Researchers reveal neurons that regulate sensitivity to threat in mice

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Neuroscientists have discovered how the brain bidirectionally controls sensitivity to threats to initiate and complete escape behavior in mice. These findings could help unlock new directions for discovering therapies for anxiety and post-traumatic stress disorder (PTSD).

The study, published in *Current Biology,* outlines how researchers at the

Sainsbury Wellcome Center at UCL studied a region of the brain called the periaqueductal gray (PAG), which is known to be hyperactive in people with anxiety and PTSD.

Their findings show that inhibitory neurons in the PAG constantly fire, which means that their level can be dialed up and down. The team found that this has a direct impact on escape initiation in mice and that the same neurons were also responsible for how long escape lasts.

"Escape behavior is not fixed—it's adaptable with experience. Our previous studies have shown that mice become more or less likely to escape depending on their past experience. And so, we wanted to understand how the brain regulates sensitivity to threats as this could have implications for people with anxiety and PTSD where these circuits may be misregulated," said Professor Tiago Branco, Group Leader at SWC and corresponding author on the paper.

To study how the brain controls escape behavior, the team first carried out in vitro recordings from PAG inhibitory neurons (in a dish) to look at their properties. They found that in the absence of input, the PAG inhibitory neurons always fire. They confirmed this finding through in vivo recordings using calcium imaging and head mounted miniature microscopes while mice ran around.

The team also performed some connectivity studies in the brain and showed that the PAG inhibitory neurons are directly connected to the excitatory neurons that are known to initiate escape.

"We found that the whole escape network is under direct inhibitory control. When we looked at what happens during escape, we found a group of cells where the activity goes down just before escape," explained Professor Branco.

"This means that the inhibition is removed so that escape can be initiated. We also found another group of cells where inhibition gradually increases as the animal is escaping and peaks when the animal has reached the shelter. This suggests that not only do inhibitory cells control escape initiation, but they also look to be important for telling the animal to stop when they reach safety."

To test this further, the team used a technique called optogenetics to directly manipulate the activity of neurons by exciting or inhibiting them. When they artificially increased the activity of the PAG inhibitory neurons, they found that escape probability decreased.

When they inhibited the PAG inhibitory neurons, then escape probability increased. This confirmed that the PAG inhibitory neurons are acting as dial that can be turned up and down to control how sensitive the animal is to threat.

"To check whether these neurons are also important for controlling when escape stops, we first activated the neurons after the animals had started escaping and found that they stop before they reach the shelter. Then when we inhibited the neurons, we found that mice run past the shelter and do not stop escaping. This means the neurons have access to the information that the animal uses to know when it has reached safety," explained Professor Branco.

The next step for the team is to understand how the experience of threat makes the system more or less excitable through the recruitment of these neurons.

"If we were able to reveal the specific molecular pathway that links experience to the recruitment of these neurons, then it is conceivable that drugs could be developed to target this pathway so that the sensitivity could be dialed up or down in people with anxiety and

PTSD," concluded Professor Branco.

More information: Tonically active GABAergic neurons in the dorsal periaqueductal gray control instinctive escape in mice, *Current Biology* (2024). DOI: 10.1016/j.cub.2024.05.068. www.cell.com/current-biology/f … 0960-9822(24)00745-0

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