A POTENTIAL VACCINE AGAINST COCAINE ADDICTION

Research to develop an immunizing agent for treating addiction to cocaine is underway

Suzel Tunes

Addiction to cocaine, including its derivatives such as crack, remains a global public health concern for which the medical community has yet to find an effective treatment. A team of researchers at the Federal University of Minas Gerais (UFMG) is turning to immunology to find a solution. The group is developing a novel vaccine against cocaine addiction and is currently seeking funding for its first human trials. Initial experiments on animals have demonstrated the ability of the vaccine to stimulate the production of anti-cocaine antibodies, but scientific evidence confirming its effectiveness in reducing drug dependency has yet to be obtained. The researchers plan to conduct further testing in animals before proceeding to clinical trials involving human volunteers on a to-be-determined date.

"In testing on rodents and nonhuman primates—specifically of the species *Callithrix penicillata*—our vaccine, called Calixcoca, produced no significant side effects. We only observed a mild reaction at the injection site, which did not affect the overall health of the animals," says Frederico Duarte Garcia, a professor in the Mental Health Department at the UFMG School of Medicine and the lead author of the study.

The name Calixcoca, he says, is inspired by the chemical structure of the immunizing agent, known as calixarene, so named because it resembles a chalice. This molecule serves as the carrier for the antigen, a hapten that is an analog of cocaine—carriers are high-molecular-weight substances that are capable of eliciting an immune response.

Pharmacist Paulo Sérgio de Almeida Augusto, a member of the UFMG research group, explained that haptens are tiny molecules that, due to their diminutive size, are typically not recognized by the immune system as invaders; therefore, haptens need to be combined with larger carrier macromolecules to prompt an immune response within the body. This is the case with cocaine. Augusto explains, "Cocaine represents a foreign molecule within the human body. However, it often lacks the molecular weight and chemical complexity required to elicit a substantial immune response. Although such a response may occur in individuals who frequently use high doses of the drug, it does not occur in every individual."

The researchers developed their immunizing agent by deriving a hapten from a cocaine molecule specifically modified to bind to the carrier. When coupled with calixarene, the derived hapten has a higher molecular weight and is able to elicit an immune response. If a vaccinated individual uses cocaine or crack, the antibodies will bind to the drug molecules in the bloodstream, preventing—or at least reducing—their passage through the blood–brain barrier. This barrier lines the blood vessels that vascularize the central nervous system, acting as a selective gatekeeper that controls the transport of substances into the brain.

In mice administered with the synthesized molecule, radiochemical assays conducted by UFMG researchers showed that the vaccine successfully reduced drug transport across the blood-brain barrier. "Immunized animals were treated with a radiolabeled analog of cocaine. Immunosorbent assays showed a lower concentration of this compound in the brain and a higher concentration in the bloodstream compared to those in animals that received only the placebo," explains Augusto. The study results were published in the *Journal of Advanced Research*.

The UFMG researchers hypothesize that if the vaccine is able to prevent cocaine molecules from crossing the blood-brain barrier, individuals will no longer experience the same pleasurable sensations that previously triggered the brain's reward circuitry, driving compulsive behavior. This, however, has yet to be demonstrated in clinical trials. "Without the compulsion, patients have the opportunity to reclaim their family life, pursue their professional interests, and rediscover their other pleasures and interests that were once overshadowed by addiction," explains Garcia.

LONG-STANDING CHALLENGES

The new therapeutic approach is viewed with guarded optimism by drug addiction experts. "The medical field has yet to develop an approved drug for fighting addiction. Current treatments primarily focus on managing the symptoms of withdrawal and related disorders, coupled with behavioral therapy," explains Fábio Cardoso Cruz, a professor of biochemistry in the Department of Pharmacology at the Federal University of São Paulo (UNIFESP) who was not involved in the UFMG study.

FOCA LISBOA / UFMG

Cocaine base: Cocaine is the second most consumed illicit substance in Brazil

Cruz is currently researching the neurobiological mechanisms underlying relapse to cocaine use in a FAPESP-funded project. His study aimed to answer the question of why 70% to 80% of individuals relapse during treatment. "This shows the urgent need to develop new therapeutic strategies. Vaccines are now emerging as a promising pharmacological approach," he says.

Calixcoca is not the first immunology-based therapeutic formulation developed to treat substance dependence. "The therapeutic potential of vaccines against drug addiction was first demonstrated in the mid-1970s when a conjugate of morphine and bovine serum albumin was found to mildly reduce heroin self-administration in a rhesus monkey. The first papers describing attempts to develop vaccines against cocaine and nicotine addiction were published in the 1990s," says Cruz. The rhesus monkey experiment was published in *Molecular Psychiatry* in 1974.

Despite the promising results in preclinical trials and some early clinical trials, no antidrug vaccines have yet been approved. "Several hurdles remain on the path to clinical success. Notably, not all individuals respond uniformly to these vaccines, and in some individuals, the levels of antibodies necessary for achieving the desired clinical efficacy may not be produced," says Cruz from UNIFESP.

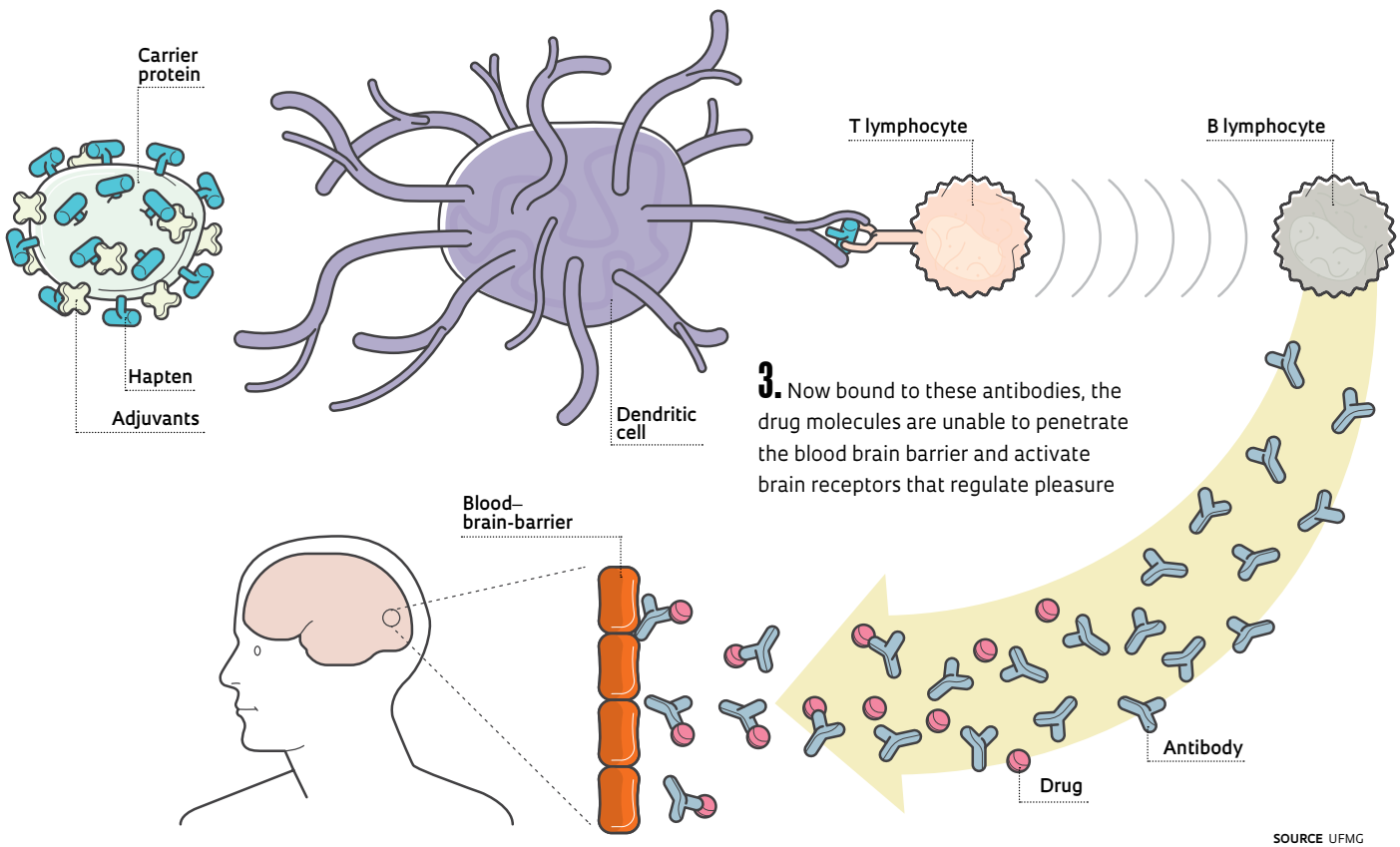
"In general, vaccines are shown to be efficient in animal models. However, when they progress to the clinical trial phase, the results often fall short of expectations," says Denise Morais da Fonseca, an immunologist affiliated with the Institute of Biomedical Sciences at the University of São Paulo (ICB-USP). In March, she collaborated

HOW THE VACCINES WORK

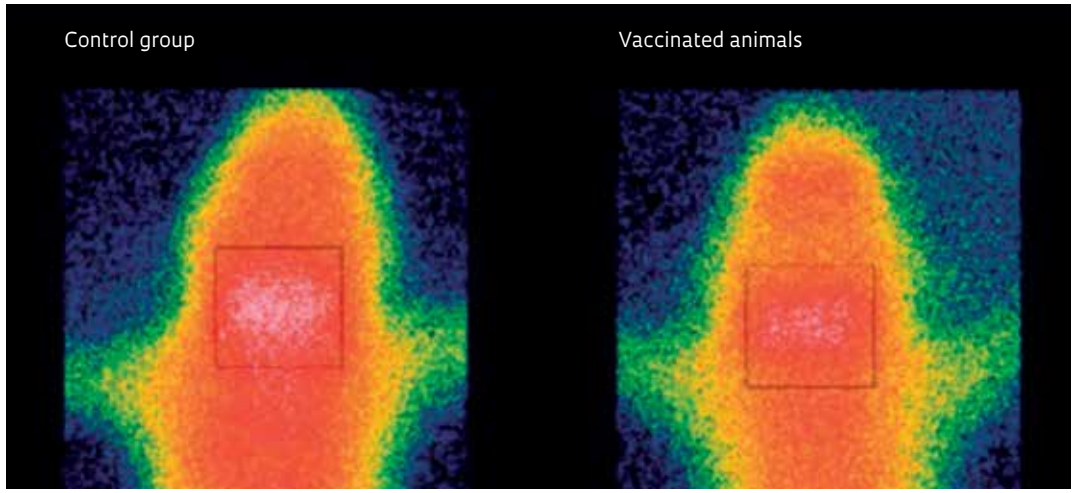
Vaccines for treating drug addiction typically consist of a hapten—a structurally modified drug molecule—conjugated to a carrier substance

1. The carrier, which has a larger molecular weight and is therefore capable of eliciting an immune response, is combined with an adjuvant that further enhances the body's immune response

2. In the bloodstream, dendritic immune cells capture antigens and present them to helper T lymphocytes. This, in turn, stimulates B lymphocytes to produce antibodies that bind to the drug



SOURCE UFMG



Radiochemical assay images showing a lower concentration of a radiolabeled cocaine analog in the brains of rodents immunized with the UFMG vaccine (*pink dots in the center of the image*) than in those of rodents in the control group

in developing an ICB course on pharmacological treatments for addiction. In preparation, she delved into the literature reviews concerning drug vaccines—obtaining rather disappointing results. "A 2022 review documented 23 clinical trials involving antidrug vaccines, with six targeting cocaine addiction—most were focused on nicotine," notes Fonseca. "Every single one of them failed."

Some vaccines, she elaborates, failed to elicit a sufficient quantity of antibodies, or the immune response waned far too quickly. The precise reasons behind these results remain unclear, although they might be attributed to genetic variability among the individuals tested—a factor absent in animal models. "In most studies, researchers use isogenic mice, meaning they are genetically identical," Fonseca explains.

Another possible explanation could lie in the behavior of the vaccine recipients themselves. "In some unsuccessful trials, individuals struggling with addiction consumed larger drug doses to achieve the desired effect," she remarks.

The UFMG researchers recognize the theoretical risk of individuals attempting to overcome the effects of the vaccine by consuming larger doses of cocaine to reactivate the brain's reward circuitry. According to Augusto, this concern will be addressed in subsequent studies using experimental models that can estimate the quantity of the drug that the vaccine is capable of blocking. "Our primary goal is to roadblock the compulsion mechanism," Garcia notes. "Beyond a certain point, increased consumption would significantly increase the cost for the user, to a point where it becomes financially prohibitive."

The UFMG group is confident that Calixcoca will outperform the other vaccine candidates in terms of efficacy. The researchers' confidence stems from the unique chemical composition of the vaccine. "The key distinction in our proposition is that the vaccine has no protein base. Calixarene is a synthetic organic substance," says Ângelo de Fátima, a professor at the UFMG Department of Chemistry who developed the vaccine's immunogenic platform.

Prior antidrug vaccine programs have relied on proteins as carriers, some of which have been used in other commercially available vaccines. This raised concerns about potential sensitization issues. "Patients reacted not only against the drug but also against these proteins. Our vaccine induces a better response because it introduces an entirely new molecule to the body," Garcia says.

Another significant advantage of the new formulation, such as its developers, lies in its production process. "Calixarene is a more stable substance and doesn't require a cold chain for production and storage. This makes the process more cost-effective," Garcia explains. A cold chain refers to the logistics of handling, storing, distributing, and transporting temperature-sensitive medications.

Even if Calixcoca proves effective in generating antibodies against cocaine in humans in future clinical studies, additional therapeutic support will be needed, Cruz notes, drawing on his research into the biological mechanisms of addiction. He notes that patients' associative memory related to drug use can be triggered by various cues, such as stress or exposure to environments and settings associated with drug use.

When a person has chronically used a particular substance, their brain associates the drug's effects with the location where it was typically consumed, the objects used to consume it, the people around during consumption, and even the clothing worn during these occasions. Exposure to these elements can ignite an uncontrollable craving for the substance. "Vaccines can be used as part of an integrated approach combining behavioral therapy, psychosocial support, and other

PHOTO UFMG **INFOGRAPHIC** ALEXANDRE AFFONSO / PESQUISA FAPESP MAGAZINE

interventions to assist individuals in overcoming addiction," says Cruz.

"Antidrug vaccines need to be thought of as a component of broader public programs," adds Fonseca from ICB-USP. She sees several ethical issues surrounding the use of vaccines. "Will we employ them as therapeutic or prophylactic vaccines? Will we screen high-risk groups for vaccination?" she asks. One potential use of the new pharmaceutical, according to Cruz, could be to protect expecting mothers and their infants from the harm caused by prenatal drug exposure. This is another facet of the UFMG group's research and a subject of Paulo Augusto's doctoral thesis in molecular medicine, which he defended in 2020.

Cruz notes that cocaine exposure during pregnancy poses risks not only to mothers, who may experience miscarriages or complications during delivery but also to fetuses and infants, with long-term implications throughout the lifetime. Prematurity, low birth weight, impaired neurobiological development, malformations, and an increased risk of developing psychiatric disorders in adolescence are among the deleterious effects associated with cocaine use during pregnancy. "The best approach to prevent prenatal cocaine exposure is to cease consumption. However, only 25% of cocaine users manage to quit while pregnant," notes Augusto.

His doctoral research served as a proof of concept for administering the anticocaine vaccine during pregnancy based on testing on pregnant rats. Published in *Molecular Psychiatry* in 2021, his paper describes the first study to report the efficacy of an immunizing agent during gestation. This project ran when Calixcoca was still being developed, so Augusto chose to use a vaccine created by American researcher Kim Janda, known as GNE-KLH. This vaccine, based on the culmination of studies dating back to the 1990s, demonstrated promising results in preclinical testing but failed to yield the anticipated effects in clinical trials.

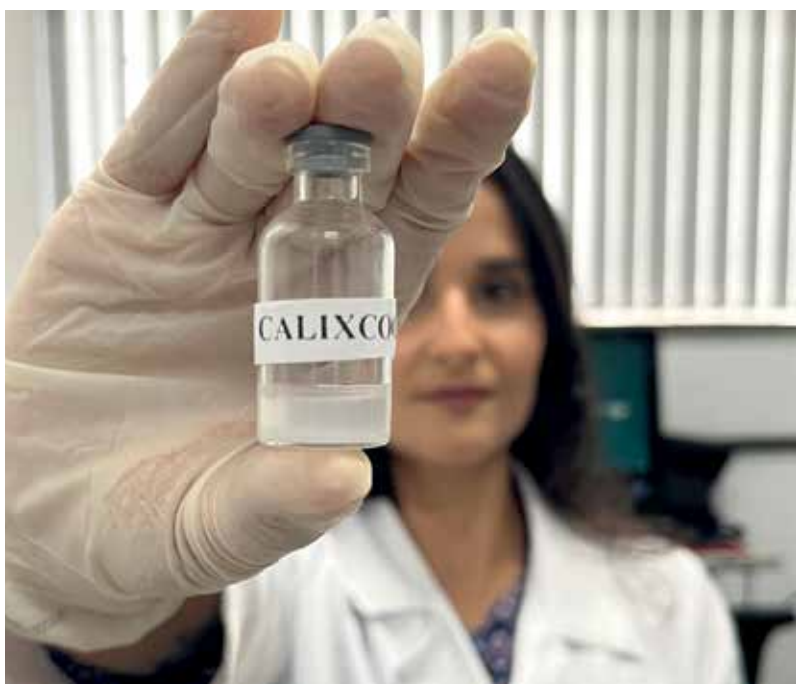
However, in animal testing, the outcomes were positive. "Compared to mothers treated with a placebo, those vaccinated during pregnancy exhibited greater gestational weight gain and larger litters," the researcher reports. "Anticocaine antibodies were detected in fetuses, newborns, and even breast milk."

These antibodies also helped to mitigate the hyperactivity and hyperlocomotion effects induced by cocaine in newly weaned offspring. To validate this hypothesis, the rodents received doses of cocaine and were subsequently placed inside boxes for observation. "The typical behavior of pups is to huddle in a corner of their box. Under the influence of cocaine, the pups became more uninhibited, moving throughout the box. However, those administered antibodies exhibited normal behavior," the researcher adds. The UFMG group plans to replicate the same experiment using Calixcoca.

As mentioned by Cruz, scientists must seek to gain an understanding of the mechanisms of addiction to find novel approaches for treatment. "Addiction has not yet been treated with the compassion it deserves. It's not a character flaw or lack of willpower; it's a lifelong illness," says Cruz.

The UFMG group has been in discussions with potential funders for clinical trials. In June, the municipal government of São Paulo announced an R$4 million grant for the project and its intention to evaluate the administration of the vaccine among eligible groups, including people recovering from drug addiction, in the next phase of trials. Conversations are also underway with the São Paulo state government and the Butantan Institute. "We'll require R$30 million for the Phase I and II clinical studies, which are expected to take between two and three years to complete," says Cruz.

The researchers have already filed a patent for the candidate vaccine on behalf of UFMG and the Minas Gerais State Research Foundation (FAPEMIG), which is funding the project. In May, the UFMG study was selected as a finalist for the 2nd Euro Innovation in Health Award, an international initiative recognizing medical innovations sponsored by the Brazilian pharmaceutical company Eurofarma. ■



Raissa Pereira, a PhD student at UFMG, holding a vial containing the Calixcoca vaccine formulation

UFMG

The projects and studies consulted for this article are referenced in the online version.