Lipidomic approach of the biological activity of tacrine and two tacrine-analogues on non-synaptic rat brain mitochondria

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Tacrine is an acetylcholinesterase (AChE) inhibitor used as a cognitive enhancer in the treatment of Alzheimer's disease (AD). However, its low therapeutic efficiency and a high incidence of side effects have limited its clinical use. In this study, the molecular mechanisms underlying the impact on brain activity of tacrine and two novel tacrine analogues (T1, T2) were approached by focusing on three aspects: (i) their effects on brain cholinesterase activity; (ii) perturbations on electron transport chain enzymes activities of non-synaptic brain mitochondria; and (iii) the role of mitochondrial lipidome changes induced by these compounds on mitochondrial bioenergetics. Brain effects were evaluated 18 h after the administration of a single dose (75.6 micromoles/kg) of tacrine or tacrine analogues. The three compounds promoted a significant reduction in brain AChE and butyrylcholinesterase (BuChE) activities. Additionally, tacrine was shown to be more efficient in brain AChE inhibition than T2 tacrine analogue and less active than T1 tacrine analogue, whereas BuChE inhibition followed the order: T1 > T2 > tacrine. The studies using non-synaptic brain mitochondria show that all the compounds studied disturbed brain mitochondrial bioenergetics mainly via the inhibition of complex I activity. Furthermore, the activity of complex IV is also affected by tacrine and T1 treatments while FoF1-ATPase is only affected by tacrine. Therefore, the compounds' toxicity as regards brain mitochondria, which follows the order: tacrine >> T1 > T2, does not correlate with their ability to inhibit brain cholinesterase enzymes. Lipidomics approaches show that phosphatidylethanolamine (PE) is the most abundant phospholipids (PL) class in non-synaptic brain mitochondria and cardiolipin (CL) present the greatest diversity of molecular species. Tacrine induced significant perturbations in the mitochondrial PL profile, which were detected by means of changes in the relative abundance of phosphatidylcholine (PC), PE, phosphatidylinositol (PI) and CL and by the presence of oxidized phosphatidylserines. Additionally, in both the T1 and T2 groups, the lipid content and molecular composition of brain mitochondria PL are perturbed to a lesser extent than in the tacrine group. Abnormalities in CL 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 mitochondrial function and bioenergetics, thus compromising the activity of brain cells.

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