Cocaine addiction: Impact of genetic mutations elucidated

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Cocaine addiction is a chronic disorder with a high rate of relapse for which no effective treatment is currently available. Scientists from the Institut Pasteur, the CNRS, Inserm and the Paris Public Hospital Network (AP-HP) recently demonstrated that two gene mutations involved in the conformation of nicotinic receptors in the brain appear to play a role in various aspects of cocaine addiction. The results of the study were published in *Progress in Neurobiology*.

There are approximately 18 million users worldwide, and cocaine is implicated in more than 50% of overdose deaths in the United States and 25% in France. It is also one of the only drugs for which there is no approved pharmacological treatment.

Cocaine acts primarily in the brain by blocking the dopamine transporter, thereby increasing the concentration of this "pleasure" molecule in the reward system. But cocaine can also act directly on the nicotinic receptors1 in the brain. Several human genetics studies have recently suggested that a mutation in the gene encoding the ?5 subunit of nicotinic receptors, hereafter referred to as '?5SNP', already known to increase the risk of tobacco dependence,2 may conversely also confer 'protection' against cocaine addiction. This mutation is highly present in the general population (approximately 37% of Europeans and up to 43% of the Middle Eastern population carry it), so it is important to determine how it affects cocaine addiction and, more generally, to better understand the role of the ?5 nicotinic subunit in the effects of cocaine.

Scientists of the Integrative Neurobiology of Cholinergic Systems Unit (Institut Pasteur/CNRS) began by evaluating the role of the ?5 nicotinic subunit and the impact of the ?5SNP mutation on various processes involved in the development of cocaine addiction in animal models. The results obtained were then used to characterize more specifically its impact on humans.

The scientists observed that the ?5SNP mutation reduces the voluntary intake of cocaine upon first exposures. "These preclinical data suggest that the mutation protects against cocaine addiction by modulating an early phase in the addiction cycle," comments Morgane Besson, one of the lead authors of the study. Working in collaboration with the Paris Public Hospital Network (AP-HP) and Inserm, the scientists then confirmed this significant effect in approximately 350 patients with cocaine addiction: those with the mutation exhibited a slower transition from first cocaine use to the emergence of signs of addiction. At the same time, the authors showed that a total absence of the ?5 nicotinic subunit increased the risk of relapse after withdrawal in preclinical models. This led the scientists to identify another mutation in another nicotinic subunit, ?4, associated with a shorter time to relapse after withdrawal in addicted patients.

Taken together, these results elucidate the role played by both a highly frequent mutation in the ?5 nicotinic subunit and the subunit itself in various

stages of cocaine addiction. The research suggests that drugs modulating nicotinic receptors containing this ?5 subunit could represent a novel therapeutic strategy for cocaine addiction.

More information: Benoît Forget et al, Alterations in nicotinic receptor alpha5 subunit gene differentially impact early and later stages of cocaine addiction: a translational study in transgenic rats and patients, *Progress in Neurobiology* (2020). DOI: 10.1016/j.pneurobio.2020.101898

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