Hunting for the brain's opioid addiction switch

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New research by Steven Laviolette's research team at Western University is contributing to a better understanding of the ways opiate-class drugs modify brain circuits to drive the addiction cycle. Using rodent models of opiate addiction, Dr. Laviolette's research has shown that opiates affect pathways of associative memory formation in multiple ways, both at the level of anatomy (connections between neurons) and at the molecular levels (how molecules inside the brain affect these connections). The identification of these opiate-induced changes offers the best hope for developing more effective pharmacological targets and therapies to prevent or reverse the effect of opiate exposure and addiction. These results were presented at the 10th Annual Canadian Neuroscience Meeting, taking place May 29 to June 1 2016, in Toronto, Canada.

"Developing more effective opiate addiction treatments will require a change in the way we view the effects of opiates on the brain. Instead of addiction being a chronic, permanent disease, recent evidence is showing that addiction is controlled by molecular switching mechanisms in the brain, that can be turned on or off with the right interventions" says Dr. Steven Laviolette.

Addiction to opiates is spreading and increasing exponentially, and is currently estimated to affect 15.5 million people worldwide. Opiate drugs' addictive properties are largely due to the ability of this class of drugs to produce powerful memories associated with the intense experience of pleasure and euphoria they cause. Environmental

reminders triggering the recall of these memories can cause a relapse, and these memories can be considered the primary driver of the addiction cycle, from chronic use, to withdrawal and then memory-triggered relapse. For decades, clinical and pre-clinical research considered that opiate consumption caused permanent changes in the brain's reward circuits, resulting in a persistent vulnerability to relapse. However, more recent investigations have shown that opiates induce changes in multiple brain circuits, including reward and memory circuits, and that these changes are not static, but rather that many drug-induced adaptations could be reversed.

"A critical challenge for addiction research is identifying the precise molecular brain changes caused by addictive drugs like heroin or prescription narcotics", says Dr. Laviolette. "Once we understand this process, we can develop more effective pharmacological interventions to prevent or reverse them"

Among the targets identified by Dr. Laviolette are receptors and other proteins involved in signalling of a neurotransmitter called dopamine. More specifically, his work has shown that dopamine signalling in two connected brain regions involved in opiate-related memory processing, called the Basolateral Amygdala (BLA), a region deep within the brain, and the medial prefrontal cortex (mPFC), located near the surface of the brain, is switched by opiate exposure. His research shows that in animals that are opiate naïve, never previously exposed to opiates, the reward memory associated with opiates requires a dopamine receptor called D1R in the BLA, and a signalling molecule called extracellular signal-related kinase 1/2 (ERK1/2). Following chronic opiate exposure, however, opiate reward memory formation becomes independent of D1R, and rather depends on a second dopamine receptor, called D2r, and a protein called CaMKII. As CaMKII expression has been associated with consolidation and permanence of memories in other brain regions, this switch may reflect the formation of a stronger and more stable

opiate reward memory.

Interestingly, when Dr. Laviolette's team looked at dopamine signaling inside another brain region also involved in opiate related memory procession, and located closer to the surface of the brain, the mPFC, they found that this signaling was also switched by opiate exposure, but opposite to what was observed in the BLA. In the mPFC, opiate naïve signaling requires CaMKII, while it did not in opiate habituated animals.

Taken together, these results highlight the precise changes and adaptations that occur in the brain following opiate exposure and development of addiction. New pharmacological approaches to target these changes will provide much needed and more effective treatments to reduce the power of drug-related associative memories that drive opiate addiction.

Dr. Laviolette's latest results were presented at the 10th Annual Canadian Neuroscience Meeting, on May 31 2016 in Toronto, Ontario.

More information: can-acn.org/meeting2016

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