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ORIGINAL PAPER

Flexibility of active-site gorge aromatic residues and non-gorge aromatic residues in acetylcholinesterase

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The presence of an unusually large number of aromatic residues in the active site gorge of acetylcholinesterase is a subject of great interest. Flexibility of these residues has been suspected to be a key player in controlling the ligand traversal in the gorge. This raises the question of whether the over-representation of aromatic residues in the gorge implies higher-than-normal flexibility of these residues. The current study suggests that it does not. Large changes in the hydrophobic cross-sectional area due to dihedral oscillations are probably the reason of their presence in the gorge.

Keywords: acetylcholine, acetylcholineterase, active site, gorge, aromatic residues

Introduction

Acetylcholinesterase (AChE) is the ubiquitous key enzyme responsible for breaking down acetylcholine (ACh) signals in neural synapses, and as such, it has been the subject of extensive investigation (Dvir et al., 2002; Geula & Mesulam, 1995; Gilson et al., 1994; Sussman et al., 1991). One of the well-known features of Alzheimer's disease is the reduction in the activity of cholinergic neurons, which leads to a reduction in the amount of ACh. Acetylcholinesterases rapidly hydrolyze ACh to form acetate and choline. This feature of acetylcholinesterases has been exploited to make a family of drugs such as Aricept^{TM} (Birks & Harvey, 2006) which inhibit AChE for the treatment of Alzheimer's disease. The enzyme is also central to the research in defence against nerve agents which bind AChE preventing thus proper transmission of nerve signals to voluntary muscles.

One of the remarkable features of this enzyme is the 20 Å deep gorge leading to the active site residues. This suggests a low catalytic activity of the enzyme, but in fact, AChE is one of the fastest enzymes with the $k_{cat}/K_M > 10^8$ M^{-1} s^{-1} (Quinn, 1987), making the catalysis merely diffusion-limited. A striking feature of the gorge is that over 60 % of its surface area is lined with aromatic residues (Phe120, Phe288, Phe290, Phe330, Phe331, Trp84, Trp233, Trp279, Trp432, Tyr70, Tyr121, Tyr130, Tyr334, and Tyr442 in PDB 1EA5) despite being accessible to water. This dramatic representation of only three (aromatic) of the twenty amino acids is very intriguing and has raised speculation about the function of the gorge and in particular of its aromatic residues. It was suspected in a previous work that the flexibility of these residues is key to effective transmission and selection of the substrate (Xu et al., 2008). Another set of studies has suggested that the enzyme controls the entry–exit of substrates by "dynamic selectivity" (Karplus & McCammon, 2002; Shen et al., 2002) and that the gorge strongly excludes larger-than-intended substrates by gating motions.

While the flexibility of these aromatic residues is critical for ligand traversal in the gorge, this collective set of observations raises the question "does the over-representation of aromatic residues in the gorge of acetylcholinesterase imply higher-than-normal flex-

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