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Glutamate can play key role in drug impact on brain

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(PhysOrg.com) -- Addiction disorders of various kinds are a major health and social problem, and our knowledge of how the brain's reward system functions needs to be enhanced. Uppsala researchers now shows an unexpected effect of the signal substance glutamate on the midbrain in mice. The study is published in the Web edition of *Proceedings of the National Academy of Sciences, PNAS*.

"We have found that a certain part of the brain's reward system requires not only the signal substance dopamine, as was previously thought, but also glutamate" says Ĺsa Mackenzie, who directed the study at the Department of Neuroscience, Uppsala University.

Among other things, the dopamine nerve cells in the midbrain are important for the brain's control of willed movements and for the brain's "reward system." The latter in turn is important for providing us with a feeling of pleasure and happiness, for example, when we have eaten, worked out, or been affirmed. The feeling itself is mediated by dopamine released from the midbrain's dopamine-producing nerve cells to the brain's limbic system.

But the reward system is also affected by addictive drugs, such as cocaine and amphetamine. Previous studies have shown that a small portion of dopamine cells in the reward system can also use, besides dopamine, the signal substance glutamate (neurotransmitter), and researchers have therefore suggested that these nerve cells "co-transmit" glutamate and dopamine. But it was not previously known what this

entailed for the function of the brain.

To address this question, the researchers in the current study developed a special mouse model whose dopamine nerve cells lack the ability to both use and release glutamate. When they were treated with the dopamine-releasing substance amphetamine, a clear effect was observed. Normal mice responded, as expected, with increased activity and more stereotypical movements. On the other hand, the reaction in the model mice was significantly reduced, showing that a certain part of the reward system needs not only the signal substance dopamine, as was previously believed, but also glutamate.

"Thus when we take away the glutamate signaling, the brain's reward system is numbed, which is extremely interesting", says Ĺsa Mackenzie.

The findings are robust and enhance our possibility of understanding how the reward system, and diseases that affect it, is formed and how it functions. The researchers are now continuing their study of the nerve cells involved to find out how important this system is for addiction.

"We hope our studies will ultimately provide relevant knowledge for an understanding of addiction mechanisms in humans," says Ĺsa Mackenzie.

The study, which was carried out in collaboration with colleagues at the Karolinska Institute and the University of Montreal, Canada, has been funded by Uppsala University, the Swedish Research Council, the Swedish Brain Foundation, STINT, the Knut and Alice Wallenberg Foundation, the National Board of Health and Welfare, the Ĺhlén Foundation, and the Magnus Bergvall Foundation.

More information: VGLUT2 in dopamine neurons is required for psychostimulant-induced behavioral activation. Birgner, C.,

Nordenankar, K., Lundblad, M., Mendez, J.A., Smith, C., LeGrevčs, M., Galter, D., Olson, L., Fredriksson, A., Trudeau, L-E., Kullander, K., Wallén-Mackenzie, Ĺ.