multimerization and its interaction with GluN2B, whereas CaMKII T286 autophosphorylation and kinase activity were dispensable. Notably, persistent segregation of STG and kinase activity were dispensable. Notably, persistent segregation of STG and CaMKII–GluN2B condensates and the peripheral CaMKII–GluN2B phase of four-component condensates could be disrupted by inhibition of the CaMKII–GluN2B interaction. These data indicate that CaMKII activation induces LLPS-mediated segregation of NMDARs and AMPARs. Indeed, segregation of post synaptic proteins might lead to a corresponding segregation of presynaptic components, as suggested by the observation that the PSD95-interacting adhesion protein neuriligin 1 (NLGN) segregated with PSD95 and STG in the centre of four-component condensates when Ca²⁺ was present.

Finally, the authors used super-resolution microscopy of dissociated hippocampal neurons to investigate whether CaMKII-mediated segregation of glutamate receptors occurs in vivo. Antibody-labelled GluA2 and GluN1 (an NMDAR subunit) formed distinct nanodomains in postsynaptic membranes, and inhibition of the CaMKII–GluN2B interaction increased the overlap of these two nanodomains, as well as the overlap between GluN1 and NLGN at synapses in cultured neurons.

These findings suggest that activity-dependent, CaMKII-mediated LLPS induces persistent segregation of postsynaptic proteins at excitatory synapses and possibly coordinated changes in presynaptic proteins, thereby representing another potential mechanism of synaptic plasticity.

Grant Otto

ORIGINAL ARTICLE Hosokawa, T. et al. CaMKII activation persistently segregates postsynaptic proteins via liquid phase separation. Nat. Neurosci. https://doi.org/10.1038/s41593-021-00843-3 (2021)

RESEARCH HIGHLIGHTS

IN BRIEF

SYNAPTIC TRANSMISSION

Stress-induced switching

The integrated stress response (ISR) has roles in proteostasis, learning and memory. Here, the steady-state levels of ISR activation in mouse brain were low except in tonically active striatal cholinergic interneurons (CINs). Pharmacological inhibition of the ISR in CINs reversed the normal response to dopaminergic neuromodulation from a reduction to an increase in CIN firing rate. Inhibition of the ISR also improved performance in two skill-learning models, suggesting that the ISR has a role in modulating CINs and learning behaviour.

ORIGINAL ARTICLE Helseth, A. R. et al. Cholinergic neurons constitutively engage the ISR for dopamine modulation and skill learning in mice. Science https://doi.org/10.1126/science.abe1931 (2021)

CELLULAR NEUROSCIENCE

Mitochondrial defence tactics

In Caenorhabditis elegans, exposure to the pathogen Pseudomonas activates the mitochondrial unfolded protein response (UPRmt), a stress response involved in proteostasis and mitophagy. Here, perturbing the mitochondrial fusion gene fzo-1 in neurons increased neuronal UPRmt activation, which in turn induced UPRmt and mitochondrial fragmentation in non-neuronal tissues via the release of multiple neurotransmitters and neurohormones. Activation of neuronal UPRmt by disruption of fzo-1 upregulated genes associated with defence and immunity and increased resistance to pathogenic Pseudomonas infection, suggesting a role for neuronal UPRmt activation in pathogen defence.

ORIGINAL ARTICLE Chen, L.-T. et al. Neuronal mitochondrial dynamics coordinate systemic mitochondrial morphology and stress response to confer pathogen resistance in C. elegans. Dev. Cell https://doi.org/10.1016/j.devcel.2021.04.021 (2021)

NEUROLOGICAL DISORDERS

Complementary expression patterns

Increased expression of complement component 4 A (C4A) is a risk factor for schizophrenia. In this study, large-scale human genetic and brain transcriptomic datasets were analysed for potential functional interaction of C4A with other complement genes and schizophrenia risk genes. Co-expression network analyses using C4A as a seed gene revealed a number of neuronal and synaptic genes that were downregulated when C4A expression was increased and showed strong convergent enrichment for schizophrenia genetic risk. This reveals a possible interaction between C4A and synaptic processes in schizophrenia risk.

ORIGINAL ARTICLE Kim, M. et al. Brain gene co-expression networks link complement signalling with convergent synaptic pathology in schizophrenia. Nat. Neurosci. https://doi.org/10.1038/s41593-021-00847-2 (2021)

COGNITIVE NEUROSCIENCE

Measuring mental alerterness

Alerterness can affect cognitive and behavioural performance, but it can be challenging to assess in studies using functional MRI (fMRI), often used to measure spatiotemporal changes in human brain activity during cognitive tasks. The authors identified a marker of alerterness in fMRI data that could be used to assess alerterness during behavioural responses to incoming sensory stimuli on a trial to trial basis. Taking alerterness into account increased the statistical detection of task-activated brain areas, suggesting that this approach could be used to enhance fMRI studies of neural variability in health and disease.

ORIGINAL ARTICLE Goodale, S. E. et al. fMRI-based detection of alerterness predicts behavioral response variability. elife https://doi.org/10.7554/elife.62376 (2021)