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Brain deletion of FK506-binding protein enhances repetitive behaviors in mice

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A new study reveals a link between dysregulation of a common signaling pathway and repetitive behaviors similar to those associated with multiple neurological and neurodegenerative disorders including, autism spectrum disorders, obsessive compulsive disorder, schizophrenia, and Huntington's disease. The research, published by Cell Press in the December 11th issue of the journal *Neuron*, identifies a critical role for a molecule linked to immunosuppression in learning, memory, and repetitive behavior and may lead to the development of new treatments for perseverative behaviors.

FK506-binding proteins (FKBPs) mediate the pharmacological activities of immunosuppressants such as FK506 and rapamycin and regulate multiple signaling pathways, including mammalian target of rapamycin (mTOR). "Previous studies have shown that mTOR plays a key role in cell growth and the control of protein synthesis and that mTOR is critical for convergence the of multiple signaling pathways involved in learning and memory," explains senior study author Dr. Eric Klann from the Center for Neural Science at New York University.

Dr. Klann and colleagues were interested in examining whether conditional brain-specific disruption of the FKBP12 gene would alter mTOR signaling, synaptic plasticity, and memory. The researchers created a FKBP12 conditional knockout (cKO) mouse with selective ablation of FKBP12 late in development in the hippocampus and forebrain. Deletion of FKBP12 was associated with increased interaction between mTOR and Raptor, a protein that facilitates mTOR signaling,

and enhanced phosphorylation of S6K, a downstream target of mTOR. These findings suggest that FKBP12 is normally involved in the suppression of mTOR signaling.

The FKBP12 cKO mice also displayed enhanced long-lasting long-term potentiation (LTP) in the hippocampus. LTP, a process that strengthens the communications between neurons, is thought to be a cellular mechanism for learning and memory. Behavioral studies revealed that the FKBP12 cKO mice demonstrated enhanced associative contextual fear memory, perseveration for familiar objects in a novel object recognition test, and exhibited repetitive behaviors in other behavioral tests.

These findings show that FKBP12 constrains mTOR signaling during synaptic plasticity, memory, and perseverative behaviors. "Our studies may offer insight into the molecular underpinnings of repetitive and perseverative behaviors associated with autism spectrum disorders, obsessive-compulsive disorder, schizophrenia, and neurodegenerative disorders," offers Dr. Klann. "Given that FKBP12 is a modulator, but not a required component of mTOR signaling, it may be an ideal target for therapeutic drug development aimed at ameliorating some of the mTOR-related pathologies of neurological disease."

Source: Cell Press