

Psychedelic drugs reopen 'critical periods' for social learning

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Summary: Neuroscientists have long searched for ways to reopen 'critical periods' in the brain, when mammals are more sensitive to signals from their surroundings that can influence periods of brain development. Now, researchers say a new study in mice shows that psychedelic drugs are linked by their common ability to reopen such critical periods, but differ in the length of time the critical period is open -- from two days to four weeks with a single dose.

FULL STORY

Neuroscientists have long searched for ways to reopen "critical periods" in the brain, when mammals are more sensitive to signals from their surroundings that can influence periods of brain development. Now, researchers at Johns Hopkins Medicine say a new study in mice shows that psychedelic drugs are linked by their common ability to reopen such critical periods, but differ in the length of time the critical period is open -- from two days to four weeks with a single dose.

The findings, published June 16 in the journal *Nature*, provide a new explanation for how psychedelic drugs work, say the scientists, and suggest potential to treat a wider range of conditions, such as stroke and deafness, beyond those in current studies of the drugs, such as depression, addiction and post-traumatic stress disorder. The scientists also provide a new look at molecular mechanisms impacted by psychedelics.

Critical periods have been demonstrated to perform such functions as help birds learn to sing and help humans learn a new language, relearn motor skills after a stroke and establish dominance of one eye over the other eye.

"There is a window of time when the mammalian brain is far more susceptible and open to learning from the environment," says Gül Dölen, M.D., Ph.D., associate professor of neuroscience at the Johns Hopkins University School of Medicine. "This window will close at some point, and then, the brain becomes much less open to new learning."

Building on her laboratory's experience studying social behavior, Dölen's team has been researching how psychedelic drugs work by reopening these critical periods. In 2019, her team found that MDMA, a psychedelic drug that arouses feelings of love and sociability, opens a critical period in mice.

At the time, Dölen thought MDMA's prosocial properties smooth the way for opening the critical period, but her team was surprised, she says, to find in the current study that other psychedelic drugs without prosocial properties could also reopen critical periods.

For the current study, Dölen's team looked at the reopening potential of five psychedelic drugs -- ibogaine, ketamine, LSD, MDMA and psilocybin -- shown in numerous studies as able to change normal perceptions of existence and enable a sense of discovery about one's self or the world.

The research team conducted a well-established behavioral test to understand how easily adult male mice learn from their social environment. They trained mice to develop an association between an environment linked with social interaction versus another environment connected with being by themselves. By comparing time spent in each environment after giving the psychedelic drug to the mice, the researchers were able to see if the critical period opened in the adult mice, enabling them to learn the value of a social environment -- a behavior normally learned as juveniles.

For mice given ketamine, the critical period of social reward learning stayed open in the mice for 48 hours. With psilocybin, the open state lasted two weeks. For mice given MDMA, LSD and ibogaine, the critical period remained open for two, three and four weeks, respectively.

The researchers say the length of time that the critical period stayed open in mice seems to roughly parallel the average length of time that people self-report the acute effects of each psychedelic drug.

"This relationship gives us another clue that the duration of psychedelic drugs' acute effects may be the reason why each drug may have longer or shorter effects on opening the critical period," says Dölen.

"The open state of the critical period may be an opportunity for a post-treatment integration period to maintain the learning state," she adds. "Too often, after having a procedure or treatment, people go back to their chaotic, busy lives that can be overwhelming. Clinicians may want to consider the time period after a psychedelic drug dose as a time to heal and learn, much like we do for open heart surgery."

Next, the scientists looked at psychedelic drugs' impact on molecular mechanisms. First, in mouse brain cells, they examined a binding point, known as a receptor, for the neurotransmitter serotonin. The researchers found that while LSD and psilocybin use the serotonin receptor to open the critical period, MDMA, ibogaine and ketamine do not.

To explore other molecular mechanisms, the research team turned to ribonucleic acid (RNA), a cousin to DNA that represents which genes are being expressed (producing proteins) in the mice's cells. The researchers found expression differences among 65 protein-producing genes during and after the critical period was opened.

About 20% of these genes regulate proteins involved in maintaining or repairing the extracellular matrix -- a kind of scaffolding that encases brain cells located in the nucleus accumbens, an area associated with social learning behaviors that are responsive to rewards.

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