IN BRIEF

NEURAL CIRCUITS

Navigating by neural orchestra

Many hippocampal place cells show variable responses during spatial navigation, suggesting that navigation is encoded across a population of neurons. Calcium imaging of hundreds of CA1 and dentate gyrus neurons in mice freely exploring their environment showed that spatial position could be encoded by ensembles of neurons that included, surprisingly, non-place cells. This suggests that spatial information is highly distributed across hippocampal neurons and that monitoring population activity provides an accurate picture of spatial encoding.

ORIGINAL ARTICLE Stefanini, F. et al. A distributed neural code in the dentate gyrus and in CA1. *Neuron* https://doi.org/10.1016/j.neuron.2020.05.022 (2020)

SLEEP

Sleeping like a newborn (neuron)

Adult-born neurons (ABNs) in the dentate gyrus are important for memory formation. Monitoring calcium activity in these neurons during and after a fear learning task showed that most young ABNs (4 weeks old or younger) that were sparsely active during learning were also active (at an even lower level) during post-learning REM sleep. Optogenetic silencing of these neurons during REM sleep reduced fear memory, suggesting that activity of ABNs during REM sleep contributes to memory consolidation.

ORIGINAL ARTICLE Kumar, D. et al. Sparse activity of hippocampal adult-born neurons during REM sleep is necessary for memory consolidation. *Neuron* https://doi.org/10.1016/j.neuron.2020.05.008 (2020)

SPATIAL NAVIGATION

Cooling off time

The medial septum (MS) is crucial for the generation of theta rhythms, which support hippocampal memory formation and spatial navigation. To determine whether the MS acts as a 'pacemaker' or coordinates hippocampal activity patterns through reciprocal connections the authors cooled the MS in mice. Theta oscillation frequency and power were reduced, and errors in a spatial navigation task were increased, but there was no effect on spatial coding by individual place cells or the spatial map. This suggests that theta phase coordination is achieved by reciprocal MS–hippocampus connections.

ORIGINAL ARTICLE Petersen, P. C. & Buzsáki, G. Cooling of medial septum reveals theta phase lag coordination of hippocampal cell assemblies. *Neuron* https://doi.org/10.1016/j.neuron.2020.05.023 (2020)

NEURODEGENERATIVE DISEASE

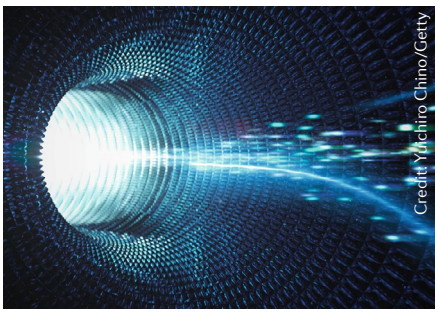
Clogged filter

In Alzheimer disease, cerebral amyloid angiopathy (CAA), which disrupts blood–brain barrier (BBB) function, is especially prevalent in carriers of the E4 variant of APOE. Here, human induced pluripotent stem cells containing different combinations of APOE variants were used to generate a 3D culture that recapitulated many BBB features. 3D cultures containing APOE4-containing pericyte-like cells showed more CAA than those in which other APOE combinations were present in pericytes or other cell types. This CAA was linked to an upregulation of APOE driven by increased calcineurin–NFAT signalling. Dysregulated NFAT and APOE were also seen in human hippocampal APOE4-containing pericytes, suggesting this pathway as a possible therapeutic target for reducing CAA.

ORIGINAL ARTICLE Blanchard, J. W. et al. Reconstruction of the human blood–brain barrier in vitro reveals a pathogenic mechanism of APOE4 in pericytes. *Nat. Med.* **26**, 952–963 (2020)

NEURODEGENERATIVE DISEASE

A channel for degeneration



Mutations in the transient receptor potential cation channel subfamily V member 4 (TRPV4) gene can cause degenerative disorders of the peripheral nervous system, but the mechanisms are not clear. A new study shows that mutant TRPV4 impairs mitochondrial transport and causes axonal degeneration and neuronal dysfunction in flies.

In humans, *TPRV4* mutations are associated with early life disease and the onset of progressive symptoms later in life. Here, the authors generated flies that expressed $TRPV4^{R269C}$ — a neuropathy-causing TRPV4 variant — and showed that they were unable to expand their wings properly after emerging from their pupae. By contrast, flies expressing $TRPV4^{R269C}$ with an additional, engineered mutation that blocked the ion-conducting pore of TRPV4 ($TRPV4^{R269C+M680K}$) showed normal wing expansion. Inducing TRPV4 neuronal expression in young adult flies revealed that $TRPV4^{R269C}$ flies were poorer at climbing than flies expressing wild-type (WT) TRPV4 or $TRPV4^{R269C+M680K}$. These findings suggest that $TRPV4^{R269C}$ can cause early-onset and later-onset neural dysfunction in flies but only if it has a functional ion channel pore.

$TRPV4^{R269C}$ expression led to a marked loss of the axonal projections of C4da neurons — sensory neurons with dendrites in the body wall of third instar fly larvae — and a reduction in C4da dendritic arborizations. This suggests that $TRPV4^{R269C}$ causes neural dysfunction and neurodegeneration.

The authors used screening approaches to identify fly genes that modified the effects of $TRPV4^{R269C}$ on wing expansion. Knocking down Ca^{2+}/calmodulin-dependent kinase II (CaMKII) inhibited this and other $TRPV4^{R269C}$-associated phenotypes, suggesting it is required for $TRPV4^{R269C}$-induced neurotoxicity.

Crustacean cardioactive peptide-expressing neurons are key regulators of wing expansion in flies. $TRPV4^{R269C}$ expression led to increases in the spontaneous firing rate of these neurons and their intrinsic excitability. Ca^{2+} chelation, TRPV4 antagonism or CaMKII knockdown blocked these effects, suggesting that $TRPV4^{R269C}$ causes hyperexcitability via a mechanism involving CaMKII.

$TRPV4^{R269C}$ C4da neurons showed a faster Ca^{2+} response in the neuronal somata to a TRPV4 agonist and higher levels of spontaneous Ca^{2+} transients in axonal projections than did $TRPV4^{WT}$ C4da neurons. Cultured mouse trigeminal neurons expressing reporter-tagged $TRPV4^{R269C}$ also showed a faster and greater Ca^{2+} response to the TRPV4 agonist than those expressing $TRPV4^{WT}$. Inhibiting CaMKII attenuated these effects. These data suggest that the R269C mutation sensitizes TRPV4 in flies and mice and that CaMKII is required for TRPV4-mediated Ca^{2+} influx.

Mitochondrial axonal transport is highly regulated by intracellular Ca^{2+} levels. Expression of $TRPV4^{R269C}$, but not $TRPV4^{WT}$, markedly impaired such transport in Cd4a neurons. However, $TRPV4^{WT}$ Cd4a neurons did show mitochondrial axonal transport deficits if they were treated with a TRPV4 agonist. Thus, TRPV4 activation, via mutation or an agonist, impairs this process.

Together, these data indicate that, in flies, CaMKII-dependent Ca^{2+} influx via mutant TRPV4 impairs mitochondrial axonal transport and causes axonal degeneration and neuronal dysfunction.

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ORIGINAL ARTICLE Woolums, B. M. et al. TRPV4 disrupts mitochondrial transport and causes axonal degeneration via a CaMKII-dependent elevation of intracellular Ca^{2+}. *Nat. Commun.* **11**, 2679 (2020)