

New insights into the neural basis of anxiety

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People who suffer from anxiety tend to interpret ambiguous situations, situations that could potentially be dangerous but not necessarily so, as threatening. Researchers from the Mouse Biology Unit of the European Molecular Biology Laboratory (EMBL) in Italy have now uncovered the neural basis for such anxiety behaviour in mice. In the current issue of *Nature Neuroscience* they report that a receptor for the messenger serotonin and a neural circuit involving a brain region called the hippocampus play crucial roles in mediating fear responses in ambiguous situations.

A mouse that has learned that a certain cue, for example a tone, is always followed by an electrical shock comes to associate the two and freezes with fear whenever it hears the tone even if the shock is not delivered. But in real life the situation is not always so clear; a stimulus will only sometimes be followed by a threat while other times nothing might happen. Normal mice show less fear towards such ambiguous cues than to clearly threatening stimuli.

A team of researchers led by Cornelius Gross at the EMBL Mouse Biology Unit now discovered that this response to ambiguous stimuli requires a specific receptor molecule for serotonin, a signal many brain cells use to communicate. Mice that lack the serotonin receptor 1A have problems processing ambiguous stimuli and react to them with full-fledged fear responses. The cause is wrongly connected cells in their brains. Serotonin signalling is very important for brain development and if the receptor 1A is missing, defects arise in the wiring of the brain that affect the behaviour of mice later on in life.

"In humans serotonin signalling has been implicated in disorders including depression and anxiety and like our mice patients suffering from these conditions also overreact to ambiguous situations," Gross says. "The next step was to identify the brain regions that are responsible for such complex fear behaviour and the processing of ambiguous cues."

Using a new technique to switch off neural activity in selective brain cells in living mice, Gross and his colleagues discovered that a specific part of the hippocampus is required for correct processing of ambiguous stimuli.

"Shutting down a specific circuit in the hippocampus abolished fear reactions only to ambiguous cues," says Theodoros Tsetsenis who carried out the research in Gross' lab. "The pathway must be involved in processing and assessing the value of stimuli. It seems to bias mice to interpret situations as threatening."

The hippocampus is mainly known as a region important for learning and memory, but the results reveal a more general role in evaluating information and assessing contingencies.

Neural circuits that govern fundamental behaviours like fear are often often conserved between species and patient studies suggest a role for the hippocampus in anxiety also in humans.

The new insights gained into serotonin signalling via the receptor 1A and the role of the hippocampus in fear behaviour in mice promise to shed light on the neural basis of anxiety disorders and open up new avenues for therapies.

Source: European Molecular Biology Laboratory

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