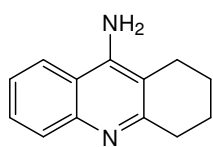


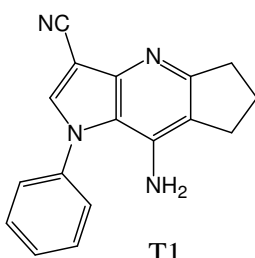
Tacrine and its analogues impair mitochondrial function and bioenergetics: A lipidomic analysis in rat brain.

Abstract

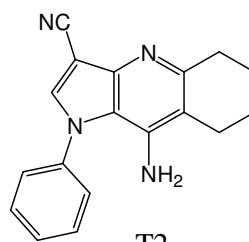
Tacrine is an acetylcholinesterase inhibitor used as cognitive enhancer in Alzheimer's disease treatment. However, the low therapeutic efficiency and the high incidence of side effects have limited its clinical use. In the present study, the molecular mechanisms underlying the brain activity of tacrine and two novel tacrine analogues (T1, T2) were approached focusing on three aspects: i) effects on brain cholinesterase activity; ii) perturbations on electron transport chain enzymes activities of non-synaptic brain mitochondria; iii) the role of mitochondrial lipidome changes induced by these compounds on the mitochondrial bioenergetics. The brain effects were evaluated 18 hours after a single dose (75.6 μ moles/Kg) administration of tacrine or tacrine-analogues. The three compounds promoted a significant reduction of brain acetylcholinesterase and butyrylcholinesterase activities. Additionally, tacrine showed to be more efficient in brain acetylcholinesterase inhibition than T2 tacrine-analogue and less active than T1 tacrine-analogue, while the butyrylcholinesterase inhibition follows the order: T1 > T2 > tacrine. The studies with nonsynaptic brain mitochondria show that all the compounds studied disturbed the brain mitochondrial bioenergetics mainly by inhibition of complex I activity. Furthermore, the activity of complex IV is also affected by tacrine and T1 treatments while FoF₁ATPase is only affected by tacrine. Therefore, the compounds toxicity to the brain mitochondria, that follow the order: tacrine >> T1 > T2, does not correlate with their ability to inhibit brain cholinesterase enzymes. Lipidomics approaches show that phosphatidylethanolamine is the most abundant phospholipid class in non-synaptic brain mitochondria and cardiolipin present greater diversity of molecular species. Tacrine induced significant perturbations in mitochondrial phospholipid profile detected by changes in relative abundance of phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol and cardiolipin and by the presence of oxidized phosphatidylserines. Additionally, in both T1 and T2 groups, the lipid content and molecular composition of brain mitochondria phospholipids are perturbed in less extent than in the tacrine group. The abnormalities in cardiolipin content and the amount of oxidized phosphatidylserines were associated with significant reductions in mitochondrial enzymes activities, mainly complex I. These results indicate that tacrine and its analogues impair the mitochondrial function and bioenergetics, compromising the activity of brain cells.



Tacrine



T1



T2

Figure 1