Introduction

Current treatment of Alzheimer’s disease (AD) is limited on the administration of cholinesterase (ChE) inhibitors and/or NMDA receptor antagonist, memantine. Tacrine, the first registered ChE inhibitor, was withdrawn from the market due to adverse effects [1]. Recently, novel tacrine and 7-methoxytaxine (7-MEOTA) derivatives have been synthesized and investigated to find less toxic compounds [2].

Further, recent research has been focused on studying the association between the intracellular amyloid beta (Aβ) cascade and the dysfunction of subcellular organelles, especially mitochondria [3]. Mitochondrial enzyme amyloid beta binding alcohol dehydrogenase (ABAD) might contribute to the neuronal dysfunction associated with AD by interacting with intracellular Aβ [1]. ABAD modulators represent one of the new strategies of AD pharmacotherapy [4, 5]. The aim of our study was to measure in vitro effects of novel ChE inhibitors and ABAD modulators on mitochondrial functions.

Methods

In vitro effects of novel compounds - ABAD modulators (K690, K691, K801, K822, K824, K931, K932, K941, K942, and K943) and ChE inhibitors (PC-6, PC-11, PC-22, PC-25, PC-33, PC-34, PC-48, PC-49, and PC-53) were examined in mitochondria isolated from pig brain. Activity of electron transport chain complexes were measured spectrophotometrically [5]. Mitochondrial respiratory rate was determined at 37°C using a titration-injection high-resolution oxygraph with Clark-type electrodes. Statistical analyses were performed using the STATISTICA data analysis software system (StatSoft, Inc., Tulsa, OK, USA). Data are presented as the mean ± standard error (SE).

Results

ABAD modulators: All the tested compounds are full or partial inhibitors of complex I-linked mitochondrial respiration; with lower potency, they also inhibit complex II-linked respiration. The most potent inhibitor of mitochondrial respiration is K824, the weakest inhibitor are K691, K690, K931, and K801 (Fig. 1). Tested ABAD modulators inhibited both complex I and complex IV activity (Fig. 2A).

ChE inhibitors: All the tested compounds inhibited complex I-linked respiration; complex I-linked respiration was strongly inhibited by PC-22. Complex II-link respiration was inhibited by PC-53, PC-22, PC-48 and PC-49 (Fig 3). Activity of complex I was found increased for PC-6, PC-11 and PC-49 compounds. Other tested PC-compounds inhibited complex I activity; the most inhibitory effect was observed after incubation with PC-22 and PC-25 compounds. Decreased complex II-III activity was observed for all the tested PC-compounds. Activity of citrate synthase (CS) was not changed (Fig. 2B).

Discussion

Mostly inhibitory effects on mitochondrial respiration have been observed. High drug concentration required for its direct mitochondrial effect indicates that non-receptor mechanisms play a role. The use of high concentrations of tested drugs in vivo experiments can be useful for the design of in vitro experiments, which should confirm or disprove the therapeutic doses.

Conclusions

Many drugs have been shown to induce inhibition of complex I. It can be presumed that drug-induced inhibition of mitochondrial respiratory rate is associated with adverse drug effects and neurotoxicity. Our results indicate that all tested drugs might affect mitochondrial functions and cause mitochondrial toxicity at high drug concentrations.

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