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Commentary

Does Aluminum Contribute to Alzheimer Disease Directly, Indirectly, or At All?

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While epidemiological studies have suggested that aluminum is a risk factor for Alzheimer disease (AD), the underlying mechanism through which aluminum leads to AD remains unknown. Despite the lack of evidence linking aluminum to AD that have motivated many to avoid using materials such as cooking utensils made with the metal, researchers have yet to investigate the precise effects of aluminum on neurons .

One reason for the lack of research on aluminum in AD is that, until recently, no sufficient model for AD was available for more investigations. AD is pathologically defined by neuronal loss, amyloid-β (Aβ) deposition, and neurofibrillary tangle (NFT) formation, and recently developed mouse models of AD show Aβ deposits or NFTs formation, and a few show both [4,6,9,14,15]. These models show only some of the pathogenic changes of AD, and, as pointed out in the accompanying commentary and review paper, are therefore incomplete representations of this disease. It is for these reasons that some researchers use the rabbits injected with aluminum-malate as a model for AD, because it shows Aβ deposition and neurofibrillary changes [1]. However, this claim is based on histochemical results; there is no biochemical evidence. In fact, the biochemical data revealed that the aluminum induced neurofibrillary changes in this model was a neurofilament [12]. Another group, using rat and rabbit animal models, confirmed this finding [3], suggesting that the aluminum-malate model does not induce NFTs that are composed of highly phosphorylated and sarcosyl insoluble tau. Hence, in the absence of evidence showing that intraneuronal fibrils are composed of highly phosphorylated tau, it would appear that the aluminum-malate injected rabbit model does not reflect the pathological changes of AD.

While the APP Tg mouse only shows Aβ senile plaques, without NFTs or neuron loss, cross breeding this mouse with a tau Tg mouse produces animals that exhibit senile plaques and NFTs [7]. In addition, when Aβ is injected into the tau Tg mouse, NFTs are induced [5], suggesting that Aβ accelerates NFT formation. Based on the Braak study [2], NFTs in the entorhinal cortex can be seen before Aβ deposition begins, while those tangles found in the limbic and isocortex stages are detected after Aβ deposition. These observations led us to assume that an aging process first affects tau, leading to NFT formation in the entorhinal cortex and that Aβ accelerates this process to spread NFT formation to limbic system and isocortex [13]. In this sense, the tau Tg mouse may mimic brain aging in humans and would explain why the APP Tg mouse can not form NFTs while the crossbred mouse can. It would also suggest that this crossbred model might show whether aluminum contributes directly to AD.

To investigate the impact of aluminum on development of AD, we broke down the disease into two pathways, 1) aging process (tau), and 2) accelerating process (Aβ). In an *in vitro* study, aluminum showed no involvement in the formation of the toxic species of Aβ aggregation. Therefore, aluminum may not be involved in Aβ-induced accelerating process. So, if aluminum is a factor in AD, it must be involved in brain

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aging process. As we described in our report [8], aluminum does form tau aggregate *in vitro*, but these aggregates do not look like a fibril with a β-sheet structure as usually seen in AD brain. Therefore, aluminum may not be directly involved in fibrillar tau formation. If aluminum accelerates aging in the brain, aluminum injection would show NFT deposits at an earlier age. Although aluminum induced tau aggregation at concentrations exceeding 50 μM in cell lines expressing tau, we were unable to determine whether aluminum induced tau aggregation *in vivo*, concentrations of aluminum higher than 20 μM are fatal in mice. Mice die before the brain concentrations of aluminum are high enough to cause tau aggregates to form. Our results suggest that aluminum may not be involved in brain aging directly. Hence, aluminum intake may affect other organs, not the brain. Savory and Ghribi mention that rodent is rather resistant to aluminum effect, and the same time referred effect of aluminum intake in APP transgenic mouse as a positive result [11].

Pratico and colleagues gave their APP Tg mouse a diet of pellets with aluminum, and found an increase in the level of Aβ deposition using biochemical and histochemical methods [10]. Vitamin E treatment rescued aluminum-induced increase of Aβ deposition. They concluded that aluminum may affect Aβ deposition through oxidative stress. Their finding also suggests that aluminum does not directly impact AD pathogenesis. However, if aluminum does affect other organs, and induces oxidative stress in brain, aluminum may indirectly impact AD pathogenesis. However, the effect of aluminum on AD development may then be small. The impact of aluminum on AD via oxidative stress may be the same at that seen in iron or copper intake, or any other oxidative stressors.

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