Morphine makes lasting -- and surprising -- change in the brain

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Morphine, as little as a single dose, blocks the brain's ability to strengthen connections at inhibitory synapses, according to new Brown University research published in *Nature*.

The findings, uncovered in the laboratory of Brown scientist Julie Kauer, may help explain the origins of addiction in the brain. The research also supports a provocative new theory of addiction as a disease of learning and memory.

"We've added a new piece to the puzzle of how addictive drugs affect the brain," Kauer said. "We've shown here that morphine makes lasting changes in the brain by blocking a mechanism that's believed to be the key to memory making. So these findings reinforce the notion that addiction is a form of pathological learning."

Kauer, a professor in the Department of Molecular Pharmacology, Physiology and Biotechnology at Brown, is interested in how the brain stores information. Long-term potentiation, or LTP, is critical to this process.

In LTP, connections between neurons – called synapses, the major site of information exchange in the brain – become stronger after repeated stimulation. This increased synaptic strength is believed to be the cellular basis for memory.

In her experiments, Kauer found that LTP is blocked in the brains of rats

given as little as a single dose of morphine. The drug's impact was powerful: LTP continued to be blocked 24 hours later – long after the drug was out of the animal's system.

"The persistence of the effect was stunning," Kauer said. "This is your brain on drugs."

Kauer recorded the phenomenon in the ventral tegmental area, or VTA, a small section of the midbrain that is involved in the reward system that reinforces survival-boosting behaviors such as eating and sex – a reward system linked to addiction. The affected synapses, Kauer found, were those between inhibitory neurons and dopamine neurons. In a healthy brain, inhibitory cells would limit the release of dopamine, the "pleasure chemical" that gets released by naturally rewarding experiences. Drugs of abuse, from alcohol to cocaine, also increase dopamine release.

So the net effect of morphine and other opioids, Kauer found, is that they boost the brain's reward response. "It's as if a brake were removed and dopamine cells start firing," she explained. "That activity, combined with other brain changes caused by the drugs, could increase vulnerability to addiction. The brain may, in fact, be learning to crave drugs."

Kauer and her team not only recorded cellular changes caused by morphine but also molecular ones. In fact, the researchers pinpointed the very molecule that morphine disables – guanylate cyclase. This enzyme, or inhibitory neurons themselves, would be effective targets for drugs that prevent or treat addiction.

Source: Brown University