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Scientists tie specific brain circuit to sociability in mice

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Social behavior in mouse models of autism spectrum disorder normalized when investigators triggered the release of a specific signaling substance, serotonin, in a single part of the animals' brains,

according to a study from the Stanford University School of Medicine.

"This points to a previously understudied brain mechanism that contributes to an inability to derive pleasure from social interactions," said Robert Malenka, MD, Ph.D., professor and associate chair of psychiatry and behavioral sciences.

The brain mechanisms underlying sociability and social deficits are poorly understood, complicating attempts to find effective treatments for autism spectrum disorders, schizophrenia and other neuropsychiatric disorders marked at least in part by social withdrawal. In the study, experimental manipulations triggered extensive release of serotonin in a region of the mice's brains called the nucleus accumbens. Malenka said drugs activating a particular subtype of serotonin receptors found in this region could prove therapeutic in ameliorating the social deficits of these neuropsychiatric disorders.

The Nancy Friend Pritzker Professor in Psychiatry and Behavioral Sciences, Malenka is the senior author of the study, whose findings will be published online Aug. 8 in *Nature*. The lead author is postdoctoral scholar Jessica Walsh, Ph.D.

There are drugs called selective serotonin reuptake inhibitors, or SSRIs, that increase overall serotonin levels in the brain. But these widely used antidepressants take weeks to have a therapeutic effect and sometimes don't work at all—or eventually stop working. They haven't shown efficacy in countering autism spectrum disorder's social deficits, either.

'Turning on the faucet to maximum flow'

"SSRIs increase serotonin levels about as much as a moderately leaky faucet," Malenka said. "What we did in this series of experiments in mice was more like turning on that faucet to maximum flow." The

researchers also tested the effects on mice's sociability of suddenly shutting off the faucet completely.

The nucleus accumbens, a midbrain structure found in all mammals, is a crucial hub of the brain's reward circuitry, which is a collection of brain areas whose networked activity makes us feel good about something we've done or are doing. This, in turn, instructs us to do more of it.

"Evolution has ensured that certain behaviors important for survival—eating, finding a mate, procreating, successfully escaping from predators or captivity—feel great," Malenka said.

In most mammals, social interaction sets off the reward circuitry, too. "Hanging out with your buddies makes sense from an evolutionary survival standpoint," Malenka said. "You're more likely to find a mate and less likely to be attacked." But people with autism spectrum disorder don't interact easily with others. They don't appear to experience the same rewarding sensation that people without these illnesses do.

In the new study, the scientists performed experiments that pinpointed the relevance of serotonin release in the nucleus accumbens to social activity in mice.

"Mice aren't little human beings," Malenka said. "We can't ask them how they're feeling about their social lives. But they provide insights into the human brain. They can be very useful for studying relatively primitive mechanisms governing social behavior. For example, if something makes a mouse want to spend more time with its buddies, that something is likely to be fun for the mouse."

Controlling cell signals with light

The scientists inserted genes encoding light-sensitive proteins into sets of

nerve cells in the mice's brains. The scientists could now stimulate these nerve cells to fire impulses, or inhibit them from firing, with laser light delivered by an optical fiber implanted in the animals' brains.

First, Malenka and his colleagues sensitized nerve cells to light in another brain area called the dorsal raphe. This structure, the brain's main source of serotonin, sends nerve-cell projections to many brain areas, including the nucleus accumbens. Then the scientists put mice in situations in which they could choose to socialize or not. Activating nerve cells in the dorsal raphe made the mice more sociable.

Next, some mice were bioengineered so that only serotonin-secreting nerve cells running from the dorsal raphe to the nucleus accumbens were responsive to light. The scientists focused laser light on the nucleus accumbens, causing just the serotonin-secreting nerve cells there to release the substance—and inducing the same increased sociability. This experimental step ruled out involvement of other types of nerve cells in the tract from the dorsal raphe.

But activating this circuitry didn't make the mice more inclined to move around or explore inanimate objects, or increase their interest in food. Serotonin release in the nucleus accumbens appears to reinforce only social behavior in the animals, Malenka said, making potential drugs that mimic or enhance this local release less likely to produce unwanted behaviors, such as drug addiction, overeating and excessive gambling.

Inhibiting rather than activating serotonin release in the nucleus accumbens dramatically reduced the sociability of normally friendly mice. This indicated that serotonin release in the nucleus accumbens plays an important role in the mice's normal social behavior.

To explore the possible connection between faulty serotonin-release circuitry in the nucleus accumbens and neuropsychiatric social deficits,

the scientists zeroed in on one particular version of the more than 10 different known subtypes of receptors for serotonin. This version, called 5HT-1b, is a major subtype found in the nucleus accumbens. Drugs targeting 5HT-1b might produce fewer side effects than drugs with more general serotonin-circuitry effects.

Malenka's group next turned to mouse models of autism. The scientists deleted a specific chunk of genetic material from a chromosome in these mice to mimic an effectively identical genetic deletion in humans that accounts for about 1 percent of all clinically diagnosed cases of autism spectrum disorder. In mice, deleting this DNA either in nerve cells throughout the brain or only in serotonin-secreting nerve cells from the dorsal raphe produced social deficits in the mice that resemble some of those associated with its human counterpart.

The researchers found that this mutation significantly weakened serotonin-secreting activity in the nerve cells originating in the dorsal raphe, in a manner reminiscent of the direct inhibition of serotonin-secreting nerve cells that caused social deficits in normal mice. By using light to directly force those nerve cells' release of serotonin in the nucleus accumbens, the researchers could restore normal social behavior in the mouse models of autism. They were also able to restore normal sociability by infusing a drug that directly targets and activates 5HT-1b receptors in the nucleus accumbens, a result suggesting similar drugs might be beneficial in treating social behavior deficits.

Malenka expressed surprise at the consistency and strength of the study's results. "They couldn't have come out any better if I'd made them up," he said. "Usually you see some variability—some mice are having a bad hair day, others are having a good hair day. This time, we got similar results in almost every single animal we tested."

Malenka is deputy director of the Stanford Neurosciences Institute and a

member of Stanford Bio-X.

More information: 5-HT release in nucleus accumbens rescues social deficits in mouse autism model, *Nature* (2018). DOI: 10.1038/s41586-018-0416-4 , www.nature.com/articles/s41586-018-0416-4

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