# Study overturns decade-old findings in neurobiology

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In findings that should finally put to rest a decade of controversy in the field of neurobiology, a team at The Scripps Research Institute has found decisive evidence that a specific neurotransmitter system -- the endocannabinoid system -- is active in a brain region known to play a key role in the processing of memory, emotional reactions, and addiction formation. The new study also shows that this system can dampen the effects of alcohol, suggesting an avenue for the development of drugs to combat alcohol addiction.

The research was published in the journal *Neuropsychopharmacology* on May 12.

"This study will change a lot in the field," said Scripps Research Associate Professor Marisa Roberto, who was first author of the paper. "I'm confident it will have a big impact."

"This is very new," said Paul Schweitzer, associate professor of the neurobiology of addiction at Scripps Research and corresponding author of the paper. "It is the first time a study has shown a direct cellular interaction between endocannabinoids and alcohol in the brain."

## The Missing Link?

The new research overturns the conclusions of a paper published by a European group in the Journal of Neuroscience in 2001. This paper

claimed that endocannabinoid receptors, in particular the most common type called CB1, did not exist in the brain region called the central amygdala.

"Yet CB1 receptors are very abundant," said Schweitzer. "They are almost everywhere in the brain and there are lots of them. The endocannabinoid system acts on appetite, mood, memory—and addiction. Addiction is why we started to study it in the central amygdala."

The Scripps Research scientists began to suspect that the 2001 study, whose conclusions had been widely accepted in the field, might have missed the CB1 receptors in the brain's central amygdala. Indirect evidence from a number of subsequent studies—including one by Scripps Research Associate Professor Loren "Larry" Parsons—had suggested that the endocannabinoid system (and by implication its receptors) were indeed active in this brain region.

The Scripps Research team decided to take a fresh look at the whole question, and set out to conduct a new physiological study specifically looking for signs of the missing CB1 receptors in the central amygdala.

"There wasn't much physiology done before this," said Roberto. "There were a lot of behavioral studies, but very few on physiology and, aside from the 2001 study, none on the physiology in the central amygdala—this brain region that is so important for drugs of abuse."

## Back on Track

Using electrophysiological techniques in brain slices to test the response of brain cells from the rat central amygdala, the scientists indeed found compelling evidence that CB1 receptors were active there.

The cells responded to a substance (agonist) mimicking the action of endocannabinoids in the brain. Up to a point, the more of the agonist the scientists applied, the bigger the effect. An inhibitor (antagonist) reversed this response.

"We saw a big and consistent physiological effect," said Roberto. "It was beautiful. The receptor had to be there or otherwise it wouldn't have worked."

With this major milestone achieved, the researchers extended their investigation to their primary area of interest—the brain's response to alcohol. Alcohol abuse can lead to devastating consequences for individuals and families. It is also associated with direct and indirect public health costs estimated to be in the hundreds of billions of dollars yearly in the United States alone.

To learn more about the effect of alcohol on the biology of the brain, the scientists focused on the transmission of one particular neurotransmitter called gamma amino butyric acid (GABA). GABA is the main inhibitory neurotransmitter in the brain, and neurons in every brain region use GABA to fine-tune signaling throughout the nervous system. Previous studies by the Scripps Research scientists indicated that GABA plays a critical role in alcohol dependence and other addictions.

"We knew ethanol in these neurons increase GABA transmission, and that cannabinoids decrease GABA transmission," said Roberto. "So the question was what happens if we activate the cannabinoid system and we put ethanol on it."

When the scientists first applied the CB1 agonist on cells from the central amygdala, it decreased GABA transmission; when the scientists proceeded to put ethanol on top, the effect of ethanol was abolished. When the team reversed the order of application, GABA transmission

first went up with the application of ethanol, then down with the application of the CB1 agonist.

"Alcohol and CB1 agonists have opposing effects on GABA," summarized Schweitzer. "Our feeling is that since the CB1 system is so widely expressed, there's a big role there in dampening the effect of alcohol."

While the team's research points to the endocannibinoid system as a potential target in the development of drugs to treat alcoholism, Schweitzer notes there are still many questions to be answered: Do CB1 agonists work the same way in brains that have become addicted to alcohol? What is the mechanism for this action? Can the effects of CB1 on alcohol metabolism be separated from its many other effects on mood, appetite, and memory?

Schweitzer also cautions against equating CB1 agonists and cannabis in interpreting the study's results. "This study does not have to do with marijuana, but the endocannabinoid system," he said. "On this level of analysis, the two don't have much in common."

**More information:** Journal paper: www.nature.com/npp/journal/vao … /abs/npp201070a.html

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