Scripps Scientists Discover Involvement of New Receptor in Cocaine Abuse

La Jolla, CA. June 18, 1993 -- Scientists at The Scripps Research Institute (TSRI) have discovered the role of a new class of brain receptors in cocaine abuse, a finding that could lead to the development of more selective and more effective pharmacologic therapies to wean addicts from cocaine as well as strategies for the prevention of addiction.

The work was announced in the June 18 issue of Science, the journal of the American Association for the Advancement of Science, by S. Barak Caine and George F. Koob, Ph.D., a member of the Department of Neuropharmacology at TSRI, in an article entitled, "Modulation of Cocaine Self-Administration in the Rat Through D-3 Dopamine Receptors."

It was funded by grants from the National Institute on Drug Abuse.

"The value of this study is that we have uncovered information about these receptors that has increased our understanding of how to modulate the reinforcing properties of cocaine and thereby design safe and appropriate therapeutics to counter its effects," said Koob, in whose laboratory the work was conducted.

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Overwhelming evidence suggests that cocaine produces its behavioral effects by increasing the activity of dopamine -- a neurotransmitter or chemical that passes between brain cells for communication -- that is believed to be a critical part of one of the brain’s pleasure systems. Further, dopamine then stimulates cell proteins called receptors, to produce its effects. Neurotransmitters can be viewed as keys to the receptors’ locks; they are able to open several locks that can then perform a variety of functions. Dopamine receptors are thought to regulate brain activities related to movement, arousal and motivation, and possibly emotions as well as other thought processes.

For nearly 15 years, investigation of the effects of dopamine on the brain has been based on D-1 and D-2 receptors, two of the five dopamine receptors currently identified. While they, too, are involved in cocaine’s reinforcing effects, they are widely distributed in areas of the brain that affect other functional activities, most notably motor movements.

In recent years, the French scientists Jean-Charles Schwartz, Daniel Levesque, and colleagues in the laboratory of Pierre Sokoloff cloned the D-3 receptor and identified the selectivity of compounds for these receptors, allowing for the experimental work in this study. An important factor in the involvement of this receptor in cocaine abuse -- and its significance in developing therapies to lessen its effects -- is its restricted localization to the "limbic" dopaminergic projection area in the brain that has been implicated as an interface between emotion, motivation and behavior -- areas important in drug reward -- possibly leaving areas responsible for motor function unaffected.

The authors note that addictive substances seem to share many common features in their actions in the brain, engaging brain circuits related to emotions, motivation and behavior. This, in part, explains how drugs can gain control over one’s behavior by playing on basic biological drives and motives.
In this study, rats, connected to a cocaine supply by intravenous tubes, are allowed to administer as much cocaine as they like for three hours each day. When limited to that time period, each rat quickly establishes a baseline stability, taking almost exactly the same amount of cocaine each day. When self-administering cocaine in combination with very small quantities of the drugs that bind to the D-3 receptor, "they take up to 60 percent less than their normal daily amount," according to co-author Caine. He notes that these low doses of the compounds were not by themselves reinforcing.

In the past, scientists have tried to lessen the cravings for cocaine by blocking the dopamine receptors, thereby blocking the effects of cocaine. However, in the presence of these compounds, rats tend to increase their cocaine intake, presumably to compensate for the antagonist's effects. Likewise in humans, this approach has lost favor because efforts to block cocaine's effects using dopamine antagonists seem to exacerbate symptoms of depression and craving, he remarked.

"In contrast to this methodology, what we're interested in achieving," Caine continued, "is a means of regulating the dopamine system and by so doing, finding compounds that reduce these symptoms without producing dependence on the compounds themselves. The drugs we have used in this study bind directly to the D-3 dopamine receptors, and produce the desired effect of reducing the amount of cocaine self-administered. However, we still don't know whether these D-3 selective drugs can reduce symptoms of craving and withdrawal."

In 1987 Dr. Koob and his associates tested a drug widely used to treat infertility and Parkinson's disease as a tool to reduce the addictive effects of cocaine. Bromocriptine, known then to bind to the D-2 receptor, but now known to bind to D-3 receptors as well, reduces cocaine intake by the same mechanism of interacting with the chemical "pleasure center" in the brain that is stimulated by cocaine. This drug has been available for more (MORE)
than a decade. It was initially studied to overcome female infertility caused by overproduction of the hormone prolactin and is also used to relieve symptoms of Parkinson’s disease.

While it was shown to reduce the craving for cocaine in animal models, the utility of bromocriptine in cocaine abuse treatment is still unclear. There may be advantages in using compounds that bind selectively to D-3 receptors rather than D-2 receptors because of their localization only to areas thought to affect cognition, emotion and motivation, but not motor function, thereby reducing side effects. To date, these compounds are experimental drugs used in basic biomedical research. While the researchers note that they were used because of their binding affinity to these receptors, more work must be done to study their safety; the abuse potential of the compounds is as yet unknown.

Koob remarks that one can generalize somewhat from the animal model to the human condition, and postulates that the next steps in their research will be to test the effects of D-3 selective drugs with animal models of withdrawal and craving. "We will continue to explore the neurobiological mechanisms of D-3 receptors which could lead us to a better understanding of the cellular mechanisms underlying cocaine’s effects," he said. "This information could lead us to the development of highly selective drugs and to breakthroughs in prevention. In addition, the information may ultimately provide insight into the neurobiological mechanisms of debilitating psychiatric disorders such as mania and depression. These are important goals."

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