Niello *et al.: Intrinsic Activity*, 2018; **6**(Suppl.1):A3.2
doi:10.25006/IA.6.S1-A3.2
published online: 20 September 2018

24th Scientific Symposium of the Austrian Pharmacological Society

Graz, 27–28 September 2018

MEETING ABSTRACT

A3.2

para-Substituted methcathinones as selective and unselective inhibitors of human dopamine and serotonin transporter

Marco NIELLO[1], Daniela CINTULOVÁ[2], Eva HELLSBERG[3], Kathrin JÄNTSCH[1], Marion HOLY[1], Oliver KUDLACEK[1], Nicolas V. COZZI[4], Michael H. BAUMANN[5], Marko D. MIHOVILOVIC[2], Gerhard ECKER[3] and Harald H. SITTE[1,*]

[1]Department of Pharmacology, Medical University of Vienna, Austria; [2]Institute of Applied Synthetic Chemistry, TU Wien, Vienna, Austria; [3]Department of Pharmacology, University of Vienna, Austria; [4]Department of Cell and Regenerative Biology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; [5]Designer Drug Research Unit, National Institute on Drug Abuse (NIDA), Baltimore, MD, USA

Background: Methcathinone (MCAT) is a compound belonging to the class of cathinones and it is targeting monoamine transporters including DAT and SERT. Despite the importance of DAT and SERT as drug targets in several neurological disorders, the key factors underlying the selectivity profile of their inhibitors is still poorly understood. Recent findings from rat synaptosomes suggested that increasing the volume of the *para* substituent of MCAT results in a swap of the selectivity between human DAT and SERT [1]. Docking studies hint towards Ser149 in DAT and Ala169 in SERT as key residues involved in the difference of activity between DAT and SERT [2]. The aims of the present biochemical and pharmacological study are to understand (i) which chemical properties (*e.g.* volume, polarity or lipophilicity) of the *para* substituent influence the selectivity profile of MCAT between DAT and SERT, and (ii) whether Ser149 in DAT and Ala169 in SERT can be experimentally verified as key residues.
Methods: We combined *in silico*-driven synthesis, mutagenesis, radiotracer flux assays and electrophysiology in HEK 293 cells expressing the human DAT and SERT wild type and respective mutants.
Results: We found that only MCAT and CF_3-MCAT showed high selectivity: 200-fold for DAT/SERT and 25-fold for SERT/DAT, respectively. This suggests that the high selectivity achieved is determined rather by specific features of these compounds than by the volume of the *para* substituent. Accordingly, we were not able to find any correlationship between the selectivity profile of the tested four MCATs with either volume, polarity and lipophilicity parameters. In addition, we have tested the *para*-substituted methcathinones in the swapping mutations DAT Ser149Ala and SERT Ala169Ser, and in line with our hypothesis these mutations did not revert the selectivity profile found in the wild-type transporters.
Discussion: Our findings provide insights on the introduction of the CF_3 group in *para* position of methcathinone showing that (i) this modification is sufficient to turn a DAT-selective agent into a SERT-selective agent, and that (ii) this effect is not dependent on the volume of the *para* substituent but on specific chemical features of the fluorine atoms which may influence the on- and off-rate of the MCAT moiety on DAT and SERT. The present study may be useful for developing new therapeutic approaches for different neurological disorders, such as depression or post-traumatic stress disorder, or for the development of new PET tracers.

*Corresponding author e-mail: *harald.sitte@meduniwien.ac.at*

Acknowledgements: This work was supported by the Austrian Science Fund FWF (DK MolTag to H.H.S. and G.F.E., and the special research programme F35 to H.H.S., G.F.E. and T.S.).

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