Cotinine and 6-hydroxy-L-nicotine attenuates memory deficits and reduce anxiety and oxidative stress in a zebrafish (Danio rerio) model of Alzheimer's Disease

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Alzheimer's Disease (AD) is a progressive neurodegenerative disorder which affects almost 47 million people worldwide representing thus the most common form of dementia. AD is characterized by progressive cognitive decline and mood changes, accompanied by a loss of cholinergic neurons. Zebrafish (Danio rerio) has been successfully used to simulate AD pathology. In the central nervous system, nicotinic acetylcholine receptors (nAChRs) are involved in higher brain functions, such as memory, cognition and learning. There is considerable interest in modulating nAChRs to treat nervous system disorders, such as AD. Nicotine is a well-known agonist of nAChRs and was reported to improve memory, learning and attention, but the therapeutic use in AD was limited by its cardiovascular and addictive side-effects. Thereby, we focused on two structural related nicotine derivatives, namely cotinine (COT) and 6-hydroxy-L-nicotine (6HLN), that previously showed to improve cognition without exhibiting nicotine's side-effects. We evaluated the impact of COT and 6HLN on memory impairment, anxiety and oxidative stress in a zebrafish model of AD induced by scopolamine (SCOP). For this, COT and 6HLN were acutely administered by immersion to zebrafish that were treated with SCOP before testing. Anxiety was measured using the novel tank diving test (NTT) and memory performances were assessed by Y-maze and novel object recognition test (NOR). The oxidative stress was measured from brain samples. We have shown that 6HLN and COT improve memory performances in Y-maze and NOR tasks and reduce the anxiety level in NTT. Moreover, our data showed that these compounds reduce SCOP-induced oxidative stress. These findings support the premise that COT and 6HLN could be used as therapeutic agents in AD.

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