Biological Psychiatry: Celebrating 50 Years

Amyloid-β–Dependent Neuronal Circuit Rearrangement in Presymptomatic Alzheimer's Disease

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With the advances of modern medicine, people are living longer than ever before worldwide. Consequently, an increase in patients with dementia has become a serious social concern, with Alzheimer's disease (AD) being the most common form of dementia. In 2015, the World Alzheimer Report estimated that approximately 46.8 million people had AD and other types of dementia worldwide. Accordingly, the number of such patients is predicted to increase to more than 131.5 million by the year 2050. Therefore, the development of new therapeutic alternatives to control AD progression and even reverse the disease is urgently needed. With the progression of AD, amyloid-β (Aβ) accumulates in the brain. Aβ is derived from the amyloid precursor protein (APP) through the actions of β- and γ-secretase. Released soluble Aβs then spontaneously aggregate into oligomers, which form senile plaques with other aged proteins in the parenchyma and blood vessels. Aβ oligomers exhibit various neurotoxic effects, including the stimulation of inflammatory processes, the alternation of synaptic transmission efficiency (1), and the development of hyperactive neurons (2). Considering that the neurotoxic effects of Aβ oligomers cause cognitive decline in AD, most therapeutic strategies targeting AD pathogenesis have been focused on the removal of Aβ deposition from the brain tissues. However, existing therapeutic agents that inhibit and/or reduce Aβ deposition do not appear to alter the progression of cognitive dysfunction. Previous studies have shown that Aβ accumulation in human AD starts 10 to 20 years before the occurrence of dementia symptoms (3). Thus, Aβ accumulation and the associated neuropathological changes begin before the onset of neural decline in patients with AD (4). Although treatments to control neuropathological changes in preclinical AD stages are receiving increasing attention, the pathophysiological events in the AD brain that start in the early phase of preclinical AD have not been completely investigated. Most AD model mice represent age-dependent AD progression. Therefore, network dysfunctions in AD model mice are believed to occur before Aβ accumulation, similar to that in human AD patients.

In this issue of *Biological Psychiatry*, Pignataro *et al.* (5) examined the pathophysiological events associated with Aβ using presymptomatic AD model mice (Tg2576). They used contextual fear conditioning (CFC) to assess fear memory formation/retrieval in 2-month-old mice, and there were no differences between Tg2576 and wild-type (WT) mice in terms of freezing behavior. During CFC encoding in Tg2576 mice they found that the expression of the neuronal activation marker c-Fos was comparable with that in WT in both hippocampal area CA1 and the basolateral amygdala (BLA). In contrast, Pignataro *et al.* (5) found that neural activation was suppressed in CA1 of Tg2576 mice after CFC recent recall (<48 hours), but BLA neurons were further activated. In other areas interconnected with CA1, such as the anterior cingulate cortex, dorsolateral striatum, and retrosplenial cortex, c-Fos expression during CFC encoding and recall were comparable between Tg2576 and WT mice, indicating a specificity for the connection. These findings suggest that the BLA likely compensates for the decline in CA1 activity to maintain a homeostatic balance between the two regions, which is consistent with the finding that the recent context memory of CFC is recalled through the hippocampal–BLA circuit (6). Pignataro *et al.* (5) also investigated altered spine density and morphology in CA1 and BLA of preclinical AD mice after CFC recall. The structure of the spine is well-correlated with the strength of synapses, and larger spine head sizes indicate stronger synaptic connections. They found that mushroom-shaped spines were increased in CA1 in WT but not in Tg2576 mice. In the BLA, mushroom-shaped spines were increased in both genotypes, but thin spines were increased excessively only in Tg2576, indicating that the reduction of mature synapses in CA1 was compensated for by generating new spines (thin spines) to maintain synaptic strength for fear memory in Tg2576 mice.

What is the mechanism that causes this compensatory neural circuit rearrangement? Several studies have explored the effect of Aβ on dendritic spine morphogenesis. Acute overproduction of Aβ from the neural membrane reduced spine density at nearby dendrites (1), and Aβ blocked the growth of new synapses. In addition, the application of soluble Aβ, a synthetic AβS26C dimer, induced hyperactivation of hippocampal neurons by in vivo two-photon calcium imaging (2). Thus, a possible mechanism for compensation appears to be the overproduction of Aβ in CA1 before the deposition of Aβ. If Aβ in hippocampal CA1 induces neuron hyperactivity, synaptic transmission efficiency may increase in BLA but not in CA1. Pignataro *et al.* (5) found that $A\beta_{42}$ and Aβ oligomer levels increased by CFC encoding in the hippocampus but not in the amygdala. In addition to CFC, Pignataro *et al.* (5) examined $A\beta_{42}$ levels in the hippocampus during the water maze task, a hippocampal-dependent spatial memory task with less stress than CFC. Interestingly, they found that $A\beta_{42}$ levels were increased by exposure of the water maze task only in the hippocampus, as observed in CFC encoding. The $A\beta_{42}$ levels produced in the water maze task were low compared with the CFC task, suggesting that $A\beta_{42}$ production is partly regulated by stress. Tg2576 mice overexpressed corticotropin-releasing

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https://doi.org/10.1016/j.biopsych.2019.06.002
ISSN: 0006-3223

factor exhibit a substantial decrease in dendritic spine density in CA1 (7), suggesting that corticotropin-releasing factor and stress may be involved in increased $A\beta_{42}$ levels. In the future, investigating whether corticotropin-releasing factor antagonists attenuate $A\beta_{42}$ production in the hippocampus and rescue the CA1–BLA circuit in preclinical AD is warranted.

Pignataro *et al.* (5) showed that the generation of $A\beta_{42}$ and the formation of Aβ oligomers in the hippocampus were inhibited by the γ-secretase inhibitor DAPT during CFC encoding. DAPT treatment also restored spine density in hippocampal CA1 to control levels and inhibited thin spine formation in BLA during CFC recall. Thus, Pignataro *et al.* (5) documented homeostatic compensation between CA1 and BLA in the alternation of neural activity and the rearrangement of dendritic spines mediated by Aβ oligomer generation in the hippocampus during CFC encoding. These findings demonstrate a novel compensatory synaptic rearrangement between the CA1 and BLA by the formation of Aβ oligomers with $A\beta_{42}$. Early detection of this phenomenon for the compensation of the CA1–BLA network and reversible Aβ oligomer generation in the earliest stage of preclinical AD may lead to the prevention of AD onset.

Although the CFC recall in CA1 produced Aβ, c-Fos–positive neurons were not elevated as noted in WT control mice. These results contradict reports that Aβ dimers induce the hyperactivity of hippocampal neurons (2). c-Fos–positive neurons have characteristic activity with higher burst rates and shorter average interburst intervals (8), suggesting that c-Fos expression has a selectivity for certain patterns of neuronal activity. It remains to be seen whether Aβ from CA1 affects neuronal activity patterns in BLA, and likewise in CA1, during behavior tasks using in vivo two-photon calcium imaging in AD model mice (9). In addition, most of the AD model mice, including the Tg2576 mice used by Pignataro *et al.* (5), are derived from APP overexpression to produce Aβ proteins. Because the overexpression of APP gives rise to toxic effects that are not observed in human AD, it remains important to test whether compensatory synaptic arrangement is also observed in the single humanized *App* knock-in mice carrying Swedish and Beyreuther/Iberian mutations with and without Arctic mutation (10). These model mice exhibit typical humanized Aβ pathology without overexpressing APP. Using these mice before the onset of Aβ pathology, Aβ generation in CA1 during CFC encoding could be captured as a reliable phenomenon in the earliest stage of preclinical AD. Future research is expected to provide further understanding as to how presymptomatic AD progresses, along with the development of a quantitative biomarker for AD before the onset of symptoms.

Acknowledgments and Disclosures

This work was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (Grant Nos. 19K16293 and 17H05695 [to KM] and 18H02528 and 18K19377 [to TS]), The Inamori Foundation (to KM), The Takeda Science Foundation (to TS), The Shimadzu Science Foundation (to TS), and The Pharmacological Research Foundation (to TS).

The authors report no biomedical financial interests or potential conflicts of interest.

Article Information

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Received Jun 4, 2019; accepted Jun 5, 2019.

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