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Researchers find gene responsible for susceptibility to panic disorder

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A study published recently in the *Journal of Neuroscience* points, for the first time, to the gene trkC as a factor in susceptibility to the disease. The researchers define the specific mechanism for the formation of fear memories which will help in the development of new pharmacological and cognitive treatments.

Five out of every 100 people* in Spain suffer from panic disorder, one of the diseases included within the anxiety disorders, and they experience frequent and sudden attacks of fear that may influence their everyday lives, sometimes even rendering them incapable of things like going to the shops, driving the car or holding down a job.

It was known that this disease had a neurobiological and genetic basis and for some time the search had been on to discover which genes were involved in its development, with certain genes being implicated without their physiopathological contribution being understood. Now, for the first time, researchers from the Centre for Genomic Regulation (CRG) have revealed that the gene NTRK3, responsible for encoding a protein essential for the formation of the brain, the survival of neurones and establishing connections between them, is a factor in genetic susceptibility to panic disorder.

"We have observed that deregulation of NTRK3 produces changes in brain development that lead to malfunctions in the fear-related memory system", explains Mara Dierssen, head of the Cellular and Systems Neurobiology group at the CRG. "In particular, this system is more

efficient at processessing information to do with fear, the thing that makes a person overestimate the risk in a situation and therefore feel more frightened and, also, that stores that information in a more lasting and consistent manner".

Different regions of the human brain are responsible for processing this feeling, although the hippocampus and amygdala play crucial roles. On the one hand, the hippocampus is responsible for forming memories and processing contextual information, which means that the person may be afraid of being in places where they could suffer a panic attack; and on the other, the amygdala is crucial in converting this information into a physiological fear response.

Although these circuits are activated in everyone in warning situations, what the CRG researchers have discovered is that "in those people who suffer from panic disorder there is overactivation of the hippocampus and altered activation in the amygdala circuitry, resulting in exaggerated formation of fear memories", explains Davide D'Amico, a PhD student at the CRG, co-author of the work and the article published in the Journal of Neuosciences, together with Dierssen and the researcher Mónica Santos.

They have also found that Tiagabine, a drug that modulates the brain's fear inhibition system, is able to reverse the formation of panic memories. Although it had already been observed to alleviate certain symptoms in some patients, "we have discovered that it specifically helps restore the fear memory system", points out Dierssen.

Panic disorder

Panic attacks are a key symptom of panic disorder. They can last several minutes, be sudden and repeated, and the sufferer has a physical reaction similar to the alarm response to real danger, involving palpitations, cold

sweats, dizziness, shortness of breath, tingling in the body, nausea and stomach pain. On top of this, they feel continuously anxious when faced with the prospect of suffering another attack.

This study by the CRG researchers reveals that the way in which the memories resulting from a panic attack are stored is what ultimately ends up producing the disorder, which usually appears between 20 and 30 years of age. Although it has a genetic basis, it is also influenced by other environmental factors, such as accumulated stress. This is why the authors of the paper consider elevated environmental stress in Spanish society to have led to an increase in the occurrence of these disorders.

Currently, there is no cure for this disease, which is treated with medicines that block the more serious symptoms, as well as with cognitive therapy, which aims to help the person learn to survive the attacks better. "The problem is that drugs have many side effects and psychotherapy is not really aimed at specific moments in the process of forming and forgetting fear memories. In our work we have defined a specific creation mechanism for these fear memories that could help in the development of new drugs and, also, in identifying the key moments for applying cognitive therapy", indicates D'Amico.

More information: Monica Santos, Davide D'Amico, Ornella Spadoni, Alejandro Amador-Arjona, Oliver Stork and Mara Dierssen. Hippocampal Hyperexcitability Underlies Enhanced Fear Memories in TgNTRK3, a Panic Disorder Mouse Model. Neurobiology of Disease | The *Journal of Neuroscience*, 2013; DOI: 10.1523/JNEUROSCI.2161-13.2013

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