EFFECTS OF SEROTONIN (5-HT)$_{1B}$ RECEPTOR LIGANDS ON AMPHETAMINE-SEEKING BEHAVIOR IN RATS

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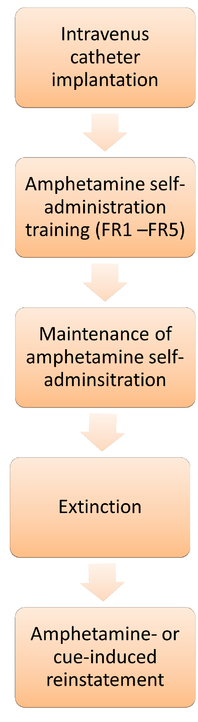
INTRODUCTION

It is well-established that the reinforcing effects produced by psychostymulant drugs are dependent on their ability to increase dopamine concentrations in mesocorticolimbic system. However, the important role of the serotonin system, especially the 5-HT$_{1B}$ receptor subtype, in modulating the dopamine-dependent behavioral responses cannot be omitted [Miszkiel et al. 2011]. In contrast to cocaine, there is still little known about involvement of those receptors in amphetamine addiction. Up to date, it was proven, that whereas tonic activation of the 5-HT$_{1B}$ receptor was not engaged in the rewarding properties of either psychostymulant [Przegaliński et al 2007; Miszkiel et al. 2012], the pharmacologic stimulation of those receptor enhanced the rewarding activity of cocaine [Przegaliński et al. 2007] but not amphetamine [Miszkiel et al. 2012].

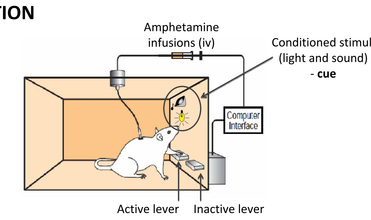
AIM

The aim of the present study was to evaluate the role of 5-HT$_{1B}$ receptors and their pharmacological stimulation on the reinstatement of extinguished seeking behavior induced by amphetamine or amphetamine-associated cue. To achieve that we employed the extinction/reinstatement model in intravenous self-administration in rats and the 5-HT$_{1B}$ receptor agonist (CP 94253) and antagonists (SB 216641).

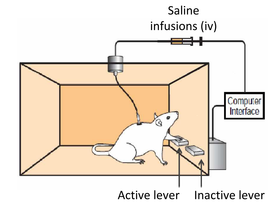
METHODS



AQUISITION AND MAINTENANCE OF THE AMPHETAMINE SELF-ADMINISTRATION

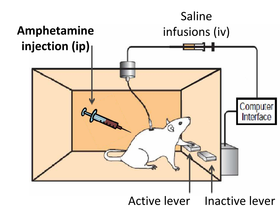


EXTINCTION

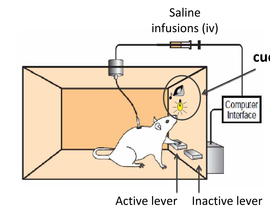


REINSTATEMENT OF AMPHETAMINE SEEKIENG BEHAVIOR

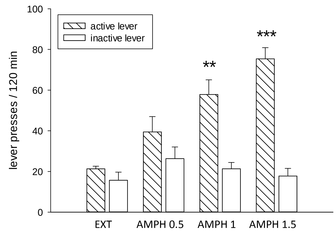
Amphetamine-induced reinstatement



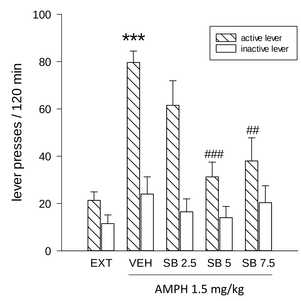
Cue-induced reinstatement



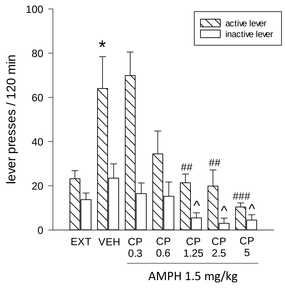
AMPHETAMINE-INDUCED REINSTATEMENT

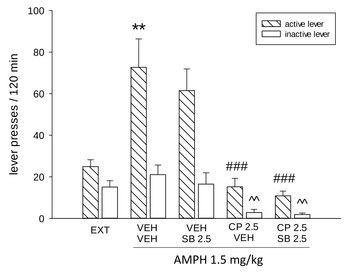


Amphetamine administered in a dose 1 and 1.5 mg/kg (i.p.) evoked the reinstatement of amphetamine seeking behavior, expressed as an increased number of active (but not inactive) lever presses.



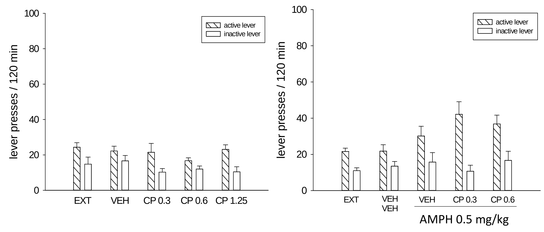
SB 216641 (5 - 7.5 mg/kg, i.p.) attenuated the amphetamine-induced amphetamine seeking behaviour, reducing only the number of active lever presses.





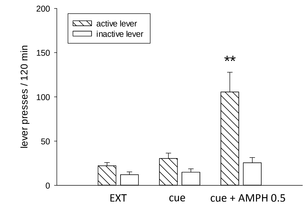
CP 94253 (1.25 - 5 mg/kg, i.p.) attenuated the amphetamine-induced amphetamine seeking behaviour, reducing the number of active but also inactive lever presses. Observed effect was not blocked by SB 216641.

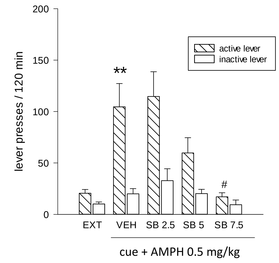
CP 94253 (0.3 – 1.25 mg/kg, i.p.) did not evoked the amphetamine seeking behaviour.
CP 94253 (0.3 – 0.6 mg/kg, i.p.) did not enhance the rewarding properties of threshold dose of amphetamine (0.5 mg/kg i.p.)



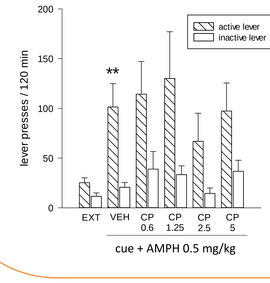
CUE COMBINED WITH THRESHOLD DOSE OF AMPHETAMINE-INDUCED REINSTATEMENT

Animals showed no response to cue-induced reinstatement, however, when the cue was combined with threshold dose of amphetamine rats exhibited the amphetamine seeking behaviour.





SB 216641 (7.5 mg/kg, i.p.) attenuated the cue combined with threshold dose of amphetamine-induced amphetamine seeking behaviour (decreasing the number of active lever presses).



CP 94253 (0.6 – 5 mg/kg, i.p.) had no effect on cue combined with threshold dose of amphetamine-induced amphetamine seeking behaviour.

CONCLUSIONS

Our findings indicate that 5HT$_{1B}$ receptors antagonists may be considered as a potential therapeutic strategy for amphetamine dependence, particularly preventing amphetamine craving.

REFERENCES
Miszkiel, J., Filip, M., Przegaliński, E. 2011. Role of serotonin (5-HT)1B receptors in psychostimulant addiction. Pharmacol Rep. 63, 1310-1315.
Miszkiel, J., Adamczyk, P., Filip, M., Przegaliński, E., 2012. The effect of serotonin 5HT$_{1B}$ receptor ligands on amphetamine self-administration in rats. Eur J Pharmacol. 677, 111-115.
Przegaliński, E., Gołda, A., Frankowska, M., Zaniewska, M., Filip, M., 2007. Effects of serotonin 5-HT$_{1B}$ receptor ligands on the cocaine- and food-maintained self-administration in rats. Eur. J. Pharmacol. 559, 16

STATISTICAL ANALISES
Data were analyzed by t-Student test or by one- or two-way analysis of variance followed by Dunnett or Newman-Keuls tests.

*p<0.05; **p<0.01; ***p<0.001vs respective EXT;
#p<0.05; ##p<0.01; ###p<0.001 vs respective VEH;
^p<0.05; ^^p<0.01 vs respective VEH.

DISCLOSURE
This study was supported by grant no. N N401 050836 from the Ministry of Science and Higher Education (Warszawa, Poland). Conflict of interest: None.