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Drug dependence: a new unexpected mechanism discovered

Research

Researchers at the ULB Neuroscience Institute, UNI have discovered a major new mechanism in drug dependence, and in particular cocaine addiction. Their study, published in the journal Nature Communication, opens the door to new therapeutic avenues.

Every year, drug addiction causes almost 12 million deaths worldwide, more than all cancers put together, and in the United States it is the leading cause of death among 18-45 year olds!.

Drug dependence is defined as a chronic recurrent disorder characterised by the compulsive seeking and taking of drugs despite the harmful consequences. The primum movens of addiction is the 'artificial' increase, following the taking of drugs, in the concentration of dopamine, the neurotransmitter associated with the reward system, in the main region of this system, the ventral striatum. This artificial increase hijacks the reward system and induces changes in the brain that lead to addiction.

This psychiatric illness is due to both genetic and environmental factors. The genetic component of a person's vulnerability to addiction is 40-60% and involves specific genes linked to neurotransmitters and their actions, such as dopamine, opioid, nicotinic and cannabinoid receptors.

In a previous study, **Alban de Kerchove d'Exaerde's team at the Université libre de Bruxelles (UlB), Faculty of Medicine and ULB Neuroscience Institute, Welbio investigator in the WEL Research Institute**, used mouse models to demonstrate the central role of an unsuspected

gene in cocaine dependence: Maged1. Its inactivation in the entire brain of mice rendered them totally insensitive to the effects of cocaine.

In this new publication, recently published in *Nature Communication*, the same team demonstrated that the region of the brain where this gene Maged1 plays its essential role in addiction was in fact located outside the reward circuit, which was completely unexpected.

Following the identification of this new key region (the paraventricular thalamus), the mechanisms underlying the major effects of Maged1 in cocaine addiction were uncovered. The mechanisms identified are just as novel as the paraventricular thalamus in the addiction phenomenon. They involve specific epigenetic modifications, i.e. changes in DNA structure rather than mutations. These epigenetic alterations influence the expression of many genes. In addition, inhibition of one of the new genes identified as a partner of Maged1 for these epigenetic modifications, USP7, also abolishes addictive behaviours. Environmental factors also implicated in addiction also induce epigenetic modifications that are stable over time and may explain the chronic nature of this disease.

Finally, to demonstrate the relevance to humans of these mechanisms identified and discovered in mice, a study of cocaine-dependent patients was carried out in collaboration with a team of psychiatrists from the Université de Paris Cité.

This study in humans demonstrated that specific genetic modifications to the Maged1 and USP7 genes are associated with highly significant consequences on behaviours directly linked to cocaine addiction.

All these results, which also demonstrate the value of animal models in research into psychiatric illnesses, offer hope of new treatments for drug addiction, particularly cocaine addiction, for which there is currently no effective treatment.

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