Research explores cause of differences in psychostimulant duration and intensity of effect

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Psychostimulants interacting with the dopamine transporter are found in the therapy of neuro-psychiatric disorders, such as ADHD or depression, as well as on the illicit drug market. In order to better understand their exact mode of action and undesirable effects, a research team led by

Harald Sitte from the Center for Physiology and Pharmacology at the MedUni Wien/Vienna has been working on the question of why different substances in this group of substances have different effects.

According to their results, the answer lies in the respective binding time of the substances to the dopamine transporter. This study has just been published in the journal *Proceedings of the National Academy of Sciences* (*PNAS*).

In a series of in-vitro and in-vivo studies, as well as computer simulations, the team investigated the pharmacological effects of various psychostimulants, used medically, but also abused, which interact with the dopamine transporter. These include, inter alia, substances such as α-Pyrrolidinovalerophenon (also known as α-PVP or "Flakka?"), and 3,4-methylendioxypyrovalerone (also known as MDPV or "Cloud9"), as well as the classical psychostimulant cocaine and methylphenidate, a drug commonly used to treat ADHD (attention deficit hyperactive disorder).

"In our cell culture models, some of these substances showed a pronounced persistent effect which we were then able to see as well in the in-vivo mouse models," reports the study leader, Harald Sitte from the Institute for Pharmacology at the MedUni Vienna's Center for Physiology and Pharmacology, from the analysis of the exact pharmacological relationships. "According to our research, it is the duration of binding to the dopamine transporter that makes the difference here."

Central role of the dopamine transporter

Dopamine transporters are proteins which are responsible for the re-uptake of the neurotransmitter, dopamine. As a messenger, which transmits signals between the nerve cells, dopamine controls emotional,

mental, but also motor reactions in the brain. It is also known as the feel good hormone, which allows us to experience happiness.

Neuro-psychiatric problems result if either too much or too little dopamine is available. The conditions associated with dopamine can be induced both by medication and abuse due to how psychostimulants work. Dopamine transporters and dopamine levels play a central role in the development of substance-use disorders.

"Our results allow the conclusion that the substances we researched interact with the dopamine transporter to different degrees, and for varying lengths of time," explains the first author, Marco Niello from the MedUni Vienna's Center for Physiology and Pharmacology.

"This, in turn, forms the molecular background for the differences in duration and intensity of the effects of various psychostimulants," Sitte adds, who then goes on to explain the medical, and indeed social relevance, of the study which was conducted in collaboration with the National Institute of Drug Abuse in Baltimore, the Paracelsus Medical University in Salzburg, as well as the University of Copenhagen.

"The findings from our research will enable us to make better predictions in future about the mode of action and undesired effects of new and unexplored street drugs, and thus contribute to a more sustainable protection of the population. In addition, our study results can form the basis for further research to improve the therapeutic application of psychostimulants."

More information: Marco Niello et al, Persistent binding at dopamine transporters determines sustained psychostimulant effects, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2114204120

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