In mice, ecstasy keeps social-developmental window open

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Referring to a drug as “mind altering” generally refers to its influence on immediate perceptions. But a lot of drugs that have been used for these effects have turned out to be mind altering in a more general sense: they can elicit longer-term changes in how the brain operates. Ketamine, for example, appears to provide rapid and sustained relief from depression.

A study released this week suggests we can shift MDMA, also known as ecstasy, into this category of mind alteration. Researchers have shown that the drug holds a developmental window open, allowing mice to learn social interactions much later in life than they otherwise would.

Social rewards

In humans and other animals, there are points in development when the brain is better able to learn specific things. Young children, for example, are able to pick up languages far more readily than older ones. The window where learning is easy is called a critical period, and these periods can been seen in a number of contexts. We know much less, however, about what opens and closes these developmental windows.

A group of scientists decided to use mice to study the process, since it’s much more ethically acceptable to mess with their brains than humans’. Mice seem to have a critical period for learning social interactions. If they’re raised in a group, they’ll generally react positively when they encounter strange mice in the future. If they’re raised on their own, their reaction to new mice is typically hostile.

To study this, researchers at Johns Hopkins and MIT collaborated on a system that let them track the ability of mice to learn that social interactions are rewarding. To do this, they raised mice in a group, then kept them alone in a cage divided in two, with each half having a different type of nest-making material in it. The mice were then allowed into a cage with just one of those two materials and a bunch of other mice. If the mice found these social interactions rewarding, they would associate that type of nest material with positive rewards. That could be tested by putting them back in the cage with two different materials and seeing which side the mice spent their time on.

In other words, the setup allowed mice to train themselves to associate a specific bedding material with the rewards of social interactions.

Holding a window open

With that system in place, the researchers explored how readily mice can learn to value social contact. They found that it changes with time. Early in adolescence, mice were amenable to this sort of social learning, a tendency that peaked around 40 days after birth. From there, they entered a slow decline until about 90 days after birth, at which point adult mice were no longer able to make that association. The critical period had closed.

From here, the researchers made a number of logical leaps. They knew a brain structure called the nucleus accumbens is

involved in rewards processing. They also knew that young mice saw changes in this brain region driven by the hormone oxytocin. Neurons in this area exposed to oxytocin tend to be locked in to a lower-activity state that persists long after the hormone is removed.

So, it's reasonable to hypothesize that oxytocin could be involved in setting a critical period for social learning. And, in fact, the researchers were able to show that the decline in social learning with age correlated nicely with a decline in oxytocin activity in this brain region.

The real leap came when the researchers decided to focus on ecstasy based on the fact that it activates neurons that are receptive to oxytocin, even though it doesn't mimic oxytocin's activity. That's not a lot to base a hypothesis on, but it worked out here. MDMA led to activity in the brain that looked remarkably similar to oxytocin's, and adding an inhibitor of oxytocin blocked the effect. So, the researchers took the next obvious step: give the mice some ecstasy and put them back through the social learning test.

No agony, just ecstasy

If age slammed the critical window shut on this sort of learning, MDMA cracked it open again. A single dose of MDMA restored the ability to associate nest material with social rewards in older mice in as little as six hours, and the effect would persist for four weeks.

Again, blocking oxytocin signaling eliminated the changes brought on by MDMA, while genetically activating oxytocin neurons expanded the critical period without the need for the drug. In addition, the authors showed that the primary target of MDMA, a serotonin receptor, was needed for all the effect. So, it appears that the effect of the drug is indirect, activating neurons that then go on to activate oxytocin signaling. Still, the results indicate that ecstasy truly is

mind altering, at least when it comes to mice.

Of course, it would be tempting to ascribe more to the drug than is actually happening. We already knew that MDMA alters serotonin signaling; here, it's mostly being used as a tool to help us understand how serotonin signaling influences oxytocin activity in a specific brain tissue. The fact that the brain tissue can generate a sense of reward and does so in response to social interactions is mostly a matter of chance. By looking at a different bit of brain tissue, it might be possible to find similar effects for things that aren't related to the drug's reputation—say, a love of cats.

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