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MEETING ABSTRACT

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"Second generation" mephedrone analogs, 4-MEC and 4-MePPP, differentially affect monoamine transporter function

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Background: The increase in the use of synthetic psychoactive "designer drugs" followed by the ban of 4-methyl-*N*-methylcathinone (mephedrone) is a cause for grave concern. This newly emerging threat of "second generation" mephedrone analogues including 4-methyl-*N*-ethylcathinone (4-MEC) and 4-methyl-α-pyrrolidino-propiophenone (4-MePPP) are skillfully designed to evade law and require thorough investigation to understand their physiological effects and pharmacological action on their targets, the monoamine transporters.

Methods: An array of techniques was used to analyse the effects of 4-MEC and 4-MePPP including molecular, cellular and whole animal methods. *In vitro* transporter assays served the purpose to elucidate the inhibitory and release properties of the drugs at the serotonin transporter (SERT) and dopamine transporter (DAT). Microdialysis was used to assess the *in vivo* neurochemistry. Transporter-mediated currents were detected in oocytes expressing SERT. Computational docking was used as a tool to shed light to understanding the differences in their pharmacological profile.

Results: 4-MEC displayed a "hybrid" profile acting as a SERT substrate and DAT blocker. It also produced a large increase in extracellular 5-HT, a small increase in dopamine and very minimal motor stimulation. It also evoked inward current in SERT-expressing oocytes. 4-MePPP is a blocker for both SERT and DAT, produced selective increase in dopamine levels and robust motor stimulation. The inability of 4-MePPP to influence the SERT was supported by computational docking of the two drugs at the binding pocket of SERT and DAT revealing subtle differences in their binding mode at the SERT binding pocket.

Discussion: The above findings reflect the importance of understanding the pharmacology of newly emerging drugs and highlight the central role of structure–activity relationship of the drugs and its profound influence on the pharmacology. For the full publication of the data see [1].

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Reference

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