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The role of the serotonin 2A receptor in the fabric and modulation of personal meaning in LSD-induced states

Katrin H. Preller, Marcus Herdener, Thomas Pokorny, Amanda Planzer, Rainer Kraehenmann, Philipp Stämpfli, Matthias Liechti, Erich Seifritz, Franz X. Vollenweider

1Department of Psychiatry, Psychotherapy and Psychosomatics, University Hospital for Psychiatry Zurich, Zurich, Switzerland
2Department of Biomedicine and Department of Clinical Research, University Hospital Basel, Basel, Switzerland

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Introduction

- Abnormalities in the attribution of personal relevance to stimuli are critical features of many psychiatric disorders [1].
- The neuropharmacological substrates enabling meaningful and personally relevant experiences are largely unknown.
- Lysergic acid diethylamide (LSD) is a prototypical hallucinogen which has high affinity at serotonin (5-HT) and dopamine receptors (R) and increases the sense of meaning of objects [2].
- Ketanserin is a selective 5-HT2AR antagonist.

Objective

To investigate the role of the 5-HT2AR system in personal meaning attribution by applying pharmacological functional brain imaging using LSD with and without pre-treatment with ketanserin.

Methods

Design: Double-blind, randomized, cross-over, placebo-controlled

Drugs: Placebo + Placebo (Pla), Placebo + LSD (100µg) (LSD), Ketanserin (40mg) + LSD (100µg) (Ket+LSD)

Task: 20s of music followed by a rating and a jittered IT

Participants: 22 healthy volunteers

Dependent variables: FMRI: BOLD contrast, Meaningfulness Ratings, Altered States of Consciousness Questionnaire

Statistics: General Linear Model as implemented in SPM12, Repeated-measures Analyses of Variance

Results Subjective Drug Effects

- LSD increased ratings on all 5D-ASC scales compared to Pla and Ket+LSD (all p<0.05) (Fig. 1).
- Placebo + Placebo (Pla) and Ketanserin + LSD (Ket+LSD) scores did not differ.
- LSD increased ratings on all 5D-ASC scales compared to Pla and Ket+LSD (all p<0.05) (Fig. 1).

Results FMRI

Meaningful music compared to neutral and meaningless music was associated with increased BOLD signal in medial and lateral frontal brain areas in the LSD condition compared to both Pla and Ket+LSD conditions (all p<0.05, FWE corrected, Fig. 3 & 4).

Conclusion and implication

- LSD increased the attribution of personal relevance to previously meaningless stimuli.
- This effect appears to be attributable to 5-HT2AR stimulation.
- LSD-induced effects were blocked by 5-HT2AR antagonism.
- The current results emphasize the pivotal role of the 5-HT2AR in the generation of personal meaning in medial and lateral frontal brains structures implicated in self-referential processes.

These findings may be relevant for increasing our understanding of the biochemical underpinnings of personal meaning processing and may reveal prospective targets in the treatment of psychiatric illnesses characterized by alterations in meaning attribution.

References:


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