INTRODUCTION

And contrary to the conventional wisdom, cocaine produces an addiction only in 20% of the consumers. But what happens in the brains of consumers when they lose control of their consumption? Thanks to a new experimental technique, neuroscientists at the University of Geneva have just discovered a brain mechanism that is specific to cocaine. It has the particularity of causing a massive increase of serotonin, besides the rise of dopamine standard to all drugs. Indeed, serotonin acts as an intrinsic break on this overexcitation of the reward system elicited by dopamine - the neurotransmitter that causes addiction. These results are published in the journal Science.

UNDERSTANDING ADDICTION: A DEFINITION

Addiction refers to the compulsive search for a substance despite the adverse consequences. Dependence, on the other hand, is defined as the occurrence of withdrawal symptoms. Physical effects vary greatly from one substance to another-

when consumption is stopped abruptly. It thus affects everybody, while addiction affects only a minority of the users, even after prolonged exposure. For instance, cocaine is responsible for 20% of cases of such users getting dependent, while opiates account for 30%. "Of course, this is also true for any potentially addictive product, concludes the leader of this study, Christian Lüscher, a professor in the UNIGE Faculty of Medicine at the Department of Basic Neurosciences. "Here in Switzerland, for example, almost all adults drink alcohol from time to time, a strong activator of reward systems. Yet in only about one percent are we ever going to become alcoholics."

SEROTONIN DEFICIENCY LINKED TO TRIPLED ADDICTION

Triple addiction, no serotonin To find out in which specific region of the brain the addiction process to cocaine develops, the scientists designed a line of experiments. "Most often, scientific experiments aim to reproduce some kind of systematic mechanism. Here, the catch is in observing a random phenomenon that is possible to trigger only once in five times," says Yue Li, who is a

researcher in the team of Christian Lüscher and the first author of the study.

The researchers initially taught a large group of mice to self-administer cocaine voluntarily and then introduced a constraint: each time they self-administered cocaine, the mice received a slightly unpleasant stimulus, either an electric shock or an air jet. Two groups then clearly emerged: 80 percent of the mice stopped their consumption, while 20 percent continued despite the unpleasantness. "This compulsive behavior is precisely what defines addiction, which affects 20% of individuals, in mice as in humans," insists Vincent Pascoli, scientific collaborator in the Geneva group and co-author of this study.

In mice, the association of cocaine with the serotonin transporter no longer elicited, just the dopamine level increased when the substance was administered. 60% of the animals became addicts. The same result was obtained with other animals whose reward systems had been stimulated by a

protocol that did not act on serotonin. "If serotonin is administered to the latter group, the rate of addiction falls to 20%," says Christian Lüscher. "Cocaine, therefore, has a kind of natural brake that is effective four times out of five.”

A DELICATE SYNAPTIC BALANCE

When cocaine is ingested, there take place two opposite influences in the brain: dopamine on one side, which, by suddenly increasing, triggers compulsion, and serotonin on the other side, which has the opposite effect of breaking any kind of compulsion. Addiction would then result from the imbalance thus created between these two neuromodulators and from dopamine's increasing over its counterpart serotonin. "In reality, dopamine induces an effect of synaptic plasticity in the reinforcement of the links between synapses of the cortex and those of the dorsal striatum. This enormous activation within the reward system causes compulsive behavior. Serotonin is doing the contrary; it blocks the reinforcement triggered by

dopamine so that the reward system stays under control," says Christian Lüscher.

WHAT OF OTHER DRUGS?

Except for this gush of dopamine, each drug has some specificity in its action on the brain. If the natural power of serotonin naturally diminishes the addictive power of cocaine, what of other medications? The Geneva neuroscientists are going to turn from now on to opiates—which are much more addictive than cocaine—and to ketamine, which is much less so. This way, one obtains a detailed understanding of how the drugs work on the brain and why some individuals are far more susceptible to the adverse effects than others.