This Week in The Journal

Sirt1 and Stress Susceptibility

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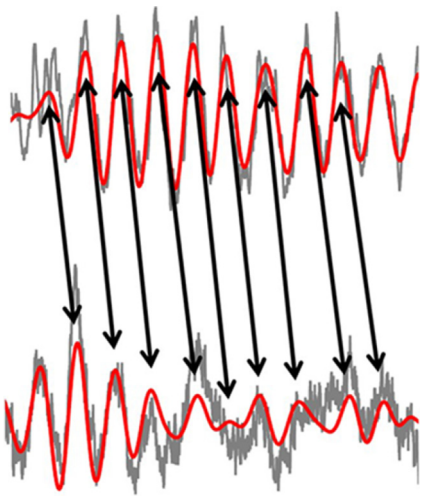
(see pages 8441–8452)

Chronic stress can lead to depression and anxiety in susceptible individuals. These states are thought to stem from stress-induced modifications in neural circuits underlying reward processing, motivation, and fear. Many people are resilient, however, and they don't experience long-lasting negative consequences after exposure to stress. Although the factors responsible for stress susceptibility and resilience are poorly understood, they are likely to include genetic, epigenetic, and environmental influences.

Mice, like humans, show differences in susceptibility to chronic stress. After repeated exposure to social defeat stress, for example, some mice show long-term reductions in social interaction and increased avoidance of open areas, whereas others do not exhibit such depression- and anxiety-like behaviors. Comparing susceptible and unsusceptible mice can therefore provide insights into the molecular mechanisms of stress resilience.

Kim et al. have discovered that one difference between susceptible and resilient mice is activation of Sirt1, a histone deacetylase that produces epigenetic modifications. Sirt1 expression increased in the nucleus accumbens (NAc) only in stress-exposed mice that subsequently showed decreased social interaction. Knocking down *Sirt1* or blocking Sirt1 signaling in the NAc increased social interaction after social defeat stress, and it also decreased anxiety-like behaviors in open fields and elevated-plus mazes. In contrast, overexpressing *Sirt1* made mice more susceptible to social defeat stress—that is, they showed social avoidance after fewer exposures. Moreover, *Sirt1* overexpression or Sirt1 activation in the NAc increased anxiety- and depression-like behaviors in open-field, elevated-plus-maze, sucrose-preference, and/or forced swim tests even in unstressed mice. These effects were replicated by overexpressing *Sirt1* selectively in NAc neurons that express D1 dopamine receptors, whereas overexpressing *Sirt1* selectively in D2-receptor-expressing neurons did not affect these behaviors.

These results suggest that chronic stress induces depression and anxiety partly by increasing Sirt1 expression in D1-expressing neurons in the NAc. Thus, genetic variations in Sirt1 expression or activity might contribute to variations in susceptibility to depression and anxiety after chronic stress. Indeed, variations in *SIRT1* have recently been linked to major depressive disorder in Han Chinese women (CONVERGE consortium 2015 Nat 523:588). Identifying Sirt1 targets in D1-expressing neurons might therefore lead to the development of new treatments for depression and anxiety disorders.



Theta phase coherence (indicated by arrows) between dorsal hippocampus (top) and mPFC (bottom) is strong during good performance on a working-memory task. Gray, raw LFP traces; red, filtered theta oscillations. See Hallock et al. for details.

Midline Thalamic Nuclei and mPFC–Hippocampal Synchrony

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(see pages 8372–8389)

Communication between the hippocampus and medial prefrontal cortex (mPFC) is essential for spatial navigation and working memory. This communication is reflected by synchronized activity in the two regions. During spatial navigation tasks, theta-frequency (~8 Hz) oscillations in the local field potential of mPFC are in sync with those in hippocampus, and many mPFC neurons tend to spike at a specific phase of the hippocampal theta cycle. Theta coherence and phase-locking grow stronger as rats learn a spatial working memory task, and they are higher on successful trials than on incorrect trials. Finally, disrupting communication between the hippocampus and mPFC disrupts performance on spatial navigation tasks that require working memory (Colgin 2011 Curr Op Neurobiol 21:467).

How hippocampus and mPFC communicate during spatial navigation and other tasks is not entirely clear, but the reuniens (Re) and rhomboid (Rh) nuclei of the thalamic midline are likely facilitators. These nuclei are connected to both the mPFC and the hippocampus, and their inactivation disrupts performance on spatial working memory tasks. Therefore Hallock et al. asked whether inactivating Re/Rh nuclei desynchronizes mPFC and dorsal hippocampus.

Rats were trained in a T maze in which choosing the rewarded arm either did or did not require working memory. Good performance on working memory trials was associated with greater phase-locking of mPFC neurons to hippocampal theta oscillations during the inter-trial delay, greater theta coherence between hippocampus and mPFC at the maze choice point, and greater phase–amplitude coupling between hippocampal theta and mPFC gamma (30–80 Hz) oscillations at the choice point. Importantly, inactivating Re/Rh nuclei not only impaired performance on the spatial working-memory task, but also decreased the proportion of mPFC neurons that were entrained to hippocampal theta oscillations between trials and decreased mPFC–hippocampus theta coherence and theta–gamma coupling at the choice point.

Together these data support the hypothesis that communication between the dorsal hippocampus and mPFC during spatial memory tasks requires activity in ventral-midline thalamic nuclei. Whether these nuclei transmit information between hippocampus and prefrontal cortex or influence communication in other ways remains unknown. Future studies will need to address this question and determine whether other structures also participate in this pathway.

This Week in The Journal was written by Teresa Esch, Ph.D.