Neuroscience Current Issue

Neurodegenerative Disease

Disrupted Place Cell Remapping and Impaired Grid Cells in a Knockin Model of Alzheimer's Disease

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Patients with Alzheimer's disease (AD) suffer from spatial memory impairment and wandering behavior, but the brain circuit mechanisms causing such symptoms remain largely unclear. In healthy brains, spatially tuned hippocampal place cells and entorhinal grid cells exhibit distinct spike patterns in different environments, a circuit function called “remapping.” We tested remapping in amyloid precursor protein knockin (APP-KI) mice with impaired spatial memory. CA1 neurons, including place cells, showed disrupted remapping, although their spatial tuning was only mildly diminished. Medial entorhinal cortex (MEC) neurons severely lost their spatial tuning and grid cells were almost absent. Fast gamma oscillatory coupling between the MEC and CA1 was also impaired. Mild disruption of MEC grid cells emerged in younger APP-KI mice, although the spatial memory and CA1 remapping of the animals remained intact. These results point to remapping impairment in the hippocampus, possibly linked to grid cell disruption, as circuit mechanisms underlying spatial memory impairment in AD.

Acute Inflammation Alters Brain Energy Metabolism in Mice and Humans: Role in Suppressed Spontaneous Activity, Impaired Cognition, and Delirium

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used bacterial lipopolysaccharide (LPS) in female C57BL/6J mice and acute hip fracture in humans to address whether disrupted energy metabolism contributes to inflammation-induced behavioral and cognitive changes. LPS (250 μg/kg) induced hypoglycemia, which was mimicked by interleukin (IL)-1β (25 μg/kg) but not prevented in IL-1RI−/− mice, nor by IL-1 receptor antagonist (IL-1RA; 10 mg/kg). LPS suppression of locomotor activity correlated with blood glucose concentrations, was mitigated by exogenous glucose (2 g/kg), and was exacerbated by 2-deoxyglucose (2-DG) glycolytic inhibition, despite preventing IL-1β synthesis. Using the ME7 model of chronic neurodegeneration in female mice, to examine vulnerability of the diseased brain to acute stressors, we showed that LPS (100 μg/kg) produced acute cognitive dysfunction, selectively in those animals. These acute cognitive impairments were mimicked by insulin (11.5 IU/kg) and mitigated by glucose, demonstrating that acutely reduced glucose metabolism impairs cognition selectively in the vulnerable brain. To test whether these acute changes might predict altered carbohydrate metabolism during delirium, we assessed glycolytic metabolite levels in CSF in humans during inflammatory trauma-induced delirium. Hip fracture patients showed elevated CSF lactate and pyruvate during delirium, consistent with acutely altered brain energy metabolism. Collectively, the data suggest that disruption of energy metabolism drives behavioral and cognitive consequences of acute systemic inflammation.

Membrane potential dynamics underlying context-dependent sensory responses in the hippocampus

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As animals navigate, they must identify features within context. In the mammalian brain, the hippocampus has the ability to separately encode different environmental contexts, even when they share some prominent features. To do so, neurons respond to sensory features in a context-dependent manner; however, it is not known how this encoding emerges. To examine this, we performed electrical recordings in the hippocampus as mice navigated in two distinct virtual environments. In CA1, both synaptic input to single neurons and population activity strongly tracked visual cues in one environment, whereas responses were almost completely absent when the same cue was presented in a second environment. A very similar, highly context-dependent pattern of cue-driven spiking was also observed in CA3. These results indicate that CA1 inherits a complex spatial code from upstream regions, including CA3, that have already computed a context-dependent representation of environmental features.

Subregional differences in astrocytes underlie selective neurodegeneration or protection in Parkinson's disease models in culture

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Parkinson's disease (PD) is characterized by the selective degeneration of dopamine (DA) neurons of the substantia nigra pars compacta (SN), while the neighboring ventral tegmental area (VTA) is relatively spared. The mechanisms underlying this selectivity are not fully understood. Here, we demonstrate a vital role for subregional astrocytes in the protection of VTA DA neurons. We found that elimination of astrocytes in vitro exposes a novel vulnerability of presumably protected VTA DA neurons to the PD mimetic toxin MPP+, as well as exacerbation of SN DA neuron vulnerability. Conversely, VTA astrocytes protected both VTA and SN DA neurons from MPP+ toxicity in a dose dependent manner, and this protection was mediated via a secreted molecule. RNAseq analysis of isolated VTA and SN astrocytes demonstrated a vast array of transcriptional differences between these two closely related populations demonstrating regional heterogeneity of midbrain astrocytes. We found that GDF15, a member of the TGFβ superfamily which is expressed 230‐fold higher in VTA astrocytes than SN, recapitulates neuroprotection of both rat midbrain and iPSC‐derived DA neurons, whereas its knockdown conversely diminished this effect. Neuroprotection was likely mediated through the GRFAL receptor expressed on DA neurons. Together; these results suggest that subregional differences in astrocytes underlie the selective degeneration or protection of DA neurons in PD.