This Week in The Journal

Tau Inhibition of LTP Requires Prion Protein

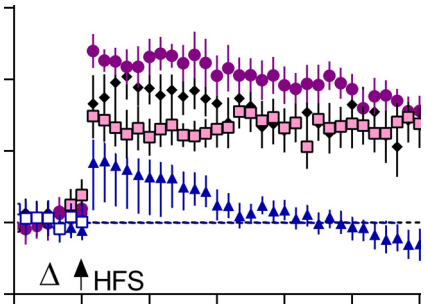
Tomas Ondrejcak, Igor Klyubin, Grant T. Corbett, Graham Fraser, Wei Hong, et al.

(see pages 10595–10606)

Alzheimer's disease (AD) is defined by the presence of extracellular plaques of aggregated β-amyloid peptides (Aβ) and intracellular tangles composed of tau fibrils. But the primary symptom, cognitive decline, likely stems from synaptic dysfunction, and for this, burgeoning evidence suggests that soluble oligomers of Aβ and tau, rather than insoluble deposits, are to blame. Numerous studies have documented the toxicity of soluble Aβ oligomers. For example, soluble Aβ from human AD brains impairs long-term potentiation (LTP), reduces dendritic spine density, and disrupts cognitive abilities in rodents. Fewer studies have examined the contribution of soluble tau aggregates to synaptic dysfunction, but recent work has suggested that they too impair synaptic plasticity and cognitive function in rodents. Furthermore, accumulation of soluble tau aggregates is correlated with cognitive decline in people with mild cognitive impairment, a forerunner of AD. Intriguingly, the synaptotoxic effects of Aβ and tau might be linked through the cellular prion protein (PrP^c). Indeed, binding of Aβ to PrP^c promotes tau phosphorylation, which promotes tau aggregation. Moreover, inhibiting Aβ–PrP^c interactions prevents disruption of LTP by soluble Aβ (Spires-Jones and Hyman, 2014 Neuron 82:756).

Ondrejcak et al. present additional evidence that soluble tau aggregates contribute to synaptic dysfunction and that this effect involves PrP^c. When injected into rat lateral ventricles, soluble aggregates of human tau prevented the induction of LTP at hippocampal synapses, whereas tau monomers and fibrils did not. In addition, some extracts from human AD brains inhibited LTP in rats even after Aβ was depleted, and this effect was prevented by depleting tau from the extracts or coinjecting anti-tau antibodies. Finally, antibodies against PrP^c blocked inhibition of LTP by both soluble tau oligomers and Aβ-depleted extracts from human AD brains.

Altogether, these results suggest that soluble tau aggregates are present in the brain of individuals with AD and that these aggregates can impair hippocampal LTP via a pathway involving PrP^c. Thus, soluble tau might contribute to cognitive decline, and inhibiting PrP^c might prevent this decline. Notably, depletion of PrP^c in animals has little apparent effect on normal function, so targeting this protein might be a viable treatment for reducing cognitive decline in AD.



High-frequency stimulation (HFS) induces LTP (black symbols) in rat hippocampus. LTP was prevented by prior (at time of open triangle) injection of soluble tau aggregates (blue), but not by tau fibrils (purple) or monomers (pink). See Ondrejcak et al. for details.

Thalamus and Hippocampus Cooperate in Regulating Dopamine

Stephanie M. Perez and Daniel J. Lodge

(see pages 10607–10618)

Schizophrenia is a complex disease in which abnormal activity in multiple brain regions leads to hallucinations and delusions (positive symptoms), as well as cognitive, emotional, and motivational deficits. The most effective treatments for the positive symptoms of schizophrenia are D2 dopamine receptor antagonists, suggesting excessive dopamine release is a major contributor. Dopamine dysregulation might be secondary to disruption of signaling via other neurotransmitters, however. Indeed, GABA production is lower than normal in people with schizophrenia, and this likely contributes to hyperactivity in several brain areas, including the hippocampus. Heightened hippocampal activity can, in turn, activate neurons in the nucleus accumbens (NAc), leading to disinhibition of dopaminergic neurons in the ventral tegmental area (VTA).

Elevated expression of the vesicular glutamate transporter vGlut2 in the NAc of people with schizophrenia supports the hypothesis that hyperactivation of this area contributes to the disease. But hippocampal afferents primarily express vGlut1, suggesting that the enhanced input arises elsewhere. Perez and Lodge pinpointed the paraventricular nucleus of the thalamus (PVT) as a possible source, because PVT neurons express vGlut2 and provide substantial input to the NAc. As predicted, activation of the PVT increased the number of spiking dopaminergic neurons in VTA. This effect was prevented by blocking NMDA receptors in the NAc, and it was replicated by selectively activating PVT projections to the NAc using designer receptors exclusively activated by designer drugs (DREADDs). Furthermore, inactivation of PVT reversed excessive activation of dopaminergic neurons in two rodent models of schizophrenia.

Oddly, when spiking in the ventral hippocampus was blocked, PVT activation no longer increased the number of active VTA dopamine neurons, but it now increased firing rate and bursting in these neurons. Likewise, when PVT spiking was blocked, hippocampal activation no longer increased the number of active dopamine neurons, but increased firing rate and bursting. These effects may have stemmed from activation of different sets of neurons in the NAc, of which ~30% responded solely to PVT stimulation, ~35% responded solely to hippocampal stimulation, and ~35% responded to stimulation of either structure.

Thus, ventral hippocampus and PVT appear to cooperate to regulate dopamine signaling via projections to the NAc. These pathways are likely important in regulation of motivated behaviors, but their hyperactivation might contribute to schizophrenia.

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