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Expert discusses MDMA research

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Neuroscientist Robert Malenka, MD, PhD, the Nancy Friend Pritzker Professor in Psychiatry and Behavioral Sciences, has conducted trailblazing inquiries into the nature of the brain's reward circuitry. This archipelago of interacting brain structures is responsible for generating sensations of pleasure in connection with survival-enhancing behaviors, such as mating and eating, but also with self-destructive behaviors, such as the use of addictive drugs.

In a recent commentary in Cell, Malenka and Boris Heifets, MD, PhD, an instructor of anesthesiology at Stanford, called for focused study of the empathogenic drug 3,4-methylenedioxymethamphetamine, or MDMA.

This call is controversial because MDMA is illegal. Science writer Bruce Goldman asked Malenka about the drug, its origins, its clinical value and why neuroscientists are interested in researching it.

Q: What is MDMA, and how and when did it get ensconced in the popular culture?

Malenka: MDMA—also known by its street name, Ecstasy—was first synthesized by Merck in the early 1900s. Merck decided not to pursue the drug's possible therapeutic actions. But in the 1970s, a San Francisco Bay Area organic chemist, Alexander Shulgin, noted that it had a structure similar to both amphetamine and the hallucinogen mescaline. Shulgin was part of a community of like-minded individuals who were willing to ingest substances they made and see what they did. This small

group quickly realized that MDMA's effects were qualitatively different from those of other drugs they had taken. It caused a powerful prosocial effect, greatly facilitating warm feelings of compassion and empathy toward all others with whom the users crossed paths. It helped stimulate a willingness to discuss personal issues and a desire to talk to others and get to know them. Fairly soon, a small group of therapists were trying out MDMA as an adjunct to therapy, with the idea that it might facilitate open communication and increased comfort in the therapeutic setting.

By the early 1980s, MDMA use had spread among the youth culture. People started taking MDMA in bars and nightclubs. Soon MDMA became a staple at large parties called raves, and its popularity spread throughout the country. However, reports started popping up of dangerous overheating and fatal electrolyte imbalances occurring among individuals on MDMA at densely packed parties. These types of events led the Food and Drug Administration to make MDMA a Schedule 1 drug. Recreational use continues to this day, but any effort to study it scientifically has become difficult.

Q: What does "Schedule 1 drug" mean?

Malenka: It's illegal. The Drug Enforcement Agency classifies drugs according to their medical utility and perceived dangerousness. Schedule 1 drugs are considered the most "dangerous" in that they're believed to have a high potential for abuse and no currently accepted medical use. It's illegal to manufacture, distribute or possess MDMA. This makes it very difficult to obtain small quantities even for strictly research purposes.

Like all psychoactive drugs, including legal substances like alcohol and nicotine and prescribed drugs such as antidepressants, MDMA can be dangerous if taken at high doses and frequently. Related drugs, such as amphetamine and cocaine, do have high abuse potential. And like any

amphetamine derivative, MDMA may have longer-lasting deleterious effects.

However, even drugs like amphetamine have therapeutic uses—for example, treatment of attention deficit hyperactivity disorder—while cocaine is a very useful local anesthetic for certain types of surgery. It's not rational to demonize any drug. Each needs to be evaluated in a rigorous scientific manner to determine how dangerous it can be and whether it might be used for therapeutic purposes. Then rational decisions need to be made as to whether that drug should be allowed to be prescribed by physicians or should be made completely illegal.

Q: What causes a chemical to be psychoactive?

Malenka: Drugs are psychoactive because they affect specific proteins in the brain and, by modifying those proteins' functions, they alter activity in specific parts of the brain. This in turn can affect how the person feels or thinks or behaves. Just think about the effects of having a beer or two or three or having several strong cups of espresso. Those psychoactive effects are because the alcohol in the beer or the caffeine in the espresso is modifying the activity in specific parts of the brain.

Q: What's MDMA's clinical value?

Malenka: MDMA is beginning to be tested as an adjunct to therapy in post-traumatic stress disorder, as well as in people with certain forms of autism in which social interactions are not normal. In very early studies, MDMA appears to be helping individuals with PTSD learn from their therapy and get relief from their often devastating symptoms. It's too early to know whether MDMA will prove useful for people with autism spectrum disorders or for other types of disorders which involve dysfunctional social behavior. But I believe it is certainly worthwhile to

perform rigorous, careful and ethical clinical trials to find out whether MDMA might have therapeutic benefit.

Q: You've called for intensive research on how MDMA works in the brain. What makes it of special interest to neuroscientists?

Malenka: The rigorous scientific study of drugs can teach us about how the brain functions. I hope that by figuring out how MDMA works in the brain, we will learn how to make new, better drugs that will have some of the same potential therapeutic benefits of MDMA while minimizing its abuse potential and any toxic effects it might have.

I don't think it's useful to study psychoactive drugs indiscriminately. Each drug needs to be considered individually, and the value of its study needs to be weighed against its potential danger and the potential usefulness of the information that studying it will generate.

MDMA is special. Unlike amphetamine, cocaine, LSD, psilopsybin, alcohol, heroin or any other known drug, it affects how one human being deals with another human being. After ingesting MDMA, it's extremely difficult if not impossible to feel anger or hostility toward another person. Studying how MDMA works in the brain might provide important insights into how the brain generates prosocial feelings and behavior. We neuroscientists hope to identify the specific molecules in the brain with which MDMA interacts and how those interactions modify activity in specific brain circuits to generate these powerful prosocial feelings and even empathy. At a time when hostility and irrational anger toward fellow human beings appears to be increasing, we cannot imagine a more important topic for neuroscientists to investigate.