 min during 20 min; Tremor: intensity/5 min during 20 min, scale 0-2; 0=absent; 1=periodic; 2= continuous)

Statistical analysis: one or two-way ANOVA following Newman-Keuls multiple comparison test. Statistical significance has been set at the 95% confidence level (two-tailed)

SUMMARY

✓The natural hallucinogen 5-MeO-DMT (0.1 mg/Kg i.v.), in combination with clorgyline, altered pyramidal discharge (increasing and decreasing de activity of 51% and 35% of the recorded neurons, respectively) and concurrently reduced LFCO (to 64±2% of basal values) in rat mPFC.

✓5-MeO-DMT (1 mg/kg s.c.) reduced LFCO in mPFC differently in WT (to ~45% of basal values) and KO2A (transiently to ~75% of basal values) mice

✓The reduction in LFCO induced by 5-MeO-DMT in rat mPFC is reversed by WAY100635 (5-HT_{1A} receptor antagonist) and M100907 (5-HT_{2A} receptor antagonist). Likewise, WAY100635, prevented the reduction in LFCO in KO2A mice.

✓Subcutaneous administration of 5-MeO-DMT (1 mg/Kg) altered monoaminergic neurochemistry in mPFC via 5-HT_{1A}-R in mice.

✓Local perfusion of 5-MeO-DMT (100-300 µM) altered 5-HT release in mPFC via 5-$HT_{1A/2A}$ -R in mice. The dose of 100 µM altered DA release in mPFC via 5-HT_{1A}-R

✓5-MeO-DMT (1 mg/Kg s.c.) induced Head twitch response in WT but not in KO2A mice and tremor differenty in WT and KO2A mice.

✓The subsequent administration of the antipsychotics haloperidol, risperidone and clozapine reversed 5-MeO-DMT effects on mPFC activity in rats and WT mice

✓5-MeODMT (0.1 mg/Kg i.v.) in combination with clorgyline, produced negative BOLD responses in visual and medial prefrontal cortices

✓5-MeO-DMT also altered LFCO in somatosensory, auditive and visual primary cortices in WT mice and in visual primary cortex in KO2A mice.

CONCLUSIONS

Together with previous findings (1-3), the present results indicate that reductions in LFCO are a common neurophysiological signature of hallucinogens. The reversal of these effects by antipsychotic drugs with different mechanisms of action suggests a clear association with their therapeutic activity, regardless of their initial pharmacological target. This supports the usefulness of the LFCO model in PFC to examine the neurobiological basis of hallucinations and in target identification during antipsychotic drug development.

Moreover the present results point to the prefrontal and sensorial cortical areas as sites of action of this hallucinogen and suggest the involvement of 5-HT_{1A} receptors in the action of indoleamine hallucinogens, in addition to their well-known action on 5-HT_{2A} receptors.

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SUPPORT

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Authors declare no conflict of interest