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Alzheimer's: A New Approach to Treating an Old Disease

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"Memory is all we are. Take a man's memories and you take all of him." (Mark Lawrence).

Alzheimer's disease (AD) is the most common form of dementia. It is the only one of the top ten causes of death in the US for which there is no significant treatment that can prevent, delay, slow or stop its progression. To date all of the late stage clinical trials for AD drugs to halt disease progression have failed.

Why has drug development for AD treatment proven so challenging? There are several likely reasons.

First, almost all of the drug discovery efforts for AD have focused on a pathway implicated in the familial form of the disease. However, familial AD only accounts for 1-3% of the total AD cases. The vast majority of AD cases are due to aging.

Second, a number of harmful changes occur in the brain (and other tissues) with aging. It is not clear how each of these changes contributes to the development of AD. Moreover, the contributions of these changes may vary between individuals. Thus, a drug that only targets one of these changes is unlikely to be successful in treating the disease.

A number of years ago my laboratory, along with the laboratory of my colleague David Schubert, decided to try a different approach to drug discovery for AD. We developed a battery of experiments with cells that mimic the different changes that occur in the aging brain, testing natural products to identify the ones that were highly active, exerting a beneficial effect. We focused on natural products because these compounds frequently have multiple activities that might be effective against many of the changes that occur in the brain with aging. Using this approach, we identified the flavonoid fisetin, a natural product found in strawberries, as a potential drug candidate for the treatment of AD.

In our earlier research, we found that fisetin reduced the cognitive deficits related to AD in mice genetically engineered to develop the disease. However, since these mice are a model of the familial form of AD and not the much more common sporadic form of the disease, we decided we needed a more relevant animal model for our preclinical testing. To that end, we turned to a strain of laboratory mice (SAMP8 mice) that exhibit accelerated aging. By 10 months of age, these mice show external signs of aging such as hair loss, increased curvature of the spine and reduced physical activity. More importantly, these mice demonstrate memory deficits similar to those seen in the genetically engineered AD mice along with other pathological changes in the brain consistent with sporadic AD.

For this study, we fed 3-month-old SAMP8 mice a daily dose of fisetin with their food for 7 months, until they reached 10 months old. Another group of the SAMP8 mice was fed the same food without fisetin. During the study period, mice took various activity and memory tests. We also examined the levels of specific markers including proteins in the mice related to brain function as well as responses to stress and inflammation.

At 10 months, the differences between the two groups were striking. Mice not treated with fisetin showed all of the external signs of aging characteristic of these mice and had difficulties with the cognitive tests as well as elevated

markers of stress and inflammation in their brains. Moreover, brain cells called astrocytes and microglia, which are normally anti-inflammatory, were now driving rampant inflammation. Mice treated with fisetin, on the other hand, were not noticeably different in external characteristics, behavior, cognitive ability or inflammatory markers at 10 months than untreated 3-month-old mice (when normally they do not show signs of illness). Importantly, in this study, as well as the earlier study with the genetically engineered mice, we found no evidence for toxicity in the fisetin-treated mice.

While mice are not people, we believe that the results of this study, especially when combined with the results of the earlier study with the genetically engineered AD mice, indicate that fisetin warrants a closer look, not only for potentially treating sporadic AD but also for reducing some of the cognitive and other changes associated with aging generally.