This Week in The Journal

APP-Derived Peptide Increases Glutamate Receptor Level

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(see pages 3188–3203)

Amyloid precursor protein (APP) was so named because its cleavage generates β -amyloid ($A\beta$), deposits of which are one of the main pathological features of Alzheimer's disease (AD). But $A\beta$ is just one of several peptides derived from APP. Notably, another cleavage product, the secreted ectodomain fragment sAPP α , promotes long-term potentiation (LTP), enhances spatial memory, and protects neurons from various stressors. Moreover, because $A\beta$ and sAPP α are generated by differential cleavage of the same stretch of APP, increases in $A\beta$ generation—which occur in familial forms of AD—are accompanied by decreases in sAPP α production. Therefore, reduction in sAPP α might contribute to cognitive decline in AD.

How sAPP α enhances LTP and memory is poorly understood, but Mockett et al. report that treating rat hippocampal slices with exogenous sAPP α increased surface levels of specific subunits of AMPA and NMDA receptors (GluA1, GluN1, and GluN2B). In addition, they found that the increases in receptor surface expression and the enhancement of both early- and late-phase LTP persisted after sAPP α was washed out, suggesting that sAPP α primes cells for subsequent LTP. In contrast, the effects were prevented by inhibiting membrane trafficking. Finally, sAPP α increased the synthesis of GluA1, and blocking protein synthesis prevented sAPP α -induced enhancement of LTP.

These results suggest that sAPP α supports LTP induction and persistence by promoting the synthesis and trafficking of AMPA and NMDA receptor subunits. Because previous work has shown that exogenous sAPP α does not affect baseline responses of AMPA and NMDA receptors, the authors suggest that sAPP α promotes the delivery of receptor subunits to extrasynaptic sites, from which they move

to synapses when LTP-inducing stimulation is applied. Given previous work suggesting that the enhancement of LTP by sAPP α depends on interactions with $\alpha 7$ nicotinic acetylcholine receptors (Richter et al., 2018, EMBO J 37:e98335), future work should determine whether these receptors are also required for sAPP α -induced increases in glutamate receptor synthesis and trafficking. In addition, other proteins regulated by sAPP α should be identified.

Levels of newly synthesized proteins (green) are higher in cultured hippocampal neurons (purple) 2 h after treatment with sAPP α (bottom) than at baseline (top). See Mockett et al. for details.

Amygdala Suppresses Rubber Hand Illusion

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(see pages 3301–3308)

Integration of sensory information from multiple modalities helps us to identify objects in the world, including parts of our own bodies. The latter is revealed by the rubber hand illusion. In this illusion, an artificial limb is placed parallel to a person's real arm, which is hidden from sight.

If an experimenter then strokes the real and fake hands simultaneously, subjects begin to feel as though the rubber hand is their own. This illusion is thought to arise because the congruent visual and tactile stimuli gain precedence over the incongruent proprioceptive information coming from the real limb. Functional imaging studies have suggested that the illusion stems from activity in the sensorimotor, premotor, and intraparietal sulcus regions of the cortex.

Spengler et al. now provide evidence that the amygdala has a negative role in the rubber hand illusion. First, they found that each of two monozygotic twins with damaged amygdalae experienced the illusion more quickly and vividly than people without such damage. Whereas it took an average of ~130 s of simultaneous stroking before healthy control subjects reported feeling ownership of the rubber hand, the patients reported hand ownership in <1 s. Moreover, among the healthy participants, the strength of the illusion was inversely correlated with the size of the amygdala: the greater the gray matter volume of the amygdala, the weaker the illusion. Finally, intranasal administration of oxytocin, which the authors previously found inhibited the amygdala, shortened the latency to illusion onset and increased the vividness of the illusion in healthy participants.

These results are consistent with the hypothesis that activation of the amygdala suppresses the rubber hand illusion. The contribution of other brain areas was not ruled out, however. Future studies should test the strength of the illusion in other patients with amygdala damage and examine amygdala activity in healthy subjects experiencing the illusion with or without oxytocin. How the amygdala suppresses the illusion—for example, by reweighting visual versus proprioceptive information or by making subjects more open to the experimenters' suggestion that the rubber hand is their own—should also be investigated.

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