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Brain's fear center is equipped with a built-in suffocation sensor

The portion of our brains that is responsible for registering fear and even panic has a built-in chemical sensor that is triggered by a primordial terror – suffocation. A report in the November 25th issue of the journal *Cell*, a Cell Press publication, shows in studies of mice that the rise in acid levels in the brain upon breathing carbon dioxide triggers acid-sensing channels that evoke fear behavior.

In addition to the insight into the normal fear response, the discovery may help to explain and perhaps even correct what goes wrong in those who suffer from panic attacks, the researchers say. (It's been known for almost a century that carbon dioxide inhalation can trigger panic attacks, and that patients with panic disorder are particularly susceptible.)

"The amygdala has been thought of as part of the fear circuitry of the brain," said John Wemmie of the University of Iowa, Iowa City. "Now we see it isn't just part of a circuit, it is also a sensor."

"It's interesting that evolution positioned an acid sensor right in this central circuit," added Michael Welsh, also of the University of Iowa. "Detecting an elevated carbon dioxide is critical for survival. When you are suffocating, this circuit triggers mechanisms for escape or relief of the problem."

The circuit in question resides in the amygdala, a structure that stimulates the sympathetic nervous system for fight-or-flight and links to other brain regions involved in the response to threat. The amygdala is known from earlier studies to play a role in both innate and learned fears.

In previous studies, Wemmie's and Welsh's team discovered that the acid-sensing ion channel-1a (ASIC1a) is particularly abundant in the amygdala and other fear circuit structures, where it is required for normal responses in tests of fear behavior. As the name suggests, ASICs are sensitive to pH and become activated when pH levels fall.

The contribution of both the amygdala and ASIC1a to fear behavior led them to suspect that a reduced pH might induce fear behavior by activating the channels, thereby allowing the amygdala to function as a chemosensor deep within the fear circuit. And that's exactly what they've now been able to show.

They found that inhaled carbon dioxide reduced brain pH and evoked fear behavior in mice. Mice breathing 5% carbon dioxide tended to avoid open spaces more than usual and, in standard tests of fear learning conducted in the presence of 10% carbon dioxide, the mice displayed exaggerated freezing behaviors.

Animals lacking those acid-sensing ion channels showed less fear, a condition that was reversed when the channels were reinstated specifically in their amygdala. Treatments that prevented the pH change reduced fear behavior, while acidic microinjections into the amygdala did just the opposite.

The new findings show that the amygdala not only senses the threat posed by carbon dioxide, but it also initiates a response. There is surely good reason for such an integrated alarm system.

"Because oxygen-breathing organisms are under a constant threat of asphyxiation, it could be argued that the threat of suffocation has had a primary influence on shaping the brain's defensive systems," wrote Stephen Marin of the University of Michigan, Ann Arbor in an accompanying commentary. "The present discovery that chemosensors in the amygdala are involved in generating fear responses to a variety of aversive stimuli suggests that a system that evolved to generate behavior to defend against suffocation was subsequently adapted to deal with both innate and learned threats in the external environment. In some regards, this is not surprising. In the grasp of a predator, suffocation is the ultimate fear—it signals imminent death."

In addition to revealing the amygdala as an important chemosensor, the new results also give a molecular explanation for how rising carbon dioxide concentrations elicit intense fear and provide

a foundation for dissecting the bases of anxiety and panic disorders, the researchers say. A single breath of carbon dioxide can trigger panic attacks in patients with panic disorder, they explained, and dysregulated brain pH has also been implicated in the condition. In addition, patients suffering from respiratory failure are also known to become extremely anxious.

"It has been proposed that panic and anxiety disorders involve a suffocation alarm gone haywire," Welsh said. "Now, this work may shed some light on this well-known phenomenon and suggests strategies for further exploration."

The findings raise the possibility that some people may be more prone to anxiety disorders, including post-traumatic stress disorder, due to genetic variants they carry in components of this ASIC pathway. They also suggest that new therapeutic strategies for panic and anxiety might target changes in brain pH or the acid-sensing channels.

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