

SHORT- AND LONG-TERM NICOTINE WITHDRAWAL EFFECTS ON BEHAVIOUR AND REWARDING PROPERTIES OF METHYLENE-DIOXYMETHAMPHETAMINE (MDMA) IN ZEBRAFISH

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Introduction: The term “gateway” is used to describe a sequential progression in the use of addictive substances from tobacco and alcohol to cannabis and to other illicit drugs. One of the most reported gateway effect is tobacco smoking that usually precedes the use of marijuana, which precedes the use of cocaine, metamphetamine and heroin. Phenethylamines have psychoactive and stimulant effects. However, if nicotine produces a gateway effect on amphetamine derivatives is still unknown. The main aim of the present study was to describe short- and long-term behavioral alterations induced by chronic nicotine exposure (for 15 days) and to evaluate them during withdrawal. In particular, emotional-like behaviour (anxiety and depression), memory profile (attention) and rewarding properties of MDMA at different intervals (from 2 to 60 days) after nicotine cessation, were investigated. To verify nicotine dependence in zebrafish, immediately after nicotine cessation the expression of different nicotinic receptor subtypes was also investigated in the whole brain.

Materials and methods: Different groups of zebrafish were exposed to nicotine (1 mg/L) dissolved in tank water for 2 weeks and at different intervals from withdrawal (2, 7, 30 and 60 days) were submitted to Novel diving test, to evaluate anxiety-like behaviour, to the Compartment Preference test, to investigate depressive-like behaviour, to the Virtual Object Recognition, to study attentional memory, and to the Conditioned Place Preference (CPP) with a subthreshold dose of MDMA (0.1 mg/kg/i.m.) to evaluate the sensitivity to the rewarding properties. Molecular changes were also evaluated (using qPCR) immediately after CPP test in the whole brain.

Results: Zebrafish previously exposed to nicotine showed a greater sensitivity to MDMA compared to control group at all the tested intervals in the CPP test. qPCR analysis revealed a slight increase in the transcriptional factor expression cFos, together with an increase in dopamine type 3 and 5-HTA receptor expression, 30 and 60 days after nicotine cessation. During spontaneous withdrawal zebrafish showed an anxiety-like behaviour, in terms of decreased time spent in the top of the tank water, reduced motivation, in terms of decreased time spent in the enriched compartment and attentional memory deficit, in terms of decreased discrimination index.

Discussions and conclusions: This project allowed to characterize, for the first time, the nicotine withdrawal syndrome in zebrafish, to elucidate the molecular mechanisms of nicotine withdrawal and to demonstrate that nicotine acts as gateway on psychostimulant drugs.