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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 IC_{50} 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 IC_{50} 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.

Biography

Clarina I. N'Da completed her Ph.D. in 2012 from the Department of Pharmaceutical Chemistry, and is busy with postdoctoral studies at the Center of Excellence for Pharmaceutical Sciences (Pharmacen), North-West University, South Africa. Her research focuses on the design, synthesis and evaluation of novel monoamine oxidase and acetylcholinesterase inhibitors that can be used in the treatment of Parkinson's and Alzheimer's diseases. She has presented her work in several national and international conferences and has published 4 papers in reputed journals. She was recently awarded the "Top 10 Cited Author Award" for 2011-2012, from the journal Bio-organic & Medicinal Chemistry.

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