

## PROSOCIAL AND ANXIOLYTIC EFFECT OF TWO SYNTHETIC PHENETHYLAMINES IN ZEBRAFISH: ROLE OF 5-HT2A/C SUBTYPE RECEPTORS

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The synthetic phenethylamines are recreational drugs known to produce psychostimulant effects. However, most of them are not yet completely controlled by international drug conventions, and may pose a public health threat. Among them, 2,5-dimethoxy-4-bromo-amphetamine hydrobromide (DOB) and para-methoxyamphetamine (PMA) are two phenethylamines frequently found in drug tablets (UNODC 2015), sold openly through websites on the internet and associated with significant hallucination activity and toxicity (Nichols 2004, 2016; Balíková, 2005; Lawn et al., 2014; Liechti, 2015; Jang et al., 2016). Recently, aquatic models have been recognized as useful models to test the toxicity of addictive drugs and to evaluate their potential clinical applications (Neelkantan et al., 2013; Kyzar et al., 2016).

Thus, the aim of our work was to investigate the effect on reward, social preference and anxiety-like behaviour of DOB and PMA, compared with the classical phenethylamine 3,4-methylenedioxymethamphetamine (MDMA). In addition, the role of serotonin 5-HT2A/C like-receptors on the above mentioned effects was evaluated. We used zebrafish, an emerging animal model useful to study the rewarding properties and the emotional-like behaviour induced by drugs in an inexpensive and quick manner (Braida et al., 2007).

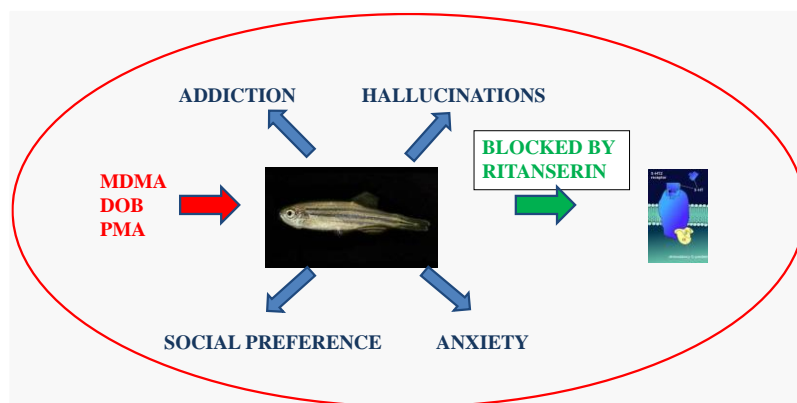


Figure A

Zebrafish were submitted to the schedule reported in Fig. A. They were treated i.m. with a wide range of doses of DOB (0.05-20 mg/kg), PMA (0.0005-2 mg/kg) or MDMA (0.25-160 mg/kg). Animals were submitted to a conditioned place preference (CPP) task for the rewarding properties, to a social preference task to evaluate social behaviour, and to the novel tank diving and light-dark tests to study emotional behaviour. Hallucinatory behaviour was evaluated in terms of appearance of a trance-like effect. The serotonin 5-HT2A/C subtype receptor antagonist

ritanserin (0.025-2.5 mg/kg/i.m.) was given in association with the maximal effective dose of MDMA, DOB and PMA.

MDMA and its derivatives exhibited dose-dependent CPP, anxiolytic effect and an increase in social preference following a biphasic trend, being PMA the most potent. These effects were accompanied, for DOB (2 mg/kg) and PMA (0.1 mg/kg), by a trance-like hallucinatory behaviour. MDMA, at a high dose as 160 mg/kg, did not induce any hallucinatory behaviour. Ritanserin significantly blocked all the effects, suggesting the involvement of serotonin 5-HT<sub>2A/C</sub> like subtype receptors.

In summary, the current study demonstrated in zebrafish a prosocial and anxiolytic effect of DOB and PMA in comparison to MDMA and focused on the mechanisms of their action by means of the serotonergic-like system, through 5-HT<sub>2A/C</sub> serotonin receptors, suggesting a potential clinical application.

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