Investigators Show Nicotine Primes Brain for Cocaine Use

A mong adults aged 18 to 34 who used cocaine at least once, more than 90 percent smoked cigarettes first. It’s also long been known that use of one addictive substance increases the risk of another, such as cigarette smoking and consumption of alcohol before use of cocaine or marijuana — the so-called “gateway sequence.” Now, for the first time, neuroscience researchers at Columbia University College of Physicians and Surgeons have shown that nicotine primes the brain for cocaine use, and they identified a molecular mechanism underlying this gateway sequence.

“These results show nicotine creates fundamental changes in the brain that increase the effects of cocaine entering the brain,” explains Denise B. Kandel, PhD, Professor of Sociomedical Sciences in Psychiatry at Columbia. Dr. Kandel conducted the study, which was published in Science Translational Medicine, with Eric R. Kandel, MD, University Professor, Fred Kavli Professor and Director, Kavli Institute for Brain Science at Columbia and a Howard Hughes Medical Institute Senior Investigator, and lead author Amir Levine, MD.

“Our study is the first to pinpoint the mechanism underlying the effect of nicotine on cocaine use on a behavioral level, on a cellular/physiological level, and on a molecular/genetic level. The concept of one agent altering the response of the brain to a second agent is called meta-plasticity.”

Elucidating Cognitive Function in Severely Brain-Injured Patients

A dapting a novel neuroimaging technique to assess capacity to communicate and establish direct communication with brain-injured subjects with impaired motor function was the focus of a study published in the March 2011 issue of Brain by researchers at Weill Cornell Medical College.

“The use of functional MRI-based paradigms to specify levels of residual cognitive capacity, as well as the extent to which they have a clear relationship to traditional bedside evaluations, are still major open questions,” says Nicholas D. Schiff, MD, the Jerold B. Katz Professor of Neurology and Neuroscience and Professor of Public Health at Weill Cornell Medical College and a neurologist at NewYork-Presbyterian Hospital/Weill Cornell Medical Center. Dr. Schiff and his research team tested a hierarchical, single-response-type, functional MRI (fMRI) methodology — previously validated in normal subjects — to provide assessments of the subjects’ capacity to utilize brain activity to follow commands and answer questions with graded levels of difficulty, as well as to maximize their efforts and afford the greatest flexibility for response output.
Can Gene Therapy Change the Landscape of Treatment for Parkinson’s Disease? Contributing faculty for this article: Blair Ford, MD

More than 1.5 million people in the United States are affected by Parkinson’s disease. At present, there is no cure nor is there any effective neuroprotective agent available to slow or halt the progression of the disease. A novel study that is much anticipated by the Parkinson’s disease community is now underway at NewYork-Presbyterian Hospital/Columbia University Medical Center and 10 other leading medical centers around the country.

The Phase 2/3 clinical trial involves an experimental therapy – CERE-120 – that may prevent the death of dopamine neurons in patients with Parkinson’s disease (PD). CERE-120 is composed of an adeno-associated virus vector carrying the gene for neurturin, a naturally occurring protein – also known as a neurotrophic factor – to repair damaged and dying dopamine-secreting neurons.

“CERE-120 therapy is the only gene therapy currently in clinical trials that delivers a nerve growth factor with the potential to slow down the progression of Parkinson’s,” says Blair Ford, MD, Professor of Clinical Neurology and the principal investigator of the study at NewYork-Presbyterian/Columbia. “Other gene therapies currently under investigation aim to reduce Parkinson’s symptoms but are not designed to help prevent the death of nerve cells in the brain.”

PD, providing a rationale for moving into human studies.

According to Dr. Ford, a unique aspect of the trial is that the patient is not given the treatment substance itself, but rather the gene to make the substance. “The gene is injected into the brain of patients with PD using the virus that ‘transfects’ brain cells, turning cells into miniature factories for neurturin, a synthetic version of GDNF, the growth factor for dopamine-producing cells,” explains Dr. Ford. “In Parkinson’s disease, the brain’s dopamine cells are dying for reasons unclear. As part of normal development in the human brain, dopamine cells are supported by GDNF. Therefore, providing this nerve growth factor or its analog seems, at least at face value, promising if it can be accomplished technically.”

NewYork-Presbyterian/Westchester Receives Planetree Designation

NewYork-Presbyterian Hospital’s Westchester Division is the first behavioral health hospital in the nation to be formally named by Planetree Inc. as a “Planetree Designated Patient-Centered Hospital.”

“Patient-centered care is central to everything we do, and it is particularly important in a behavioral health setting,” says Philip J. Wilner, MD, MBA, Vice President and Medical Director of Behavioral Health at NewYork-Presbyterian Hospital/Westchester Medical Center and Professor of Psychiatry at Weill Cornell Medical College. “Creating an environment where patients feel respected and creatively engaged in their recovery promotes healing.”

Since becoming a Planetree member in 2003, NewYork-Presbyterian/Westchester has enhanced its environment in a number of ways, including:

- renovations of the main entrance to include a welcome desk, cozy seating area, chapel, patient resource library, and small café
- renovated courtyards, enhanced landscaping, and a labyrinth for meditation and reflection
- cultural programs and an in-house gallery displaying patient artwork
- new menus and patient involvement in food preparation and cooking groups
- alternative and complementary medicine, such as aromatherapy and pet therapy

“The Planetree Designation is the only award that recognizes excellence in patient-centeredness across the continuum of care,” says Susan Frampton, President of Planetree Inc. “The designation signals to health care consumers that NewYork-Presbyterian/ Westchester is a hospital where providers partner with patients and families, and where patient comfort, dignity, empowerment, and well-being are prioritized with providing top-quality clinical care.”

Designated hospitals are also nationally recognized by the Joint Commission, which has approved the designation program as one of the awards recognized on its Quality Check website in the special quality awards section.
producing a steady supply of neurturin. This new approach intends to expose both ends of the dopamine neurons to neurturin and will hopefully halt progression of the disease.

Dr. Ford cautions that CERE-120 is still experimental and comes with risks, including those associated with neurosurgery. Viral vectors similar to that used in CERE-120 have been used in many other experimental gene therapies and have not caused serious side effects or disease, but there still may be unknown risks. The study will enroll approximately 50 patients with early Parkinson’s disease. More information about the study, including ways to enroll, is available in the clinicaltrials.gov study registry.

For more information, see the original journal article: Barolin JC, Fins JJ, Katz DI, Heerd J, Heier LA, Tabelow K, Dyke JP, Ballon DJ, Schiff ND, Voss HU. Dissociations between behavioural and functional magnetic resonance imaging-based evaluations of cognitive function after brain injury. Brain. 2011 Mar;134(Pt 3):769-82.
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Using a novel mouse model, the research team explored the effects of sequential administration of nicotine and cocaine on behavioral responses, synaptic plasticity, and gene expression, as well as acetylation of histones in the promoter regions of genes in the striatum, a brain region critical for addiction-related reward. Nicotine was administered to the mice in their drinking water, while cocaine was given via injection.

The priming cocaine first did not change the response to cocaine. For example, locomotor sensitization was increased by 98 percent and conditioned place preference (CPP) by 78 percent, a measure of the amount of time an animal spends in compartments previously associated with stimuli or reward, is a well-established measure of drug-induced conditioning and a naturalistic model of addictive behavior.

Nicotine also accentuated the reduction in long-term potentiation in the nucleus accumbens by 24 percent. The nucleus accumbens is a region of the brain where drug-related increases in dopamine are associated with reward.

Molecular studies showed that nicotine reverses the brain's response to cocaine by boosting expression of FosB, an immediate response gene implicated in addiction to many drugs of abuse and in the response to other rewarding stimuli. Nicotine also inhibited histone deacetylase, causing global histone acetylation in the striatum. Conversely, giving the mice low doses of theophylline, an asthma drug which also stimulates histone deacetylation, attenuated the response to cocaine.

The priming response was unidirectional, occurring only when nicotine was given first. The cocaine replacement therapy repeated the behavioral response of the mice to nicotine or the expression of FosB. Moreover, the two

The data also signal concerns about the use of nicotine replacement therapy among cocaine abusers who wish to stop smoking, since the nicotine may fuel their cocaine addiction.


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Clinical Infectious Diseases (CIDs) 2012;55(6):849-855. This article may not be reproduced in any form without the permission of the publisher. All rights reserved.
The current research, led by B.J. Casey, PhD, Director of the Sackler Institute and the Sackler Professor of Developmental Psychobiology at Weill Cornell Medical College, assessed the behavioral and neural correlates of delay of gratification in almost 60 adults who participated as four-year-olds in the original delay-of-gratification task and whose self-control abilities remained consistent in follow-up assessments. In the present study, we examined the extent to which individual differences in delay of gratification assessed when participants were in preschool and in their 20s and 30s predicted control over impulses and sensitivity to social cues at the behavioral and neural level when the participants were in their 40s, explains Dr. Casey.

The individuals represented either extreme of the delayed-gratification spectrum—high delayers and low delayers. Two experiments were conducted to investigate their ability to refrain from responding to alluring cues. In the first experiment, participants were tested on “hot” and “cool” versions of an impulsive control task (i.e., the go/no-go task). Because marshmallows and cookies can be less enticing to adults, the researchers substituted the treats for social cues of faces with emotional expressions that over a lifetime come to have positive value. In the “cool” test, participants looked at a screen displaying a series of faces with neutral expressions and were asked to press a button whenever one gender appeared (go), but not to the other (no-go). The go cue occurred frequently, making it more difficult to stop for the rare no-go cue. This test revealed no significant differences between the two groups. A second, “hot” test used emotional cues such as a happy or frightened face. Individuals who were less able to delay gratification as children (low delayers) performed more poorly than did high delayers when having to stop to the positive social cue of a happy face but not to a neutral or fearful face.

“Over a lifetime, smiling faces come to be associated with positive outcomes and have been shown by our group to influence behavior as much as food or money,” notes Dr. Casey. “The positive social cue interfered with the low delimiter’s ability to suppress his or her actions. The people who couldn’t delay as four-year-olds, when 40, couldn’t stop themselves from reacting to positive social cues. It’s really shocking 40 years later to see such a consistency in the behavior. A lot happens in life between four and 40.”

In a subset of the study cohort, the second test was then repeated while the participant’s brain was scanned using noninvasive functional magnetic resonance imaging (fMRI). Specifically they tested for differences between the low and high delayers when inhibiting a response to positive social cues. The results showed that the brain’s prefrontal cortex, a region involved in rational thoughts and actions, was more active for high delayers, and the ventral striatum—a brain region involved in motivation and rewards and risk taking was more active in low delayers.

According to Dr. Casey, who is a pioneer in novel uses of brain imaging to examine behavioral and brain development, “This is the first time we have located the specific brain areas related to delayed gratification. These findings could have important implications for substance abuse and obesity, which have been related to delay ability in previous studies. By finding ways to cool down cues that may drive these behaviors, we may be able to ultimately prevent these behaviors.”

Research in the field has shown that “high delay ability promotes the development of better social, cognitive, and emotional coping in adolescence and buffers against the development of a variety of dispositional physical and mental health vulnerabilities in middle age, such as higher body mass index, sensitivity to rejection, cocaine/crack use, and marital divorce/separation.”

“Our findings provide a neurobiological basis for differences in this ability,” says Dr. Casey. But, she emphasizes, the inability to delay gratification is not a fatal flaw. “The high delayers who were able to exploit the situation and thus receive two cookies may be more methodical and thoughtful in their actions, while low delayers who act in the moment may be more likely to be risk takers and pioneers, and we need both in society.”

Important news from the Neuroscience Centers and the Departments of Psychiatry of NewYork-Presbyterian Hospital. Current research projects, clinical trials, and advances in the diagnosis and treatment of patients with neurological and psychiatric diseases.

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