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How a specific synapse type regulates anxiety-like behavior

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The mechanisms behind the organization of neuronal synapses remain unclear owing to the sheer number of genes, proteins, and neuron types

involved. In a recent study, Daegu Gyeongbuk Institute of Science and Technology scientists conducted a series of experiments in genetically modified mice to clarify the role of two proteins in regulating the development of inhibitory synapses in the hippocampus, in the context of anxiety-related behaviors, paving the way to better understand the brain.

The correct functioning of our brain, as well as that of other animals, depends on a very intricate interplay between multiple types of neurons. These interactions are orchestrated by multitudes of synaptic proteins; thus, pinpointing their specific functions is extremely challenging. In particular, the molecular mechanisms that regulate the plasticity of synapses are not completely understood.

Synapse plasticity is crucial for animals to correctly respond and adapt to their environment at the behavioral level. Over the past decade, several studies have focused on two proteins that are related to synapses mediated by GABA, the most important inhibitory neurotransmitter in mammals. Npas4, the first of the two, is closely related to shaping inhibitory synapse organization, but it fulfills many different roles across various brain regions. Contrarily, IQSEC3, the second protein, is exclusively found in 'GABAergic' synapses and is believed to be a target of Npas4, though this has not been conclusively demonstrated in live animals. Now, in a recent study published in *Cell Reports*, a team of scientists from Daegu Gyeongbuk Institute of Science and Technology (DGIST), Korea, report findings of their study on mice that shed light on the specific functions of Npas4 and IQSEC3 in a specific brain region, called the hippocampus.

First, both in neuronal cell cultures and in mice, the scientists demonstrated that Npas4 promotes the expression of IQSEC3 and, most importantly, facilitates the organization of GABAergic synapses in a specific synapse of hippocampal neurons. Then, through behavioral

experiments and subsequent chemogenetic approaches applied on genetically modified mice, the scientists observed that the specific GABAergic synapses organized by Npas4 and IQSEC3 are directly linked to anxiety-like behaviors. More specifically, mice with dysregulated IQSEC3 expression responded differently from control mice in experimental scenarios that would normally induce anxiety-related responses. "Our research may help us understand how abnormalities in anxiety-like behavior occur and design circuit-based therapeutic approaches for correcting them," remarks Professor Ji Won Um from the Department of Brain and Cognitive Sciences at DGIST, who led the study.

The team plans to continue investigating the role of IQSEC3 in different type of synapses and neural circuits using even more sophisticated genetic approaches. Clarifying the molecular mechanisms of the brain will surely pave the way to breakthroughs in brain medicine, as Dr. Um explains that "understanding synapses is instrumental in grasping the pathogenesis of neuropsychiatric and neurodevelopmental disorders because various forms of synaptic dysfunctions occur in such diseases. Thus, basic neuroscience research is unquestionably essential for making progress in this regard."

More information: Seungjoon Kim et al, Npas4 regulates IQSEC3 expression in hippocampal somatostatin interneurons to mediate anxiety-like behavior, *Cell Reports* (2021). DOI: 10.1016/j.celrep.2021.109417

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