TACRINE AND ITS DERIVATIVE 7-METHOXYTACRINE: COMPARISON OF IN VITRO BIOLOGICAL PROPERTIES

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Acetylcholinesterase (AChE; EC 3.1.1.7) inhibitors are currently the main group of drugs in the treatment of Alzheimer’s disease (AD). The first centrally acting inhibitor approved for the treatment of AD was tacrine (Cognex; 1,2,3,4 tetrahydroacridin-9-amine). After a few years, tacrine was withdrawn from the therapy because of its several side effects. The Armed Forces of the Czech Republic are equipped with the antidote against the effects of incapacitating chemical warfare agents with central anticholinergic effect (e.g. 3-quinuclidinyl benzilate), which is based on the tacrine derivative, 9-amino-7-methoxy-1,2,3,4-tetrahydroacridine (7-methoxytacrine; 7-MEOTA). In our study, we evaluated and compared the in vitro biological properties of tacrine and 7-MEOTA. We tested their inhibitory activity on human AChE and butyrylcholinesterase (BChE; EC 3.1.1.8), binding inhibition of N-[methyl-3H] scopolamine (NMS) to the muscarinic M2 receptor subtype and the toxicity in different cell lines. As resulted, 7-MEOTA has a higher selectivity for AChE than for BChE and tacrine has higher affinity for BChE than for AChE. Both compounds inhibit binding of NMS to the muscarinic M2 receptor. 7-MEOTA has lower toxicity in some cell lines when compared with tacrine. According to our results, 7-MEOTA appears to be an appropriate leading structure for the preparation of new AD drugs, such as hybrid or dual AChE inhibitors. These inhibitors will have different biological activity compared to analogous compounds derived from tacrine. This work was supported by the Ministry of Defence (Czech Republic) - Grant No. MO0FVZ0000604 and by the Grant Agency of the Czech Republic - Grant No. P303/11/1907.