Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol16Issue1abst202P.pdf

In vitro and *in silico* assessment of stimulant properties of novel psychoactive substances (NPS)

J. OPACKA-JUFFRY[1], M. Sahai[1], B. Loi[2], N. Dutta[3], V. Barrese[3], C. Davidson[4]. [1]Life Sciences, University of Roehampton, London, UNITED KINGDOM, [2]University of Hertfordshire, Hatfield, UNITED KINGDOM, [3]St George's University of London, London, UNITED KINGDOM, [4]Pharmacy & Biomedical Sciences, University of Central Lancashire, Preston, UNITED KINGDOM

AimSubstances with stimulant properties have addictive potential which their users might not realise. Stimulants act at the dopamine transporter (DAT) and subsequently increase dopamine concentrations in the brain, including the reward and addiction pathways (2). This work aims to assess stimulant properties of novel psychoactive substances (NPS) by means of combined *in silico* and *in vitro* approaches.

MethodsWe used neurobiological and molecular modelling methods to characterise the stimulant properties of exemplar NPS, selected on the basis of their chemical structure and user reports; this includes the benzofuran 5-MAPB (1-(benzofuran-5-yl)-n-methylpropan-2-amine), phenethylamine derivative 5-(2-aminopropyl)indole (5-IT), diphenylprolinol (D2PM) and diphenidine (1,2-diphenylethyl)piperidine) as dissociative anaesthetic. We measured the binding of NPS to rat striatal DAT by assessing their ability to displace the selective DAT-radioligand [^{125}I]RTI-121 by means of quantitative autoradiography (1). We also evaluated the effects of NPS on electrically-evoked dopamine efflux measured by fast cyclic voltammetry in rat brain slices representing the nucleus accumbens area (5). Molecular docking or dynamic modelling was used to analyse the respective binding properties within DAT (3, 4).

Results The NPS displaced [^{125}I]RTI121 in a concentration-dependent manner, with significant effects at 10 and 30 µM (30% to 60% displacement). The voltammetry patterns of dopamine reuptake changes and reverse transport described amphetamine-like vs cocaine-like stimulant properties in the NPS studied. Molecular modelling and docking studies compared the binding site of DAT in complexes with the NPS to that of dopamine, cocaine, amphetamine and RTI-121. Molecular modelling revealed the intricacies of NPS binding modes in DAT and suggested the molecular basis for dopamine reuptake inhibition and reverse transport by NPS at DAT.

Conclusions The present study demonstrates benefits of combining computational methods with experimental neurobiological procedures to determine structural and functional properties of NPS at the dopamine transporter as the main molecular target of drugs of addiction. Such derived knowledge informs about the risk of addiction related to NPS use.

References

1. Dawson et al. (2014). Prog Neuropsychopharmacol Biol Psychiatry **48**: 57-63

2. Di Chiara,G and BassareoV (2007). Curr Opin Pharmacol **7:** 69-76

3. Khelashvili G et al. (2015a). Proteins Struct Funct Bioinforma **83**: 952-969

4. Khelashvili G et al. (2015b). ACS Chem Neurosci **6:** 1825-37