Molecular underpinnings of addiction produce strong addiction-related memories

11 January 2017

Addiction-related memories are exceptionally strong and stable, suggesting that addictive drugs remodel the brain's circuitry in a prominent and lasting way. In the past decade, researchers have used mouse models to unravel how cellular changes in the nucleus accumbens (NAc), a brain structure involved in action selection associated with arousal and reward, may contribute to addiction-related behavior. Whereas neuronal remodeling in the NAc explains a wide range of addictive behaviors, it is not required for all of them, according to a study published today in The *EMBO Journal*.

A research team led by Oliver Schlüter (University of Pittsburgh, PA, USA) found that cocaine-induced place preference in mice – returning to places where the drug was previously received – does not depend on lasting rewiring of neurons in the NAc. This finding is an important step towards a better understanding of the cellular and molecular underpinnings of addictive behavior, paving the way for the development of effective therapeutics.

Taking cocaine leads to the generation of immature neuronal contacts called silent synapses in the NAc. Silent synapses, as the name indicates, are not very active. However, after quitting drug abuse, they mature and become stronger, or "unsilenced", as researchers call it. Unsilencing synapses leads to massive NAc rewiring during drug withdrawal and forms the basis of many addictive behaviors. The process may explain why drug craving often increases over time in the first weeks of abstinence.

Previous work on silent synapse-based NAc remodeling has focused on addiction paradigms where animals learn to associate an activity, like pressing a lever or poking their nose into a hole, with receiving drugs. This type of learning is often referred to as "operational conditioning". In their present study, Schlüter and his colleagues tested a form of "Pavlovian learning", where the animal learns passively. Mice were injected with cocaine and placed into one of two compartments of a cage to learn to associate cocaine with the smell, feel and look of that location. After a withdrawal phase, the mice were tested for their memory of the drug-context association. When they were placed back into the two-compartment cage they preferred to reside in the compartment they had learned to associate with feeling high.

The researchers then tested if this learning paradigm would also lead to a rewiring of the NAc and found that it did. Just like in operational conditioning paradigms, silent synapses formed and were unsilenced during withdrawal. But was this rewiring also essential for the mice to remember place preference after withdrawal?

To address this question, the researchers made use of mice with mutations that affect different aspects of synapse unsilencing. They found that mice remember the place where they received cocaine even if synapse unsilencing in the NAc is impaired. Thus, whereas synapse unsilencing and NAc remodeling underlies many addictive behaviors, cocaine-induced place preference is not one of them. This result is an important step towards a better understanding of the molecular and cellular basis of addiction.

More information: Calcium-permeable AMPA Receptors and Silent Synapses in Cocaine-conditioned Place Preference. DOI: 10.15252/embj.201695465

Provided by European Molecular Biology Organization