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**Title: Unraveling the mechanism of action of new psychoactive substances and their phase 1 metabolites**

## **Abstract in English**

Psychostimulant abuse constitutes a growing problem on a global scale, with no effective treatments for psychostimulant addiction being available at present.

In addition to well-characterized and regulated stimulants, such as cocaine or 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"), the drug markets are flooded with new psychoactive substances (NPS). NPS are often referred to as "bath salts" or "research chemicals" and are sold as legal alternatives to scheduled substances. Due to chemical modifications, NPS bypass regulations and bring forth an overwhelming variety of substances with unknown pharmacology. The rewarding, stimulating and addictive properties of psychostimulants arise from their ability to elevate the extracellular concentrations of the monoamines dopamine, norepinephrine and serotonin. This is achieved by disrupting the function of the transporters for dopamine (DAT), norepinephrine (NET) and serotonin (SERT). Under physiological conditions, DAT, NET and SERT mediate the reuptake of exocytically released monoamines and tightly regulate the strength of monoaminergic signaling. Despite of the shared net effect, psychostimulants differ in the mechanism of action. Cocaine-like drugs act as non-transported inhibitors, whereas amphetamine-like releasers invert the transporters and cause efflux of monoamines. Furthermore, releasers act as substrates of DAT, NET and SERT and gain access to the cytosol. In the cytosol, releasers may disrupt the vesicular storage pools of monoamines and can exert neurotoxic effects. Hence, it is fundamental to unravel the molecular mechanism of action of NPS at DAT, NET and SERT. During my thesis, I tested the hypothesis if the phase 1 metabolites of 4-methylmethcathinone (mephedrone, mephedrone) possess psychoactive properties like the phase 1 metabolites of MDMA, thus might contribute to the effects of mephedrone. Mephedrone became famous as part of the group of compounds called "bath salts" and is still abused as an alternative to MDMA. Results obtained from radiotracer-flux experiments showed that the phase 1 metabolites of mephedrone act as releasers at DAT, NET and SERT. In vivo studies in rats identified one metabolite that elevated extracellular dopamine and serotonin in the Nucleus accumbens and triggered locomotion upon systemic

administration. Future studies shall investigate the pharmacokinetics of mephedrone and its metabolites in brain and plasma to estimate the overall contribution of the metabolites to the effects of mephedrone. The second study embedded in this thesis provides a pharmacological characterization of the NPS 3-fluorophenmetrazine (3-FPM) and its positional isomers 2-FPM and 4-FPM. 3-FPM is based on the scheduled drug phenmetrazine. 2-, 3- and 4-FPM were identified as releasers at DAT, NET and SERT. The marked affinity of each FPM at DAT and NET suggests addictive properties and enhanced likelihood for abuse.

In conclusion, the projects embedded in this thesis reveal that the metabolites of mephedrone might contribute to the overall-effects of mephedrone in vivo and provide a pharmacological characterization of potential future drugs of abuse.

Further, the techniques applied herein may serve as a guideline for unravelling the mode of action of psychostimulants at monoamine transporters.