In This Issue

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A brief summary of the articles appearing in this issue of *Biological Psychiatry.*

Neurodegenerative Diseases: Synaptic Mechanisms and Molecular Targets

Synaptic dysfunction causes cognitive impairment in Alzheimer's disease (AD). *Rps23rg1* is a gene recently linked to the inhibition of amyloid-β (Aβ) generation. In this study, **Zhao *et al.*** (pages 171–184) report that RPS23RG1 interacts with and stabilizes PSD-93/PSD-95 for normal synaptic function, and that *Rps23rg1* deficiency reduces PSD-93/PSD-95 levels, impairs synaptic function, and induces memory deficits in a *Rps23rg1* knockout mouse model. Further, the authors found that RPS23RG1 levels are attenuated in human AD, and an RPS23RG1-derived peptide comprising a PSD-93/PSD-95 interaction motif rescued synaptic and cognitive defects in *Rps23rg1* knockout and AD mice. These findings implicate RPS23RG1 dysfunction in the synaptic impairment associated with AD onset and suggest that restoration of RPS23RG1 function may ameliorate synaptic and cognitive defects in AD.

Alzheimer's disease is characterized by Aβ accumulation, yet some Aβ-positive individuals show intact cognition, suggesting compensatory network activity. **Pignataro *et al.*** (pages 185–195) investigated synaptic changes underlying Aβ-mediated network dysfunctions and provide evidence that contextual fear conditioning triggers Aβ production and oligomerization in the hippocampus, but not the amygdala, of presymptomatic AD-model mice. The authors also observed differential patterns of neuronal activity and synaptic rearrangements in the AD mice, relative to wild-type mice. Pharmacological prevention of hippocampal Aβ production restored activity-induced plasticity in both the hippocampus and amygdala.

Depression is the most common psychiatric condition in Huntington's disease (HD). Cyclin-dependent kinase 5 (Cdk5) has previously been associated with neuronal dysfunction in HD-model mice, and also with anxiety and depression. Here, **Brito *et al.*** (pages 196–207) report that pharmacological inhibition of Cdk5 in HD mutant mice prevented depressive-like behaviors and reduced DARPP-32 phosphorylation in the nucleus accumbens. Further, they identified a downstream molecular pathway that contributes to depressive-like behaviors via altered dendritic spine density, which could be prevented through genetic inhibition. Together, these data demonstrate that Cdk5 may critically contribute to depressive behaviors in HD and may serve as a novel target for pharmacological strategies.

Therapeutic Potential for AD, Cognition, and Late-life Depression

The ε4 allele of the gene that codes for apolipoprotein E (apoE) is a major genetic risk factor for the development of AD. In this work, **Sawmiller *et al.*** (pages 208–220) discovered that 6KApoEp, a novel antagonist that blocks apoE interaction with the N-terminal region of amyloid precursor protein, reduced multiple AD-like pathologies as well as cognitive impairment in AD model mice. 6KApoEp effects included reduced Aβ plaques, reduced neuronal apoptosis, reduced acetylated and phosphorylated tau, and increased synaptogenesis. These results suggest that disruption of the interaction between apoE and N-terminal amyloid precursor protein may hold promise as a therapeutic strategy for AD.

Older adults with late-life depression who also have slowed thinking and slowed walking speed are at increased risk of adverse health outcomes and tend to respond poorly to available antidepressant treatments. Using positron emission tomography before and after 3 weeks of open treatment with carbidopa/levodopa (L-DOPA), **Rutherford *et al.*** (pages 221–229) found that L-DOPA increased dopamine availability in the brain, dose-dependently increased processing and gait speeds, and decreased symptoms of depression. These data suggest that L-DOPA therapy may improve psychomotor speed via its effects on dopamine availability and should be investigated further in high-risk adults with late-life depression.

Forgotten memories may persist in the brain, but methods to promote their retrieval are still under investigation. Histamine has numerous physiological functions, including immune responding, sleep-wake regulation, and learning and memory. Here, **Nomura *et al.*** (pages 230–239) report that a single treatment of a histamine H_3 receptor inverse agonist before tests of memory retrieval restored forgotten memories in both mice and humans. Further, histamine increased spontaneous activity in the perirhinal cortex in mice, which reinforced reactivation of weak memory traces and enhanced retrieval of forgotten memories. These data indicate that central histamine signaling may serve as a potential target for reactivating forgotten object memories.

Accelerated Network Aging in Psychosis

Processes typical of normal aging appear to occur at an accelerated rate in psychotic disorders, a pattern known as accelerated aging. Using resting-state functional magnetic resonance imaging and cognitive data, **Sheffield *et al.*** (pages 240–248) reveal that accelerated aging of network connectivity (i.e., reduced network efficiency) in patients with psychotic disorder is specific to the frontoparietal and cingulo-opercular networks, the cognitive networks known to decline the earliest in healthy aging. Additionally, compared with healthy control subjects, the frontoparietal network showed intact connectivity in patients with early psychosis but declined at an accelerated rate in chronic psychosis. These data highlight the network abnormalities that may be targeted for early intervention to improve illness outcomes.

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