How do antidepressants trigger fear and anxiety?

24 August 2016

Credit: George Hodan/public domain

More than 100 million people worldwide take selective serotonin reuptake inhibitors (SSRIs), such as Prozac and Zoloft, to treat depression, anxiety and related conditions, but these drugs have a common and mysterious side effect: they can worsen anxiety in the first few weeks of use, which leads many patients to stop treatment. Scientists at the University of North Carolina (UNC) School of Medicine have mapped out a serotonin-driven anxiety circuit that may explain this side effect and lead to treatments to eliminate it.

"The hope is that we'll be able to identify a drug that inhibits this circuit and that people could take for just the first few weeks of SSRI use to get over that hump," said senior investigator Thomas L. Kash, PhD, the John Andrews Distinguished Professor of Alcohol Studies in the UNC School of Medicine's department of pharmacology. "More generally, this finding gives us a deeper understanding of the brain networks that drive anxiety and fear behavior in mammals."

The new study, published in *Nature*, counters the popular view of serotonin as a neurotransmitter that promotes only good feelings. SSRIs, which are taken by about one in 10 people in the United States and about one in four women in their 40s and 50s, are thought to improve mood by boosting serotonin activity in the brain. There are brain circuits through which serotonin does seem to improve mood, and some studies have linked depression to abnormally low levels of serotonin. But the short-lived promotion of anxiety in many patients on SSRIs - even suicidal thinking, particularly in younger people - has long hinted that serotonin can have negative effects on mood, depending on the precise brain circuit where it acts.

In the Nature study, for which co-authors were UNC postdoctoral researcher Catherine A. Marcinkiewcz, PhD, and UNC graduate student Christopher M. Mazzone, the researchers used an array of sophisticated methods, including advanced optogenetic and chemogenetic tools, to trace a serotonin-activated pathway in the brains of mice, a pathway that drives anxious behavior.

The team first demonstrated that a mild shock to the paws of mice - a standard method for evoking fear and anxiety behaviors - activates serotonin-producing neurons in the dorsal raphe nucleus (DRN), a brainstem region known to be involved in mood and depression. These DRN serotonin neurons project to a brain region that is called the bed nucleus of the stria terminalis (BNST) and has been shown in previous studies to have a role in serotonin's negative mood effects in rodents. Artificially increasing the activity of the DRN-to-BNST neurons enhanced anxiety-like behaviors in the mice.

UNC scientists found that the serotonin output from the DRN neurons activates their target neurons in the BNST through a specific subset of serotonin receptors, known as 2C receptors. These serotonin-activated BNST neurons then tamp down the activity of another family of BNST neurons, which, in turn, project to the ventral tegmental area (VTA)

and lateral hypothalamus (LH) - key nodes in the brain's reward, motivation and alertness networks.

The pathways from BNST to VTA and LH have been reported in previous studies to improve mood and relieve anxiety. Researchers confirmed that artificially driving the activity of these pathways has the effect of reducing foot-shock-induced fear and anxiety behaviors in the mice. By contrast, the silencing of these pathways by serotonin-activated BNST neurons effectively allows the anxiety level to rise.

Examining the impact of SSRIs, the scientists exposed 2C-receptor BNST neurons to fluoxetine (Prozac), which like other SSRIs gives a boost to serotonin levels wherever the neurotransmitter is at work. This turned out to increase the 2C-receptor neurons' inhibitory effect on the neighboring VTA- and LH-projecting neurons, worsening fear and anxiety behavior in mice.

How can this effect be blocked? Kash and his team observed that the anxiety-mediating BNST neurons expressed the stress-signaling molecule corticotropin releasing factor (CRF). When they added a compound to block CRF activity, they witnessed that fearful behaviors - which had been triggered by fluoxetine - were greatly reduced.

One of the next steps is to confirm that this serotonin-sensitive DRN-to-BNST anxiety circuit exists in humans as well. "It's logical that it would," Kash said, "since we know SSRIs can induce anxiety in people, and the pathways in these brain regions tend to be very similar in mice and humans."

Another next step will be to test drugs - ideally FDA-approved for various conditions - for their ability to alter this anxiety circuit and thereby block SSRIs' anxiety-inducing effect. In principle, a CRF-blocker might work. For years, pharmaceutical companies have been trying to develop CRF blockers to treat depression, anxiety and addiction. In practice, Kash said, CRF blockers haven't yet had success in clinical trials, so an FDA-approved one is probably still years away at least.

"Other researchers are working to develop better CRF-inhibiting compounds, so that's one potential direction to take, but there are others," Kash said. "We're now looking at the various proteins expressed by these BNST neurons, and we're hoping to identify a receptor that is already targeted by established drugs. One of them might be useful for people as they start taking SSRIs."

More information: Serotonin engages an anxiety and fear-promoting circuit in the extended amygdala, *Nature*, DOI: 10.1038/nature19318

Provided by University of North Carolina Health Care