Cysteine supplement found to reduce desire for cocaine

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Sharing substance-use equipment can lead to the transmission of many microbes, including those that can cause hepatitis B and C as well as HIV. And substance use can affect a person’s critical thinking and judgment—factors that play a role in other behaviours that facilitate the spread of HIV. An effect of addiction is that it can destabilize a user’s health and life priorities, so helping people recover is an important step on the road to better health.

Many therapies have been tested to help cocaine users try to escape their dependence, but none have proven consistently effective. Now researchers at the Center for Drug and Alcohol Programs, the Division of Clinical Neurosciences, and Department of Neuroscience at the Medical University of South Carolina (MUSC) have made discoveries that may offer cocaine addicts new hope.

Losing control

Cocaine, like many street drugs, alters the way the brain responds to future cocaine exposure, making the user want to repeat his or her experience and laying the path for the downward spiral into addiction. Experiments on rats suggest that addiction affects an area deep inside a part of the brain called the nucleus accumbens. This area of the brain is believed to be involved in initiating important survival behaviors (such as seeking out food and sex). In addiction, this area is essentially hijacked by the addictive process, making a person seek out repeated exposure to street drugs as much as and even more than food, sex or just about anything else.

Rat research helps in understanding addiction

Researchers have discovered that cocaine addiction reduces the amount of glutamate (a neurotransmitter) in the accumbens. Without enough glutamate, the accumbens cannot be properly regulated, causing it to be extremely hyper-responsive to cocaine. Fortunately, the levels of glutamate can be restored by cysteine, a common amino acid usually sold in the form of N-acetyl-cysteine (NAC). When ingested, NAC helps the body release glutamate that is kept in reserve. With glutamate levels restored, the accumbens can function more normally and presumably helps a person feel less compelled to seek out cocaine. This, in turn, is believed to help reduce the amount of cocaine craving that addicted people would otherwise experience. Research at MUSC has indicated that supplements of NAC appear to restore glutamate levels and significantly reduce cocaine-seeking behavior in rats addicted to cocaine. Based on the results of these experiments, the MUSC research team decided to test whether NAC can help people addicted to cocaine.

Safety first

Because NAC had not been previously tried in cocaine-addicted individuals, it was necessary to focus on safety issues for the first NAC study. In that study, 13 participating cocaine addicts received either NAC (600 mg) or placebo every 12 hours for three consecutive days in a hospital, both taken orally as capsules. Neither the volunteers nor the experimenters initially knew which participants received what, in order to reduce bias when interpreting the results.

The following week, participants returned for another three-day hospital stay during which the experiment was repeated. For these three days, participants who initially received placebo got NAC, and vice versa. Overall, researchers that found that NAC was “safe and well tolerated.” There were trends of reduced levels of craving in participants taking the supplement. And MRI scans revealed that these participants showed less activity in an area of
the brain known as the anterior cingulate that has been previously linked to craving \( \textit{(personal communication, Martin Malcolm, MD)} \).

**Large study begins**

Having found the use of high doses of NAC to be safe, the MUSC research team has launched a larger and longer study to assess the effectiveness of oral NAC in reducing craving for cocaine. The researchers hope to recruit 282 participants who will be randomly assigned to receive one of the following:

- NAC – 1,200 mg twice daily
- placebo – twice daily

In the large study, participants will be monitored for up to two months and will need to visit the study centre three times weekly for assessments, interviews and analyses of urine to determine cocaine use.

It will take several years before the study is completed and the results are fully analysed. Part of the reason for this is that research in the area of addiction is time-consuming and participants tend to drop out more frequently than in research on other health conditions \( \textit{(personal communication, Steven LaRowe, PhD)} \).

**Preliminary results**

In an exciting development, the MUSC team has analysed preliminary results from its clinical trial using data from 15 participants (eight females and seven males). Their average age was 37 years and they used cocaine in the following ways:

- 10 participants were “crack” smokers
- 2 snorted powdered cocaine
- 3 used cocaine in several ways, including inhaling and smoking it

Before entering the study, participants noted that they had used cocaine for nearly 40 days of the past three months. They spent an average of $95 U.S. on cocaine for each day that they used this drug. For the study, participants spent a total of six days in a research hospital. During this time, urine tests and close monitoring suggested that they did not use cocaine. Participants received NAC or placebo every 12 hours, both by mouth. The dose of NAC used was 600 mg every 12 hours for three consecutive days. After this, participants left the hospital and were away for four days. They then returned to the hospital for another three-day stay where the experiment was repeated with a different substance—people who initially received placebo were given NAC and vice versa.

The study team found that exposure to NAC was associated with a statistically significant reduction in the desire to use cocaine and participants had less interest in cocaine.

These results are promising, however, more data using a larger number of participants is needed before firm conclusions about the role of NAC in helping people recover from cocaine addiction can be drawn.

**Beyond cocaine**

The research on NAC and cocaine addiction has a sound biological basis in rats and likely in people. The theories about glutamate and cysteine that underpin the biology of cocaine addiction may also give hope to people addicted to other substances such as tobacco, heroin and crystal methamphetamine. However, NAC needs to be tested in animals addicted to these other substances before its potential for addiction recovery can be assessed. Presently, work is underway at MUSC that is assessing NAC in heroin-addicted rats; initial results have been promising.

An important aspect of recovery from addiction is counselling to help participants unlearn negative behaviours. It is therefore likely that NAC (or any other anti-addictive substance) by itself would work best as part of a long-term holistic program geared toward recovery. Indeed, the animal research suggests that NAC alone does not stop ongoing cocaine use—it only appears to be effective in rats that are undergoing an addiction recovery program.

**NAC and HIV**

The body uses amino acids, including cysteine and glutamine, to make GSH (glutathione). In turn, cells convert GSH
into the body’s premier antioxidant. This antioxidant helps to protect cells from toxic substances.

Beginning in the mid-to-late 1980s, researchers began to find that people with HIV/AIDS (PHAs) had less-than-normal levels of GSH in their blood. The reasons for this are not certain but may be related to the damaging effects of HIV on the body and a high demand for cysteine that exceeds the supply available to cells. Supplements of cysteine can significantly increase GSH levels in the blood of PHAs.

In the time before highly active antiretroviral therapy (HAART), supplements of NAC were popular among some PHAs. Short-term clinical trials found that NAC can increase CD4+ cell counts. Also, findings in that era from one study of high-dose NAC (about 4 grams daily) suggested an increased chance of survival in some PHAs.

However, HAART’s impact on CD4+ cell counts is much more dramatic and lasting than that of NAC. Nowadays, NAC is used in lower doses—often between 1 and 2 grams daily—to raise GSH levels in the hope that it may reduce the toxicity of anti-HIV medications to the liver, kidneys and other organs. Capsules of NAC are usually taken with fruit juice or cola drinks, as this can sometimes minimize side effects such as upset stomach, heartburn or diarrhea.

**Availability**

NAC is available in capsule formulation and can be found in some health food stores. A liquid formulation is available by prescription in North America and the European Union. This formulation is suitable for use in nebulizers (where it can be inhaled) or for intravenous administration. In this latter form, NAC is used to treat cases of acetaminophen (Tylenol) poisoning.

—Sean R. Hosein

**REFERENCES:**


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