Active and passive MDMA ("ecstasy") intake induces differential transcriptional changes in the mouse brain

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Introduction

3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") is a popular drug among adolescents and young adults. The repeated administration of MDMA in humans produces long-term psychiatric disorders, including anxiety and mood alterations, as well as cognitive deficits, which may be associated with persistent neuroadaptations dependent on changes in gene expression. These neuroadaptations are modulated by additional factors, such as reward predictability, and motivational aspects that can only be assessed using active drug self-administration, and thus are different from those induced by the drug itself.

Aim

To dissociate, at a transcriptomic level in the mouse brain, the neuroadaptative changes involved in learning to self-administer MDMA from those produced by the direct effect of the drug. The only similar studies to date used passive MDMA administration.

Methods

Yoked-control operant paradigm: an animal that is self-administering the drug through active responding in an operant situation, causes another subject, a yoked animal, to receive the same dose of the drug or saline passively.

The Yoked Control-Operant Paradigm

Followed by microarray expression analysis: transcriptomic profiles of the ventral striatum, frontal cortex, dorsal raphe and hippocampus were analyzed in 27 mice after 11 days of either active MDMA, yoked MDMA or yoked saline administration. The observed changes were validated by quantitative RT-PCR.

Results

Active and Passive intravenous MDMA administration

Microarray expression analysis

Volcanoplots of the MDMA comparison showing the significance (logOdds) and the Log Fold Change. Significance threshold (FDR < 5%) is represented by a horizontal red line.

Discussion/Conclusions

Active and passive MDMA administration induces a different gene expression profile in brain areas involved in the reward circuit.

MDMA exposure induces a strong direct effect on the expression of genes related to immune, inflammatory and response to stress functions, which underpin the potential neurotoxic effects of this drug.

Active, but not passive, MDMA administration produces changes in the expression of genes related to learning and memory processes in the hippocampus and dorsal raphe nucleus. While changes in the hippocampus were subtle, we identified specific gene expression changes in the dorsal raphe nucleus, an area recently shown to be involved in reward related learning [1].

References


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