Cotinine halts the advance of Alzheimer's disease-like pathology and associated depressive-like behavior in Tg6799 mice

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Alzheimer's disease (AD) is associated with cognitive and non-cognitive symptoms for which there are currently no effective therapies. We have previously reported that cotinine, a natural product obtained from tobacco leaves, prevented memory loss and diminished amyloid-? (A?) plaque pathology in transgenic 6799 mice (Tg6799 mice) when treated prior to the development of the pathology. We have also shown that cotinine reduces depressive-like behavior in normal and chronically stressed C57BL/6 mice. Here, we extend our previous studies by investigating the effects of cotinine on the progression of AD-like pathology, depressive-like behavior, and the mechanisms underlying its beneficial effects in Tg6799 mice when left untreated until after a more advanced stage of the disease's development. The results show that vehicle-treated Tg6799 mice displayed an accentuated loss of working memory and an abundant A? plaque pathology that were accompanied by higher levels of depressive-like behavior as compared to control littermates. By contrast, prolonged daily cotinine treatment to Tg6799 mice, withheld until after a mid-level progression of AD-like pathology, reduced A? levels/plaques and depressive-like behavior.

Moreover, this treatment paradigm dramatically improved working memory as compared to control littermates. The beneficial effects of cotinine were accompanied by an increase in the expression of the active form of protein kinase B and the postsynaptic density protein 95 in the hippocampi and frontal cortices of Tg6799 mice. This suggests that cotinine halts the progression of AD-like pathology while reducing depressive-like behavior by stimulating signaling pathways supporting synaptic plasticity in Tg6799 mice. The potential use of cotinine to treat cognitive and non-cognitive symptoms of AD is discussed.

Akt

Alzheimer's disease

Amyloid-?

Cotinine

Depression

Memory loss

Postsynaptic density protein 95

Protein kinase B

amyloid beta protein

cotinine

postsynaptic density protein 95

protein kinase B

Alzheimer disease

animal behavior

animal experiment

animal tissue

article

controlled study

depression

disease course

entorhinal cortex

forced swim test

frontal cortex

genotype

hippocampus

male

mental stress

mouse

nerve cell plasticity

nonhuman

signal transduction

Western blotting

working memory