ADDRESS COLLOQUIA

Venue: Medical University Vienna, Center for Physiology and Pharmacology,

Institute of Pharmacology, Conference room, 3rd floor

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Thursday 18.01.2018 13:00 s.t. **Host: Harald Sitte**

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4,4'-DMAR and its interactions with plasmalemmal and vesicular monoamine transporters

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BACKGROUND AND PURPOSE
4,4'-Dimethylaminorex (4,4'-DMAR) is an amphetamine-like substance that has been associated with the death of 31 people in Europe between June 2013 and February 2014 and adverse clinical effects have been reported. However, the pharmacology of 4,4'-DMAR remains largely unexplored.

EXPERIMENTAL APPROACH
We used in vitro assays to determine the effects of 4,4'-DMAR on the human high-affinity transporters for dopamine (DAT), norepinephrine (NET) and serotonin (SERT). In addition, we assessed its binding affinities to monoamine receptors. Furthermore, we investigated the interaction of 4,4'-DMAR with the vesicular monoamine transporter 2 (VMAT2) in rat phaechromocytoma (PC12) cells and synaptic vesicles prepared from human striatum.

KEY RESULTS
4,4'-DMAR inhibited uptake mediated by human DAT, NET or SERT, respectively in the low micromolar range (IC50 values < 2 μM). Release assays identified 4,4'-DMAR as substrate type releaser, capable of inducing transporter-mediated reverse transport via DAT, NET and SERT. Furthermore, 4,4'-DMAR inhibited both the rat and human isoforms of VMAT2 in the same tier of potency as 3,4-methylenedioxymethylamphetamine (MDMA).

CONCLUSIONS AND IMPLICATIONS
This study identified 4,4'-DMAR as a potent serotonin-norepinephrine-dopamine releasing agent (SNDRA). In contrast to aminorex and 4-methylaminorex, 4,4'-DMAR exerts profound effects on human SERT. The latter finding suggests that the fatalities associated with its abuse may be linked to serotonin syndrome. The activity at VMAT2 suggests that abuse of 4,4'-DMAR could result in long-term neurotoxicity.