Research pinpoints neural circuitry that promotes stress-induced anxiety

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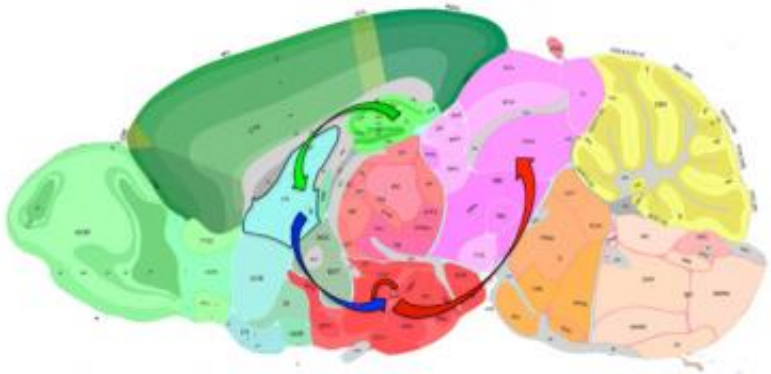

A brain schematic shows the neural circuit found by caltech researchers to play a role in anxiety. the lateral septum is outlined in black. Credit: Allen Brain Atlas

According to the National Institute of Mental Health, over 18 percent of American adults suffer from anxiety disorders, characterized as excessive worry or tension that often leads to other physical symptoms. Previous studies of anxiety in the brain have focused on the amygdala, an area known to play a role in fear. But a team of researchers led by

biologists at the California Institute of Technology (Caltech) had a hunch that understanding a different brain area, the lateral septum (LS), could provide more clues into how the brain processes anxiety. Their instincts paid off—using mouse models, the team has found a neural circuit that connects the LS with other brain structures in a manner that directly influences anxiety.

"Our study has identified a new neural circuit that plays a causal role in promoting anxiety states," says David Anderson, the Seymour Benzer Professor of Biology at Caltech, and corresponding author of the study. "Part of the reason we lack more effective and specific drugs for anxiety is that we don't know enough about how the brain processes anxiety. This study opens up a new line of investigation into the brain circuitry that controls anxiety."

The team's findings are described in the January 30 version of the journal *Cell*.

Led by Todd Anthony, a senior research fellow at Caltech, the researchers decided to investigate the so-called septohippocampal axis because previous studies had implicated this circuit in anxiety, and had also shown that neurons in a structure located within this axis—the LS—lit up, or were activated, when anxious behavior was induced by stress in mouse models. But does the fact that the LS is active in response to stressors mean that this structure promotes anxiety, or does it mean that this structure acts to limit anxiety responses following stress? The prevailing view in the field was that the nerve pathways that connect the LS with different brain regions function as a brake on anxiety, to dampen a response to stressors. But the team's experiments showed that the exact opposite was true in their system.

In the new study, the team used optogenetics—a technique that uses light to control neural activity—to artificially activate a set of specific,

genetically identified neurons in the LS of mice. During this activation, the mice became more anxious. Moreover, the researchers found that even a brief, transient activation of those neurons could produce a state of anxiety lasting for at least half an hour. This indicates that not only are these cells involved in the initial activation of an anxious state, but also that an anxious state persists even after the neurons are no longer being activated.

"The counterintuitive feature of these neurons is that even though activating them causes more anxiety, the neurons are actually inhibitory neurons, meaning that we would expect them to shut off other neurons in the brain," says Anderson, who is also an investigator with the Howard Hughes Medical Institute (HHMI).

So, if these neurons are shutting off other neurons in the brain, then how can they increase anxiety? The team hypothesized that the process might involve a double-inhibitory mechanism: two negatives make a positive. When they took a closer look at exactly where the LS neurons were making connections in the brain, they saw that they were inhibiting other neurons in a nearby area called the hypothalamus. Importantly, most of those hypothalamic neurons were, themselves, inhibitory neurons. Moreover, those hypothalamic inhibitory neurons, in turn, connected with a third brain structure called the paraventricular nucleus, or PVN. The PVN is well known to control the release of hormones like cortisol in response to stress and has been implicated in anxiety.

This anatomical circuit seemed to provide a potential double-inhibitory pathway through which activation of the inhibitory LS neurons could lead to an increase in stress and anxiety. The team reasoned that if this hypothesis were true, then artificial activation of LS neurons would be expected to cause an increase in stress hormone levels, as if the animal were stressed. Indeed, optogenetic activation of the LS neurons increased the level of circulating stress hormones, consistent with the

idea that the PVN was being activated. Moreover, inhibition of LS projections to the hypothalamus actually reduced the rise in cortisol when the animals were exposed to stress. Together these results strongly supported the double-negative hypothesis.

"The most surprising part of these findings is that the outputs from the LS, which were believed primarily to act as a brake on anxiety, actually increase anxiety," says Anderson.

Knowing the sign—positive or negative—of the effect of these cells on anxiety, he says, is a critical first step to understanding what kind of drug one might want to develop to manipulate these cells or their molecular constituents. If the cells had been found to inhibit anxiety, as originally thought, then one would want to find drugs that activate these LS neurons, to reduce anxiety. However, since the group found that these neurons instead promote anxiety, then to reduce anxiety a drug would have to inhibit these neurons.

"We are still probably a decade away from translating this very basic research into any kind of therapy for humans, but we hope that the information that this type of study yields about the brain will put the field and medicine in a much better position to develop new, rational therapies for psychiatric disorders," says Anderson. "There have been very few new psychiatric drugs developed in the last 40 to 50 years, and that's because we know so little about the brain circuitry that controls the emotions that go wrong in a psychiatric disorder like depression or anxiety."

The team will continue to map out this area of the brain in greater detail to understand more about its role in controlling stress-induced anxiety.

"There is no shortage of new questions that have been raised by these findings," Anderson says. "It may seem like all that we've done here is

dissect a tiny little piece of brain circuitry, but it's a foothold onto a very big mountain. You have to start climbing someplace."

More information: *Cell* paper: "Control of Stress-Induced Persistent Anxiety by an Extra-Amygdala Septohypothalamic Circuit"

Provided by California Institute of Technology