This Week in The Journal

Beneficial Effects of Microglial mTor in Alzheimer’s Disease

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(see pages 5294–5313)

The mechanistic target of rapamycin (mTor) is a key regulator of cell growth, proliferation, and metabolism. Inhibition of mTor signaling by rapamycin has numerous beneficial effects in animals, including extending life span and slowing the progression of several diseases. In some mouse models of Alzheimer’s disease (AD), for example, rapamycin reduces the accumulation of β-amyloid (Aβ) peptides and tau protein, improves cerebral blood flow, and slows cognitive decline. Such findings have led to calls for clinical trials of rapamycin to treat AD (Kaeberlein and Galvan, 2019, Sci Transl Med 11:eaar4289). Work by Shi et al. raises concerns about such trials, however.

The authors knocked out Tsc1, an endogenous inhibitor of mTor, in microglia of adult mice. The resulting increase in mTor activity was associated with increased microglial proliferation and morphological changes suggestive of microglial activation. Tsc1 deletion also increased the expression of numerous genes, including genes involved in protein degradation by lysosomes and several AD-linked genes, such as Trem2, which encodes a transmembrane protein involved in removing Aβ plaques. Consistent with this, cultured Tsc1-deficient microglia had higher levels of lysosomal activity and took up more Aβ than controls. Moreover, when microglial Tsc1 was knocked out in 5xFAD mice—a model of AD—levels of insoluble Aβ and the size of Aβ plaques were reduced, while the number of microglia associated with Aβ plaques increased. Notably, these effects were eliminated when Trem2 was knocked out along with Tsc1. Perhaps more importantly, treating 5xFAD mice with rapamycin for 2–3 months reduced microglial Trem2 levels and eliminated the beneficial effects of Tsc1 deletion.

These results suggest that long-term inhibition of mTor with rapamycin may reduce the clearance of Aβ plaques in AD brains. There is still reason to hope that rapamycin will help people with AD, however. First, levels of soluble Aβ, thought to be the main driver of synaptic loss in AD, was not affected by Tsc1 deletion. Second, although the deletion of Tsc1 rescued dendritic spine density and spatial memory impairment in 5xFAD mice, whether rapamycin would reverse these phenotypes is unknown. Finally, it is possible that the beneficial effects of rapamycin on neurons and astrocytes will outweigh the negative effects on microglial uptake of Aβ.

Reduced Habituation to Repeated Sounds in People with Autism

Sijia Zhao, Yajie Liu, and Kunlin Wei
(see pages 5427–5437)

Autism spectrum disorders (ASDs) are characterized by atypical social interactions and stereotyped repetitive behaviors, but attention is also affected. In fact, altered attention can be detected in infants before other ASD symptoms appear, and differences in attentional allocation might contribute to the development of other autistic traits.

Attention relies on several brain areas, including the locus coeruleus—the sole source of norepinephrine in the brain. Tonic norepinephrine release produces ongoing, low-level arousal needed for detecting stimuli, and transient spikes in release produce an alerting response that shifts attention from the current focus to salient novel stimuli. One component of the phasic response is dilation of the pupils, which provides a simple readout of locus coeruleus activity.

Several groups have used pupil dilation responses to assess attention in people with autism. These studies have yielded differing results, however, likely because they used different tasks that required various cognitive functions in addition to attention. To eliminate this confound, Zhao et al. examined pupil dilation while children were presented with auditory stimuli that required no additional, because they used different tasks that required various cognitive functions in addition to attention. To eliminate this confound, Zhao et al. examined pupil dilation, which provided a simple readout of locus coeruleus activity.

Stimuli included standards—pure tones that were delivered repeatedly over a block—and deviants—white noise or the sound of laughter played occasionally. All children showed a pupil dilation response when a standard was played, but the response was longer lasting in children with autism than in controls. This difference became more pronounced over the course of a block, as responses to standards declined more with repetition in people without autism. In contrast, the pupil response to deviants was smaller in the autism group than in controls. This was particularly true for the sound of laughter. Notably, the pupillary responses to standards and laughter were correlated with the severity of autistic traits: the longest standard-evoked responses and the smallest differences between standard- and laughter-evoked responses were found in children that scored highest on assessments of autism.

These results suggest that the locus coeruleus does not habituate as much to repetitive stimuli in children with autism as in other children. Consequently, novel stimuli, particularly those with social content, produce less distinct alerting responses in people with autism. This may help to explain deficits in social interactions in ASD.

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