Immunotherapy for Cocaine Addiction

Newly developed compounds derived from the immune system may help combat cocaine abuse by destroying the drug soon after it enters the bloodstream

by Donald W. Landry

The epidemic of cocaine abuse that has raged through the U.S. for more than a decade has left no part of the nation untouched. Millions take the drug, with medical consequences that include severe psychological disturbance and sudden heart attack. The social effects of illegal cocaine distribution have contributed to the devastation of many cities, draining both human and financial capital that might otherwise be put to productive use.

Many factors have contributed to the present crisis, including the social acceptance of drug taking, the ineffective antismuggling policies that have led to increased availability of inexpensive cocaine, and the development of a higher-potency, smokable form of the drug, "crack." Unfortunately, as a society we have not been able to reverse the tide, and biomedical science has thus far failed to offer a pharmacological solution.

In fact, despite decades of effort, medical research has not yet produced any agent able to treat effectively either cocaine addiction or cocaine overdose. This protracted failure has prompted my colleagues and me at Columbia University to embark on a radically new approach. Traditional therapeutic research has attempted to interfere with cocaine in the brain; our strategy aims to destroy the drug before it has any chance of reaching the brain at all.

The appeal of this new approach is based on the peculiarities of cocaine's effects on the brain. Essentially all addictive drugs stimulate a neural "reward pathway" that evolved in the ancestors of mammals more than 100 million years ago. This pathway activates the so-called limbocortical region of the brain, which controls the most basic

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CRACK and powdered cocaine are the two forms of the drug.

emotions and behaviors. In preconscious creatures, activation of reward pathways during behaviors as diverse as feeding and copulation aided learning and undoubtedly conferred a survival advantage. The same structures persist today and provide a physiological basis for our subjective perception of pleasure. When natural brain chemicals known as neurotransmitters stimulate these circuits, a person feels "good."

Substance abuse is rooted in the normal neurobiology of reinforcement. Every substance that people commonly self-administer to the point of abuse—alcohol, nicotine, barbiturates, amphetamines, heroin, cannabis or cocaine—stimulates some part of the reward pathway, thereby "teaching" the user to take it again. Furthermore, these substances alter the normal production of neurotransmitters so that abandoning the drugs once the addiction has taken root can trigger withdrawal: physical or psychological upsets whose effects vary from deeply unpleasant to dangerous. Humans and other animals will perform work, sacrifice other pleasures or endure pain to ensure a continuing supply of a drug they have come to depend on.

The magnitude of reinforcement differs intrinsically among the addictive drugs. It also rises with the amount of drug that reaches the brain and the speed with which the drug's concentration mounts. Intravenous injection typically provides the most efficient delivery. For substances that can be vaporized, however, such as cocaine in its crack form, smoking is equally effective in producing the experience that addicts want. Cocaine, particularly when injected or smoked as crack, is the most potent of the common reinforcers. Its peculiar mechanism of action makes it unusually difficult to combat.

The Cocaine Challenge

Cocaine works by locking neural switches in the reward pathway into the "on" position. Reward pathways, like all neural circuits, contain synapses—points of near contact between two neurons—that are bridged by neurotransmitters. When a neuron on one side of the synapse fires, it releases a transmitter, such as dopamine, into the narrow gap between cells, and the neuron on the other side of the synapse responds by changing its own rate of firing. To prevent excessive signaling, the first neuron actively takes up the neurotransmitter from the synaptic space.

Cocaine interferes with this system. Removal of dopamine from a synapse relies on transport proteins that carry the neurotransmitter from the outside of the cell to the inside. Cocaine prevents the transport proteins from working, and so, when the drug is present, too much dopamine remains in the synapse. The dopamine overstimulates the reward

pathway and reinforces cocaine use.

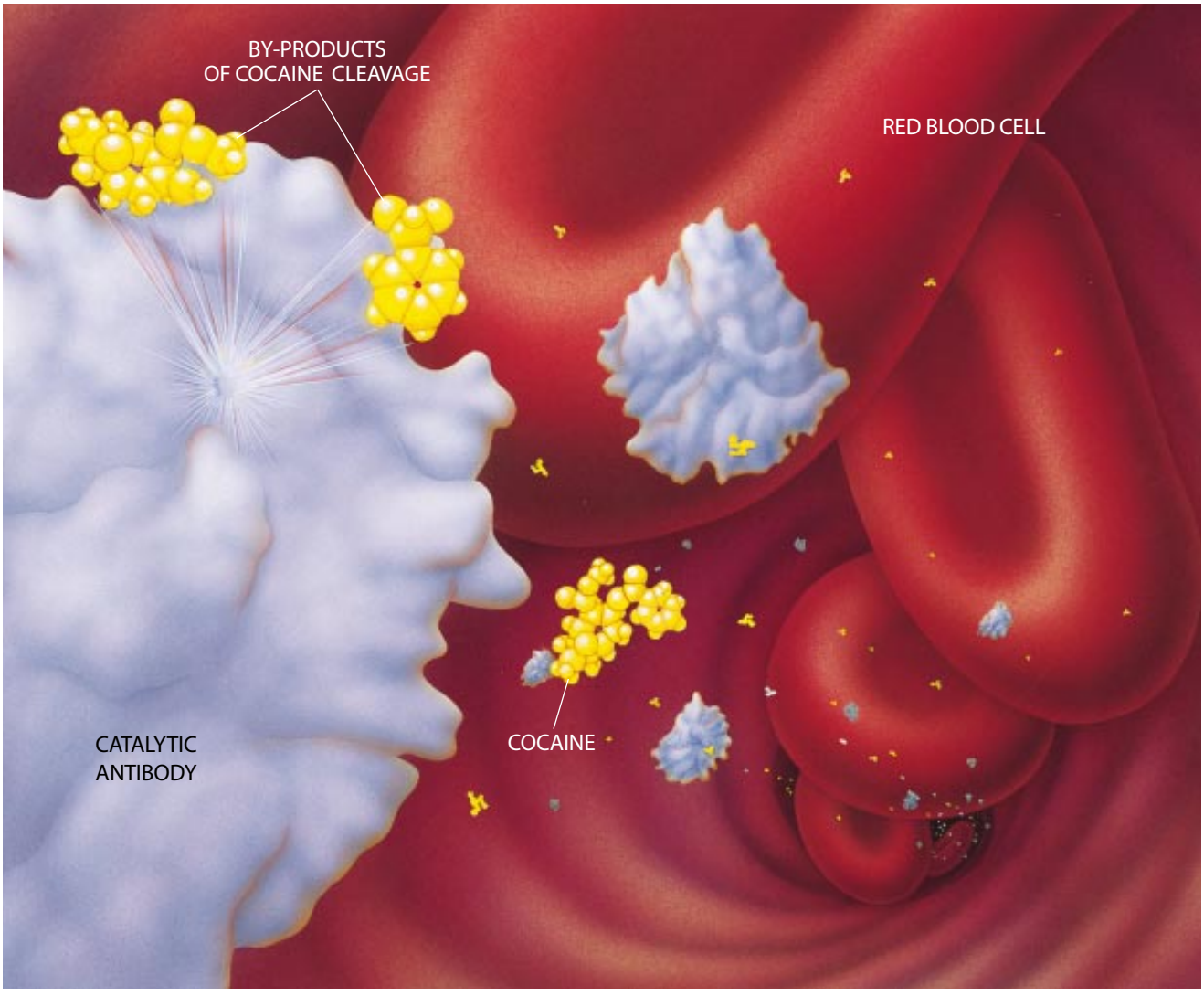
Contrast the way cocaine works with the way heroin works: heroin binds to a neurotransmitter receptor and stimulates reward pathways directly. Cocaine stimulates the same circuits indirectly, by prolonging the action of neurotransmitters that are already present. This difference is what makes interfering with cocaine such a challenge. Heroin can be stopped by inactive, dummy compounds (such as naltrexone) that bind to the same receptors and thereby block heroin's access to them. But any agent that impedes cocaine's access to its target—the dopamine transporter—will also most likely disrupt the transporter's ability to remove dopamine from the synaptic space. It will thus have virtually the same effect as cocaine. Newly discovered subtleties in the ways dopamine and cocaine interact with the transporter suggest that a usable cocaine blocker may eventually be found, but so far intensive efforts have not borne mature fruit.

As an alternative approach, my colleagues and I began several years ago to consider whether it might be possible to interrupt the delivery of cocaine to the brain. Regardless of how cocaine enters the body, it must be carried to the brain by circulating blood. The natural choices for blood-borne interceptors are antibodies—molecules of the immune system designed by nature to bind to a variety of target molecules. We found an exciting, almost forgotten report published in 1974, in which Charles R. Schuster, now at Wayne State University in Detroit, discovered in monkeys that immunization with a heroin analogue (which induced the immune system to make antibodies against the analogue) blocked some of the drug's effects.

Unfortunately, the circulating antibodies quickly vanished from the bloodstream as they formed complexes with their target. Because cocaine addiction involves taking repeated doses, it was clear to us that an anti–cocaine antibody would need to eliminate the drug without itself being inactivated or eliminated. Furthermore, cocaine can bind 250 times its weight in antibody—even a single dose of 100 milligrams or so would overwhelm any reasonable amount of a typical circulating antibody.

Luckily, advances in organic chemistry since 1974 had provided just the practical solution we needed: catalytic antibodies. In the late 1980s Richard A. Lerner of the Scripps Research Institute and Stephen J. Benkovic of Pennsylvania

APPROACH UNDER STUDY for combating cocaine addiction would deliver antibody molecules to the bloodstream, where they would trap cocaine and break it apart. The antibodies would thus inactivate the drug before it had a chance to work in the brain.



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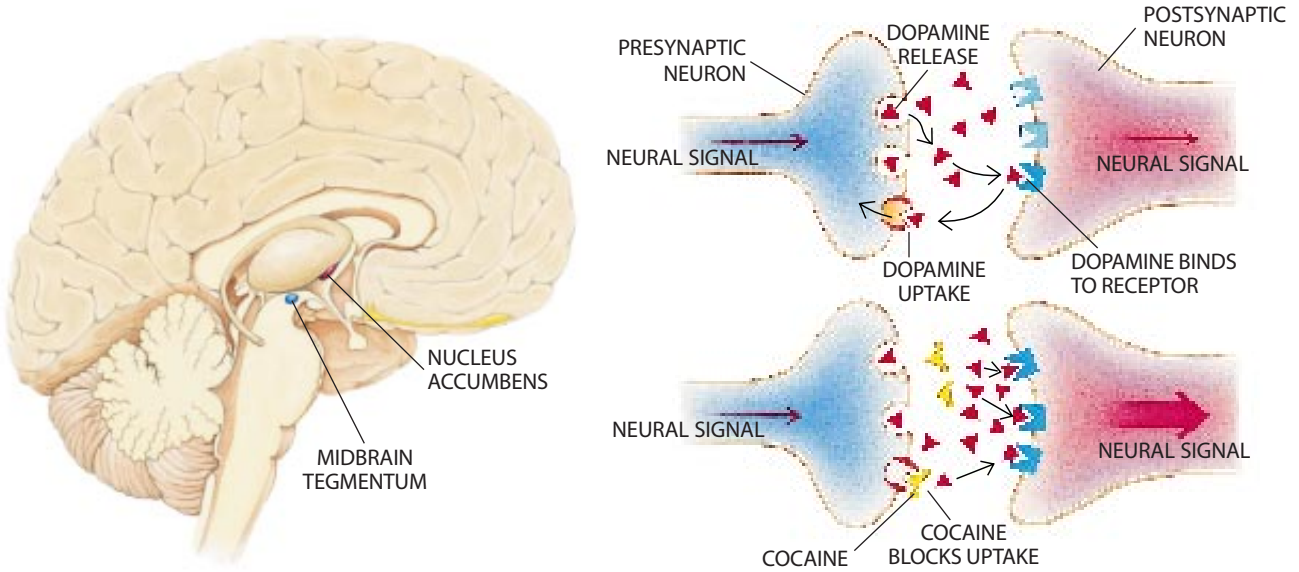

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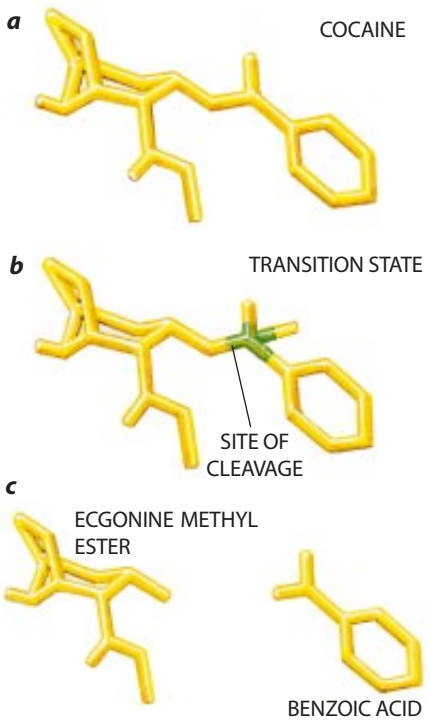
COCAINE FOSTERS ADDICTION by overexciting a brain circuit that gives rise to exhilaration. This circuit includes (*diagram at left*) neurons that extend from the midbrain tegmentum and form contacts, or synapses, with neurons of the nucleus accumbens. Stimulation occurs (*top diagram at right*) when the neurotransmitter dopamine binds to receptors on postsynaptic cells. In the nondrugged brain, the signaling is dampened because the dopamine is cleared from the synapse by the neurons that release it. Cocaine blocks this clearance (*bottom diagram*), causing dopamine to accumulate in the synapse and to activate the circuit intensely.

State University and, independently, Peter G. Schultz of the University of California at Berkeley discovered that they could make antibodies that would both bind to selected molecules and facilitate chemical reactions leading to their breakup. Once the chemical change has taken place, the catalytic antibodies release the products and emerge unchanged, ready to bind again. Some antibodies with particularly potent catalytic activity can drive scores of reactions a second. Such high turnover rates, we realized, would allow a small amount of antibody to inactivate a large quantity of drug.



TOMO NARASHIMA

BREAKUP OF COCAINE involves altering its structure. The native form (*a*) is converted to a less stable, transition state (*b*). Then it is cleaved to yield two inactive substances (*c*).

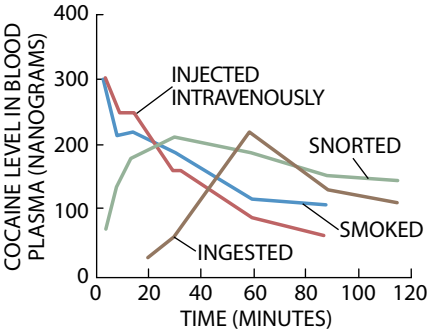
Easy to Break Up

Cocaine seemed a great candidate for the catalytic antibody approach in part because it can be deactivated by a simple cleavage reaction that yields two inactive products. An enzyme in human blood promotes precisely this reaction, but too slowly to blunt the addicting high. In contrast, cleaving heroin produces morphine and so merely exchanges one addictive drug for another.

We also knew that some of the catalytic antibodies able to degrade esters—a class of chemical structures that includes cocaine—acted quite efficiently. Antibodies can catalyze more than 40 distinct chemical transformations, but the reaction rates vary widely and are frequently low. Yet certain antibodies that cleave esters (otherwise known as esterases) are nearly as efficient as natural enzymes, and so we had reason to think that antibodies to cocaine could work fast enough to deprive an abuser of most of the drug's effect. They would thereby break the cycle of reinforcement that maintains addiction.

As a proof of this concept, we could also look to a fascinating experiment involving natural cocaine and its biologically inactive mirror image, known as (+)-cocaine. (The two compounds have the same constituents, but their structures differ as do our left and right hands.) When both compounds were injected into a monkey, only natural cocaine reached the brain. It turns out that the biological enzyme that degrades cocaine also degrades the mirror-image compound, but 2,000 times faster. The half-life of (+)-cocaine in the bloodstream is only five seconds. An enzyme that had the same kind of effect on natural cocaine would make snorting or smoking the drug essentially innocuous.

My colleagues and I therefore set out to develop catalytic antibodies able to degrade cocaine. Our plan was to create a cocaine analogue that would spur the immune systems of laboratory animals to produce antibodies to cocaine; these antibodies could then be purified and manufactured in quantity. More specifically, we wanted to create a molecule whose structure resembled that of cocaine in what is called its transition state. The folds, pockets and active sites of a catalytic antibody are not shaped for the normal configuration of the target compound but rather for its transition state—the shape the molecule takes in the midst of a chemical reaction. As a result, the antibody encourages the target to take on this configuration, there-



JOHNNY JOHNSON

SOURCE: Marian Fischman, Columbia University

SMOKING OR INJECTING cocaine raises blood (and brain) levels of the drug more quickly than snorting or ingesting it does and so produces a stronger effect. Antibody therapy may not eliminate the drug completely. But it should reduce cocaine's appeal by decreasing its potency.

by making the reaction more likely. The state of the art for designing transition-state analogues is a combination of theory and empiricism. Despite researchers' best efforts, some analogues idiosyncratically fail to elicit catalytically active antibodies.

We made our transition-state mimic by replacing one atomic grouping in the transition state with another that would stabilize the structure yet maintain the normal transition architecture. We had to devise a new method for synthesizing this particular compound because all known methods failed to produce the desired structure. Once our cocaine mimic had been made, we had to attach a carrier protein to it to ensure that it would engender an immune response. Small molecules such as cocaine do not generally elicit antibodies by themselves—which is why, for example, people do not make antibodies to aspirin.

We immunized mice with our compound and isolated cells that produced antibodies to it. Among those cells, we found two strains making antibodies that bound cocaine, degraded the drug, released inactive products and repeated the cycle—the first artificial enzymes to degrade cocaine. Since then, we have synthesized two additional transition-state analogues and now have nine different catalytic antibodies. Each molecule of our most potent agent to date can degrade more than two cocaine molecules per minute. Such activity is sufficient for initial animal studies.

We will very likely want a more active antibody for human use. An addict's bloodstream would need to contain 10 grams or more of our current best performer to neutralize a 100-milligram snort of cocaine. If we can achieve a turnover rate of two reactions per second, 500 milligrams of antibody—which could easily be injected by syringe—would be sufficient to exclude a large dose of cocaine from the brain. Because catalytic antibodies with activities greater than 40 turnovers per second have been reported, this goal seems realistic.

To improve the chemical activity, we are pursuing a three-pronged approach. First, we have developed a strategy for designing additional transition-state analogues that should elicit highly active catalytic antibodies—any antibodies that bind our new analogues will warp cocaine into a particularly fragile configuration that cleaves almost spontaneously. We are also developing screening methods that will allow us to select antibodies directly for catalytic activity rather than first selecting for tight binding to a transition-state analogue. Finally, we have cloned our catalytic antibodies, creating pure populations of each type, so that we can alter their structures selectively.

Putting Antibodies to Work

Even after we have developed a catalytic antibody that can degrade cocaine efficiently, we will have to face other hurdles to devising an effective drug treatment. Physicians cannot immunize addicts with a transition-state analogue directly, because only a small fraction of the various antibodies a patient produced against it would likely be catalytic. To ensure high levels of a catalytic antibody in the blood, doctors would have to infuse it directly—a process known as passive immunization. That being the case, manufacturers would have to develop cell lines able to make large amounts of these antibodies. Monoclonal antibodies have become established pharmaceutical agents, however, so this task seems manageable.

A catalytic antibody could be designed to remain in the body for several weeks or more, roughly as long as natural human antibodies. Such a long duration would be essential to simplify treatment programs, as a single injection could block cocaine for a month. That would be long enough for the most intense psychological pangs to subside and for conventional treatment of addiction to be established. The majority of those participating in current treatments continue to take cocaine even as they undergo counseling and other therapy designed to wean them from the drug. If the cocaine could be blocked, other treatments might be more effective; heroin treatment programs that employ both counseling and methadone to block that drug's effects report abstinence rates between 60 and 80 percent, in contrast with 10 to 30 percent for treatment regimens that rely on behavioral changes alone.

Even if a cocaine blocker does not prevent every bit of the drug from reaching a user's brain, it may still act against addiction by blunting the intensity of the drug's high. The rush of smoking a large dose of crack might be reduced to the less overwhelming level of snorting a few milligrams of powdered cocaine. And that difference could be enough to start addicts on the road to recovery. SA

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Further Reading

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