The Mixed and Reversible Inhibition of Rat Cerebral Acetylcholinesterase (AChE) Activity by the Selenoorganic Compound Ebselen

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Introduction: Acetylcholinesterase (AChE) is an important biological catalyst responsible by hydrolysis of the neurotransmitter acetylcholine, which is known to be important in learning and memory processes. The impaired function of cholinergic system has been related to cognitive deficits, as observed in Alzheimer's Disease (AD). With few exceptions, AChE inhibitors are the only class of drugs currently approved for the treatment of AD. In this way, the selenoorganic compound ebselen (Ebs) has shown some pharmacological properties, among them in vitro cerebral acetylcholinesterase inhibition (IC$_{50}$ of 40 µM). Thus, the present study aimed to evaluate the enzymatic kinetic and the reversibility of this inhibition.

Material and methods: AChE activity was determined by the method of Ellman, using rat brain homogenates. The inhibition kinetic was carried out with different concentrations of acetylthiocholine (0.1–2 mM, as substrate for AChE) and V$_{max}$ and K$_m$ were calculated with or without Ebs at IC$_{50}$ concentration. The reversibility of AChE inhibition by Ebs (IC$_{50}$) was evaluated by dialysis over the period of 60 min.

Results and Discussion: Ebs demonstrated a mixed inhibition of AChE activity since it decreased V$_{max}$ and increased K$_m$ significantly (Lineweaver-Burk method/t-test). The dialysis results showed that Ebs reversibly inhibited the AChE activity with complete reversal observed at 60 min after starting the dialysis (repeated measures two-way/Bonferroni test), which excludes the possibility that Ebs inhibits AChE activity by covalent binding to this enzyme. The reversible inhibition of AChE activity is important, because irreversible inhibitors are generally very toxic, leading to muscle overstimulation, as observed in organophosphates poisoning.

Conclusions: Ebs positively modulates the cholinergic system, by reversibly inhibiting the cerebral AChE activity in rats. More studies dealing with memory behavioral tasks and toxicological profile are needed to support the use of Ebs as a therapeutic approach for treatment of cognitive deficits.

Keywords: Acetylcholinesterase, ebselen, kinetics profile

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