Why are we so drawn to places of happy memories?

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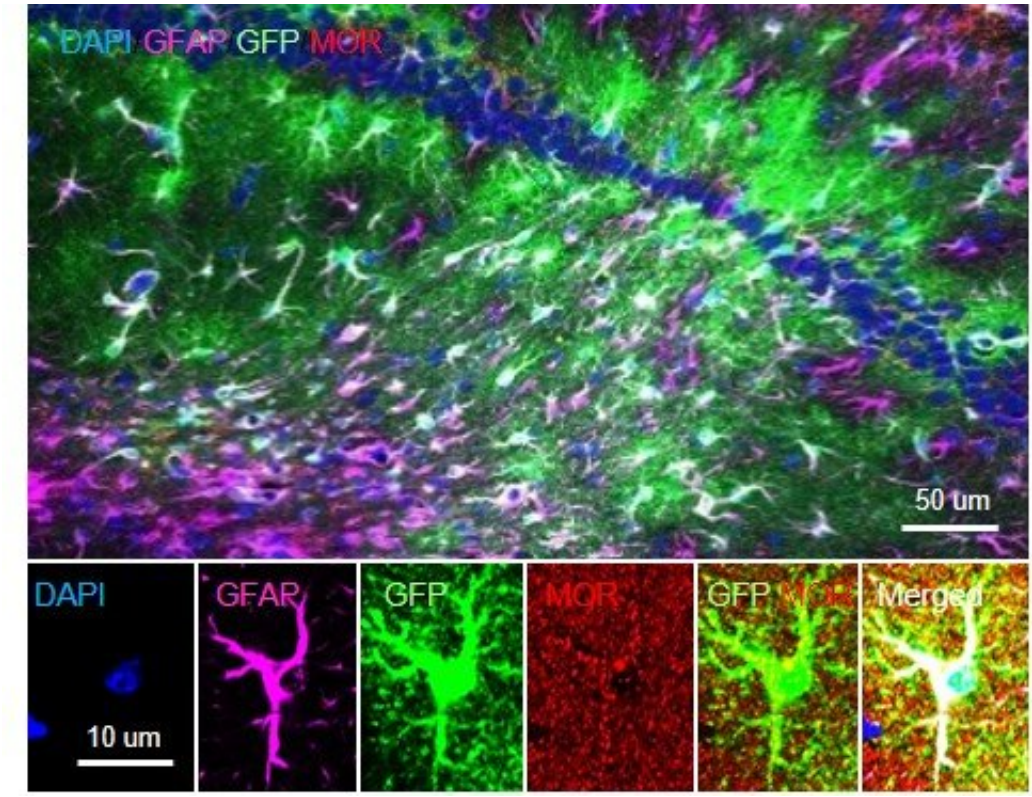


A representative image of MOR over-expression in hippocampal astrocytes of MOR-KO mice. Credit: Institute for Basic Science

If somebody asks me "are you a coffee addict?" I may say, "Yeah it seems like, but on the one condition, only in my office." I don't have that much craving for coffee at home, but just being in the office, where I used to drink coffee all the time seeking to get caffeine jitters, seems to

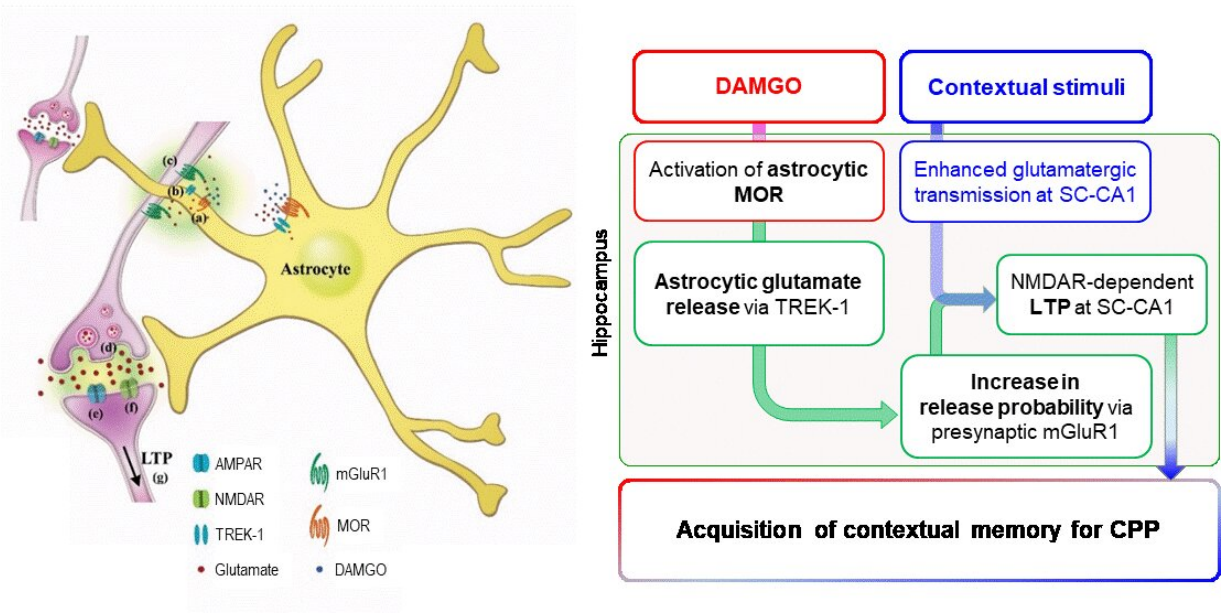
trigger my caffeine-addicted brain.

It is often said that breaking bad habits or additions is all about a person's willpower. However, as behavior study researcher Bruce Alexander put it, "Addiction is an adaption. It's not you—it's the cage you live in." (Source: *Chasing the Scream: The First and Last Days of the War on Drugs* [audiobook]). Studies have revealed that environmental stimuli such as places are a strong force behind our addiction. For example, studies on heroin-addicted Vietnam war veterans found that changes in their living place—returning home from the battlefield—were the hidden force necessary to break their drug addictions so effectively.

When you feel happy or pleasant, several areas of the brain take part in feeling, remembering, and working to repeat the action. Specifically, the hippocampus is responsible for spatial memory acquisition. People may remember where such feeling-good experience takes place and revisit the place to remind themselves of such experiences. However, things get quite problematic if the experience involves drug abuse. The Conditioned Place Preference (CPP) is an experimental paradigm to study the mechanism of addictive behaviors associated with pleasant experience. It was long believed until recently that the release of the hormone dopamine in the mesolimbic pathway of the brain is the key to CPP. However as dopamine-deficient mice were found to exhibit CPP, the brain's CPP pathways have remained elusive. Meanwhile, the hippocampus, the brain region responsible for spatial memory, has not been considered to be involved in CPP.

Led by Dr. C. Justin Lee, researchers at the Center for Cognition and Sociality within the Institute for Basic Science (IBS) in Daejeon, South Korea have identified a new mechanistic element of CPP, mu-opioid receptors (MORs) expressed in astrocytes of the hippocampus. Opioids include endorphins (our brain's feel-good transmitters) or morphine (a

major painkiller) that can make people feel relaxed or happy, and can be addictive. Much has been studied on neuronal MORs, but we have currently failed to form a comprehensive understanding of the CPP mechanism. The research team looked at seemingly unlikely cells that had been deemed to only provide support and protection for neurons—astrocytes (i.e. a cell type of non-neuron cells) in the brain. They narrowed their target range to the astrocytic MORs in the hippocampus, as it is the place where spatial memory is formed.



Schematic model of contextual memory formation for CPP through activation of astrocytic MOR. Activation of astrocytic MOR elicits glutamate release from astrocytes to increase release probability via presynaptic mGluR1 activation. The enhanced glutamatertic transmission by both contextual stimuli and astrocytic MOR activation leads to long-term potentiation at Schaffer collateral-CA1 synapses in the hippocampus, which accounts for acquisition of contextual memory for CPP. Credit: Institute for Basic Science

In their mouse experiments, the researchers placed mice in two separate spaces with one door in the middle. One compartment was black with a stainless steel grid rod floor and another one was black and white striped. At first, they let mice move around the two spaces through the door in order to find their preferred and non-preferred places. Then they gave mice DAMGO or morphine in their non-preferred spaces to condition for opioid control of the mice's CPP. After this conditioning, the researchers again let the mice freely explore the two separate spaces, and observed which room the mice prefer. The experiments demonstrated the injection of exogenous opiod (DAMGO) or morphine activates astrocytic MORs in the hippocampus to release glutamates. These excitatory neurotransmitters increase the synaptic transmissions at the Schaffer collateral-CA1 synapse in the hippocampus, which is responsible for the acquisition of spatial memory to induce CPP. The increased synaptic activity is technically called long-term potentiation (LTP).

To see whether the astrocytic MORs are the essential component to initiate opioid-induced CPP, the researchers performed astrocyte-specific gene-silencing of MORs in the hippocampus to see if CPP is induced by DAMGO treatment. The researchers found that CPP was not induced by DAMGO treatment without hippocampal astrocytic MORs. These findings indicate that hippocampal astrocytic MORs are critical for CPP induction, in addition to mesolimbic neuronal MORs. The first author of this study, Dr. Min-Ho Nam says, "There have been long-believed dogma about conditioned place preference (CPP): Interneuronal MOR in mesolimbic dopamine system is the only key for CPP. To overcome this dogma, we adopt multidisciplinary strategies including genetics, histology, electrophysiology, and behavioral assays."

Notably, this study verified that the astrocytic MORs in the hippocampus is where both artificial (morphine) and biological opioids (endorphin replaced by DAMGO) begin to induce the acquisition of

contextual memory associated with pleasure. "Astrocyte is the most abundant cell type in the brain. This astrocyte-oriented study allows us to step forward in understanding how humans prefer a certain place where a happy memory is associated. We expect this study to fuel the move from a neuro-centric to glio-centric view in the brain science field," explains the corresponding author of this study Dr. Lee.

More information: Min-Ho Nam et al. Activation of astrocytic mu-opioid receptor causes conditioned place preference. *Cell Reports*, DOI: 10.1016/j.celrep.2019.06.071

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