Researchers one step closer to cocaine antidote

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Researchers at the University of Copenhagen have gained new insight into the mechanism behind a protein dopamine transporter that could help in the development of future medical treatment against cocaine addiction.

"If we have a better understanding of the dopamine transporter function we will become more proficient in developing an antidote against cocaine addiction," says Associate Professor Claus Juul Loland from the department of Neuroscience and Pharmacology. Currently there is no available medical treatment for cocaine addiction.

The results have been published in the *Journal of Biological Chemistry*.

Discovery of crucial mechanism

Dopamine is a signaling molecule in the brain which is involved in our sensation of reward, motivation and, thus, addiction. The dopamine transporter functions as a molecular vacuum cleaner removing the released dopamine, thereby controlling its signaling. The researcher's discovery is an interaction, a so-called gate, which controls access for dopamine to its binding site in the protein. "We found two amino acids in the proteins that dynamically breaks and forms an interaction. The dynamic is therefore crucial for the transport process," says Loland.

Besides controlling function, the constellation of the two amino acids is

important for the overall structure of the protein: "The breakage of the interaction could therefore be a signature for the binding of cocaine and cocaine-like drugs," he adds.

Towards a cocaine antidote

Cocaine acts as an inhibitor of the dopamine transporter but the researchers found other inhibitors that even though they did bind to the dopamine transporter with the same strength as cocaine, did not produce the same stimulatory response when administered to rats.

By using molecular pharmacology and biochemistry, they were able to characterize dopamine transporter mutants and how their function deviated from the non-mutated transporter. In contrast to cocaine, the non-stimulatory - or atypical - drugs seem to bind a more closed form of the dopamine transporter.

If the researchers can figure out - on the molecular level - why they are different then they will be better prepared for the targeted development of non-stimulatory inhibitors that will prohibit the subsequent binding of cocaine and help them towards producing an antidote. "Our objective here is that cocaine will not then work anymore as the antidote will inhibit the stimulatory response of taking this drug," concludes Loland.

Provided by University of Copenhagen

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