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Extended Abstract
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MedChem & CADD-2013: The inhibition of acetylcholinesterase by dantrolene and ondansetron

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Alzheimer's disease (AD) is an irreversible, progressive neurodegenerative disorder, and the most common cause of dementia among the elderly. Although the pathogenesis of AD is unknown, as the disease progresses, degeneration of basal forebrain cholinergic neurons occurs, and the levels of acetylcholinesterase (AChE) in the brain decreases significantly. Acetylcholine also plays an important role in cognitive, learning and particularly memory functions. This association of memory impairments in patients suffering from AD with cholinergic hypofunction has prompted considerable interest in cholinergic replacement therapy. A promising approach for treating AD is to enhance the levels of acetylcholine in the brain with AChE inhibitors, which block the catabolism of acetylcholine and increase acetylcholine concentrations in the synaptic cleft. Drug repositioning or drug repurposing is one of the latest strategies in use to find new clinical applications for existing drugs. This study attempted to identify AChE inhibitors among a virtual library of drugs. Virtual screening of a library of approved drugs was conducted to identify compounds with AChE inhibition properties. Those compounds that were hits were further evaluated in vitro as potential AChE inhibitors using the Ellman method. The reversibility of inhibition of the active compounds was investigated by measuring the degree of recovery of enzyme activity after dilution of enzyme-inhibitor mixtures. The results obtained were compared to those of the standard reference compounds, tacrine and PMSF. Among the compounds examined, ranitidine, dantrolene and ondansetron were found to be AChE inhibitors. Ranitidine, a histamine H2-receptor antagonist and known AChE inhibitor was found to be a potent inhibitor of AChE with an IC50 value of 3.37 µM. Dantrolene and ondansetron on the other hand, were found to be moderate inhibitors of the enzyme. Dantrolene, a skeletal muscle relaxant exhibited an IC50 value of 12.8 µM, while ondansetron, a serotonin 5-HT3 receptor antagonist used mainly as an antiemetic had an IC50 value of 37.1 µM. For comparison, tacrine, a reversible AChE inhibitor, exhibited an IC50 value of 0.144 µM. Similar to tacrine, these compounds are also reversible inhibitors. This study showed that amongst the approved drugs, compounds do exist with AChE inhibitory properties. Such compounds may therefore be proposed for the symptomatic therapy of Alzheimer's disease.

Acetylcholinesterase, also called AChE or acetylhydrolase, is the body's main cholinesterase. It is an enzyme that catalyzes the breakdown of acetylcholine and certain other choline esters that function as neurotransmitters. At the neuromuscular junctions and in chemical synapses of the cholinergic tyoe, the AChE is majorly focused. It is the main target of inhibition by organophosphorus compounds such as nervous agents and pesticides. AChE is a hydrolase that hydrolyzes choline esters. The AChE active site includes 2 sub-sites: the anionic site and the esteric sub-site.

The structure and mechanism of action of AChE have been elucidated from the crystal structure of the enzyme. The anionic subsite hosts the positive quaternary amine of acetylcholine as well as other cationic and inhibitory substrates. The cationic substrates are not linked by a negatively charged amino acid in the anionic site, but by the interaction of 14 aromatic residues which line the throat leading to the active site. The 14 amino acids in aromatic throats are highly conserved in different species. Among the aromatic amino acids, tryptophan 84

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is critical and its substitution by alanine leads to a 3000-fold decrease in reactivity. The throat penetrates halfway through the enzyme and measures approximately 20 angstroms. From the bottom of the molecule, the active site is located 4 angstroms.

Dantrolene sodium is a postsynaptic muscle relaxant. In muscle cells, it decreases the excitation-contraction coupling. It does this by inhibiting the release of Ca2 + ions from sarcoplasmic reticulum stores by antagonizing ryanodine receptors. It is the main medication used for the treatment and prevention of malignant hyperthermia, a rare and potentially fatal disorder triggered by general anesthesia. It is also used in the management of neuroleptic malignant syndrome, muscle spasticity (for example after stroke, paraplegia, cerebral palsy or patients with multiple sclerosis) and 2,4-dinitrophenol poisoning , and related compounds dinoseb and dinoterb.

Ondansetron is used to prevent nausea and vomiting that may be caused by surgery, cancer chemotherapy, or radiation therapy. Ondansetron can be used for purposes not listed in this medication guide. Serious side effects of ondansetron include blurred vision or temporary vision loss (lasting only a few minutes to several hours), a slow heartbeat, difficulty breathing, anxiety, restlessness, chills, feeling faint, and less frequent urination than usual or not at all. Ondansetron may affect your thinking or your reactions.

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