

SUMMARY

Rationale: The current standard treatment of Alzheimer's disease (AD) is represented by acetylcholinesterase (AChE) inhibitors. In the pathogenesis of AD, cholesterol is directly involved. Its blood and brain levels positively correlate with amyloid β ($A\beta$) - a peptide characteristic for AD and capable of increasing AChE activity. Based on these data, we may suppose that cholesterol-lowering medication such as statins and alendronate might confer protection against dementia, probably via modulation of cholesterol synthesis in the brain. The aim of the present studies was to investigate possible influence of two lipophilic statins (simvastatin and atorvastatin) and alendronate on cholesterol synthesis in selected parts of the rat central nervous system (CNS) and other parameters relevant to Alzheimer's disease pathophysiology.

Methods: We have performed 3 similar experiments on awaked rats that were administered simvastatin, atorvastatin, alendronate or aqua. At the conclusion of experiments, blood and brain parts were isolated and analyzed for cholesterol, lathosterol, hydroxymethylglutaryl-coenzyme A reductase protein, acetylcholinesterase activity, amyloid beta (40 and 42) and cholesterol synthesis rate.

Results: All drugs at higher doses were able to lower cholesterol in the plasma, but none elicited an effect on total brain cholesterol. Significant reductions of lathosterol and cholesterol synthesis rate were observed after simvastatin- and atorvastatin- treatment, whereas amyloid beta and hydroxymethylglutaryl-coenzyme A reductase levels remained unaffected. Both statins elicited comparable effects on cholesterol synthesis rate irrespective of the examined brain part. In alendronate group, the experiments brought inconsistent results concerning its influence on brain cholesterol synthesis. Both simvastatin and alendronate inhibited acetylcholinesterase activity in frontal cortex.

Conclusions: Our studies bring additional evidence of the role of statins in the brain cholesterol synthesis and are the first to show an influence of statins and alendronate on AChE activity in the rat brain. However, our data question the relationship between amyloid beta, acetylcholinesterase activity and cholesterol synthesis. For comparison of the effects of statins in selected parts of the brain, the deuterium technique was utilised for the first time.