Nature Reviews Neuroscience | Published online 22 Feb 2018; doi:10.1038/nrn..2018.21

EMOTION

‘Anxiety cells’ drive avoidance

> vCA1 neuronal activity both represents anxiogenic environments and promotes avoidance.

The hippocampus is functionally heterogeneous: as well as its well-known roles in memory and spatial navigation, it has been implicated in mood-related behaviours. However, the mechanisms by which the hippocampus contributes to these behaviours are unclear. In their new paper, Jimenez et al. describe the identification of ‘anxiety cells’, a population of hypothalamus-projecting hippocampal neurons that represent anxiety-related information about an animal’s environment and control anxiety-like behaviours, in mice.

In recent years, the variation in the projection patterns and functions of neurons along the dorsoventral axis of the hippocampus has become apparent. Jimenez et al. here performed calcium imaging in the hippocampal CA1 region of mice as they explored the elevated plus maze (EPM). During periods spent in the anxiogenic open arm compartments of the maze, the ventral CA1 (vCA1) showed an increase in calcium activity, which correlated with the degree to which the mice avoided these compartments and which was not observed in the dorsal CA1 (dCA1).

Brain light/Alamy Stock Photo

When the authors examined the activity of individual vCA1 neurons, they found that 51% (primarily pyramidal neurons) were selectively activated by the open arm of the EPM, compared with only 35% of dCA1 neurons. Furthermore, many of the open arm-selective vCA1 neurons, but not the dCA1 open arm-selective neurons, also exhibited elevated activity in the central zone of an open field arena. This suggests that they respond selectively to anxiogenic stimuli in different contexts. Indeed, few of these anxiety cells responded to changes in other aspects of the environment (such as the presence of a novel object), and they were shown to be poor encoders of spatial information.

To determine the importance of vCA1 activity for anxiety-driven avoidance behaviour, the authors used an optogenetic approach to silence vCA1 neurons. Selective silencing during the exploration of the open arms of the EPM or the central zone of the open field arena increased the time spent in these areas, suggesting that vCA1 neuronal activity both represents anxiogenic environments and promotes avoidance.

To investigate the downstream targets of vCA1 anxiety cells that mediate these effects, the authors injected retrograde tracers into two regions that receive inputs from vCA1 — the basal amygdala (BA) and the lateral hypothalamus (LHA) — and discovered that two largely spatially segregated populations of vCA1 neurons project to these regions. Optogenetic stimulation of the LHA-projecting population increased avoidance behaviour in the open field test and caused the mice to avoid an environmental context in which the stimulation took place in a place-preference assay, but had little effect on contextual fear conditioning (CFC). By contrast, activation or inhibition of BA-projecting neurons disrupted CFC but did not alter avoidance behaviour. In line with these findings, selective imaging of calcium activity in these two vCA1 neuronal populations revealed an enrichment of anxiety cells among the LHA-projecting population.

These findings demonstrate the existence of a hippocampal–hypothalamic pathway that encodes anxiogenic sensory information and drives the normal avoidance behaviour that is required for an animal to stay safe in its environment. Further unpicking the circuitry of such anxiety-driven avoidance behaviour may help researchers to identify the changes in these circuits that result in pathological anxiety.

Katherine Whalley

ORIGINAL ARTICLE Jimenez, J. C. et al. Anxiety cells in a hippocampal-hypothalamic circuit. *Neuron* **97**, 670–683 (2018)