Accumulating evidence suggests that the earliest stages of Alzheimer's disease (AD) reflect a disruption in communication between brain cells (neurons) before they start to die. Thus, understanding the mechanisms responsible for age-related decline in neural communication will likely be critical for developing effective treatment and early diagnostics. Long-lasting changes in neural communication, termed synaptic plasticity, are thought to be the cellular basis of cognitive functions such as learning and memory. Our lab is studying the proteins PICK1 and KIBRA, which act together to regulate communication between neurons. Molecular and genetic evidence from humans and animal models implicate PICK1 and KIBRA dysfunction in AD pathology. Indeed, recent studies have found that the PICK1/KIBRA complex is targeted by both Amyloid β (Aβ) and Tau, the two hallmark pathogenic proteins in AD. Brain cells exposed to Aβ show a dramatically impaired ability to communicate with each other. Previous work suggested that Aβ may inhibit neural communication in part by hijacking the normal function of PICK, and that removing the PICK1 protein from brain cells protected them from Aβ. However, PICK1 is also important for normal learning and memory. Our previous studies in mice show that deleting PICK1 from birth results in significant learning and memory impairment in adult animals. However, it is possible that removal or partial inhibition of PICK1 once animals reach adulthood could make brain cells resilient to the effects of Aβ without the treatment itself causing learning and memory impairment. Towards this end, we have selectively removed PICK1 from adult animals, and are examining the ability of neurons to communicate with each other under these conditions.

Large-scale genetic studies demonstrate that the *Kibra* gene contributes to normal human memory performance, and recent work from human AD patients suggests that pathological forms of tau may decrease the levels of the KIBRA protein in brain cells, potentially contributing to cognitive decline. However, whether loss of KIBRA selectively in adult neurons is indeed sufficient to impair brain cell function and cognition remains unknown. We have begun to test this idea by removing KIBRA from brain cells after mice become adults and measuring the ability of neurons to dynamically communicate with each other. We have exciting new data indicating that removing KIBRA from adult neurons dramatically impairs synaptic plasticity. While a great deal of work remains to be done, these preliminary findings suggest that understanding how to maintain KIBRA function in aging brain cells could contribute to better maintenance of cognition in the aging/AD brain.

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