Molecular and Cellular Cognition: How molecular studies in mice are helping us to understand human cognition

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Our laboratory is studying molecular and cellular mechanisms of learning and memory, including those associated with learning disabilities. This poorly understood class of disorders affects more than one in 20 people world wide, but unfortunately there are no treatments. Because of the difficulties of unraveling the causes for these disorders in humans, we have used mouse models. For example, mutations in the Neurofibromatosis Type 1 (NF1) gene, encoding Neurofibromin, a p21Ras GTPase Activating Protein (GAP), cause learning disabilities and attention deficits. Our studies have shown that the learning and memory deficits of a mouse model of NF1 (*nf1*$^{+/-}$) are caused by excessive p21Ras/MAPK signaling leading to hyperphosphorylation of synapsin I, and subsequent enhanced GABA release, which in turn result in impairments in long-term potentiation (LTP), a cellular mechanism of learning and memory. Consistent with increased GABA-mediated inhibition, we (collaboration with Katie Karlsgodt and Ty Cannon) found evidence for brain hypoactivation in fMRI studies of NF1 patients. Recently, we discovered that statins, at concentrations ineffective in controls, can reverse the enhanced p21Ras activity in the brain of *nf1*$^{+/-}$ mice, rescue their LTP deficits, and reverse their spatial learning and attention impairments. Strikingly, recently completed pilot clinical trials (collaboration with Elgersma *et al*, U. Roterdam) demonstrated that statins can also reverse cognitive deficits in children with NF1. Similarly, we have also been studied another complex disorder that affects a molecular pathway related to p21Ras/MAPK signaling: tuberous sclerosis. This is a single-gene disorder caused by heterozygous mutations in either the *TSC1* or *TSC2* gene, and is frequently associated with learning disabilities, mental retardation, and other neurological symptoms. Even TSC patients with a normal IQ (approximately 50%) are commonly affected with specific neuropsychological problems, including long-term and working memory deficits. We found that mice with a heterozygous, inactivating mutation in the *Tsc2* gene (*Tsc2*$^{+/-}$ mice) show deficits in learning and memory. Cognitive deficits in *Tsc2*$^{+/-}$ mice emerge in the absence of neuropathology and seizures, demonstrating that other disease mechanims are involved. We show that hyperactive hippocampal mTOR signaling (downstream of p21Ras/MAPK signaling) leads to abnormal hippocampal CA1 LTP and consequently to deficits in hippocampal-dependent learning. These deficits include impairments in spatial learning, and in contextual discrimination. Remarkably, we demonstrate that a brief treatment with the mTOR inhibitor rapamycin in adult mice can rescue not only the synaptic plasticity, but also the behavioral deficits in this animal model of TSC. These results reveal a biological basis for some of the cognitive deficits associated with TSC and they show that treatment with mTOR antagonists may ameliorate cognitive dysfunction in a mouse model of this disorder. Current studies are testing this hypothesis in clinical trials. Altogether the results described above outline a research program designed to unravel mechanisms of learning disorders in mice and bridge these findings with related human studies. This effort not only will elucidate mechanisms and cures for cognitive disorders, such as learning disabilities, it will narrow the current divide between behavioral and cognitive neuroscience.