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Study explains how the brain remembers pleasure and its implications for addiction

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Key details of the way nerve cells in the brain remember pleasure are revealed in a study by University of Alabama at Birmingham researchers published today in the journal *Nature Neuroscience*. New details of the molecular events that form "reward memories" also suggest they differ from those created by drug addiction, despite the popular theory that addiction hijacks normal reward pathways.

Brain circuits have evolved to encourage behaviors proven to help our species survive by attaching pleasure to them. Eating rich food tastes good because it delivers energy and sex is desirable because it creates offspring. The same systems also connect in our mind's environmental cues with actual pleasures to form reward memories.

This study in rats supports the idea that the mammalian brain features several memory types, each using different circuits, with memories accessed and integrated as needed. Ancient memory types include those that remind us what to fear, what to seek out (reward), how to move (motor memory) and navigate (place memory). More recent developments enable us to remember the year Columbus sailed and our wedding day.

"We believe reward memory may serve as a good model for understanding the molecular mechanisms behind many types of learning and memory," said David Sweatt, Ph.D., chair of the UAB Department of Neurobiology, director of the Evelyn F. McKnight Brain Institute at UAB and corresponding author for the study. "Our results provide a leap

in the field's understanding of reward-learning mechanisms and promise to guide future attempts to solve related problems such as addiction and criminal behavior."

The study is the first to illustrate that reward memories are created by chemical changes that influence known memory-related genes in nerve cells within a brain region called the ventral tegmental area, or VTA. Experiments that blocked those chemical changes—a mix of DNA methylation and demethylation—in the VTA prevented rats from forming new reward memories.

Methylation is the attachment of a methyl group (one carbon and three hydrogens) to a DNA chain at certain spots (cytosine bases). When methylation occurs near a gene or inside a gene sequence, it generally is thought to turn the gene off and its removal is thought to turn the gene on. This back-and-forth change affects gene expression without changing the code we inherit from our parents. Operating outside the genetic machinery proper, epigenetic changes enable each cell type to do its unique job and to react to its environment.

Furthermore, a stem cell in the womb that becomes bone or liver cells must "remember" its specialized nature and pass that identity to its descendants as they divide and multiply to form organs. This process requires genetic memory, which largely is driven by methylation. Note, most nerve cells do not divide and multiply as do other cells. They can't, according to one theory, because they put their epigenetic mechanisms to work making actual memories.

Natural pleasure versus addiction

The brain's pleasure center is known to proceed through nerve cells that signal using the neurochemical dopamine and generally is located in the VTA. Dopaminergic neurons exhibit a "remarkable capacity" to pass on

pleasure signals. Unfortunately, the evolutionary processes that attached pleasure to advantageous behaviors also accidentally reinforced bad ones.

Addiction to all four major classes of abused drugs—psychostimulants, opiates, ethanol and nicotine—has been linked to increased dopamine transmission in the same parts of the brain associated with normal reward processing. Cues that predict both normal reward and effects of cocaine or alcohol also make dopamine nerve cells fire as do the experiences they recall. That had led to idea that drug addiction must take over normal reward-memory nerve pathways.

Along those lines, past research has argued that dopamine-producing neurons in the VTA—and in a region that receives downstream dopamine signals from the VTA called the nucleus accumbens (NAC)—both were involved in natural reward and drug-addiction-based memory formation. While that may true to some extent, this study revealed that blocking methylation in the VTA with a drug stopped the ability of rats to attach rewarding experiences to remembered cues but doing so in the NAC did not.

"We observed an important distinction, not in circuitry, but instead in the epigenetic regulation of that circuitry between natural reward responses and those that occur downstream with drugs of abuse or psychiatric illness," said Jeremy Day, Ph.D., a post-doctoral scholar in Sweatt's lab and first author for this study. "Although drug experiences may co-opt normal reward mechanisms to some extent, our results suggest they also may engage entirely separate epigenetic mechanisms that contribute only to addiction and that may explain its strength."

To investigate the molecular and epigenetic changes in the VTA, researchers took their cue from 19th century Russian physiologist Ivan Pavlov, who was the first to study the phenomenon of conditioning. By

ringing a bell each day before giving his dogs food, Pavlov soon found that the dogs would salivate at the sound of the bell.

In this study, rats were trained to associate a sound tone with the availability of sugar pellets in their feed ports. This same animal model has been used to make most discoveries about how human dopamine neurons work since the 1990s, and most approved drugs that affect the dopamine system (e.g. L-Dopa for Parkinson's) were tested in it before being cleared for human trials.

To separate the effects of memory-related brain changes from those arising from the pleasure of the eating itself, the rats were separated into three groups. Rats in the "CS+" rats got sugar pellets each time they heard a sound cue. The "CS–" group heard the sound the same number of times and received as many sugar pellets—but never together. A third tone-only group heard the sounds but never received sugar rewards.

Rats that always received sugar with the sound cue were found to poke their feed ports with their noses at least twice as often during this cue as control rats after three, 25-sound-cue sessions. Nose pokes are an established measure of the degree to which a rat has come to associate a cue with the memory of a tasty treat.

The team found that those CS+ rats (sugar paired with sound) that were better at forming reward memories had significantly higher expression of the genes Egr1 and Fos than control rats These genes are known to regulate memory in other brain regions by fine-tuning the signaling capacity of the connections between nerve cells. In a series of experiments, the team next revealed the methylation and demethylation pattern that drove the changes in gene expression seen as memories formed.

The study demonstrated that reward-related experiences caused both

types of DNA methylation known to regulate gene expression.

One type involves attaching methyl groups to pieces of DNA called promoters, which reside immediately upstream of individual gene sequences (between genes), that tell the machinery that follows genetic instructions to "start reading here." The attachment of a methyl group to a promoter generally interferes with this and silences a nearby gene. However, ancient organisms such as plants and insects have less methylation between their genes, and more of it within the coding regions of the genes themselves (within gene bodies). Such gene-body methylation has been shown to encourage rather than silence gene expression.

Specifically, the team reported that two sites in the promoter for Egr1 gene were demethylated during reward experiences and, to a greater degree, in rats that associated the sugar with the sound cue. Conversely, spots within the gene body of both Egr1 and Fos underwent methylation as reward memories formed.

"When designing therapeutic treatments for psychiatric illness, addictions or memory disorders, you must profoundly understand the function of the biological systems you're working with," Day said. "Our field has learned from experience that attempts to treat addiction with something that globally impairs normal reward perception or reward memories do not succeed. Our study suggests the possibility that future treatments could dial down drug addiction or mental illness without affecting normal rewards."

More information: DNA methylation regulates associative reward learning, DOI: 10.1038/nn.3504