NEUROGENETICS

Fear not

Fear helps animals — including humans — to survive, as it allows them to avoid predators and dangerous situations. However, too much fear, or inability to control it, can be detrimental and result in phobias, pathological anxiety or post-traumatic stress disorder. The identification of the gene stathmin as an important mediator of both instinctive and learned fear might shed light on these disorders and help us to develop ways to erase unwanted fear.

The role of stathmin in emotional regulation was first proposed a couple of years ago. Gleb Shumyatsky and colleagues conducted a differential gene expression screen of single cell cDNA libraries derived from neurons of the hippocampus and the lateral nucleus of the amygdala (LA). They identified two genes, gastrin-related peptide (*Grp*) and stathmin, which are highly enriched in the LA but are almost absent from the hippocampus. As the LA lies at the crossroad where sensory information is transmitted from the auditory cortex and auditory thalamus to the amygdala — a crucial process for fear processing — the researchers set out to study whether these genes have a role in fear.

Writing in *Cell*, they show that mice lacking stathmin are fearless daredevils. Knockout mice do not seem to have instinctive fear, venturing bravely into potentially dangerous environments, such as open fields or elevated platforms, which normal mice would usually avoid.

Stathmin-knockout mice also have weaker memories for past aversive experiences. Shumyatsky *et al.* tested this using the fear conditioning paradigm. During training, mice were given a conditioned stimulus (a loud tone), which was immediately followed by an unconditioned one (a mild electric footshock). Normal mice make an association between the stimuli and freeze up when they hear the tone during testing the next day. However, the stathmin-knockout mice performed poorly in this test, which indicates that they are inept at forming fear-related memories.

To ensure that this was not due to changes in other features that might have resulted from lack of the gene, the researchers tested the mutant animals' sensitivity for pain. It was normal, as was their performance in spatial memory, which indicates that the effect of stathmin on learned fear is genuine and specific.

How does stathmin affect fear-related memory? It turns out that stathmin can inhibit the dynamics of microtubule formation. Microtubules in the amygdala of the mutant mice are more stable (less flexible) compared with those of their normal counterparts. As new memories involve the formation of new synapses, which may require asembly and disassembly of microtubules, the researchers conjecture that this might explain why mice lacking stathmin cannot effectively form fear-related memories. Consistent with this hypothesis, there was a significant decrease in long-term potentiation in the cortico-amygdala and thalamo-amygdala pathways of mutant mice.

This elegant study represents a significant step forward in our understanding of fear. Although stathmin is conserved across many species, including humans, whether this gene is also expressed in the human amygdala remains to be seen.

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ORIGINAL RESEARCH PAPER Shumyatsky, G. P. *et al. stathmin*, a gene enriched in the amygdala, controls both learned and innate fear. *Cell* **123**, 697–709 (2005)
FURTHER READING Phelps, E. A. & LeDoux, J. E. Contribution of the amygdala to emotion processing: from animal models to human behavior. *Neuron* **48**, 175–197 (2005)
WEB SITE
Bolshakov's laboratory: http://www.hms.harvard.edu/dms/neuroscience/fac_bolshakov.html