Acetylcholinesterase Inhibitors for Treatment of Alzheimer's Disease

Summary:
Novel acetylcholinesterase (AChE) inhibitors for the symptomatic treatment of Alzheimer's disease.

Overview:
Amyloid beta accumulation is one of the primary known causes of Alzheimer's disease (AD) pathogenesis. Acetylcholinesterase augments the neurotoxic effect of amyloid beta by accelerating the formation of beta amyloid deposits in the brain. It is known that 1) acetylcholine (ACh) deficiency is associated with Alzheimer's disease (AD); and 2) inhibiting acetylcholinesterases (AChEs) can beneficially increase ACh levels in the brain. Therefore, AChE inhibition (AChEI) has become one of the primary goals in AD drug development and one of the major therapeutic approaches to the treatment of AD. AChE inhibitors (AChEIs) promote memory function and delay cognitive decline. Dr. Yan's discovery is a family of highly selective AChEIs that preserve all the desirable features of AChEIs on the market today with additional design features achieved by binding to two distinct sites on the AChE enzyme.

Application:
Alzheimer's Disease

How It Works:
Using the 3D structure of AChE from native Torpedo californica (TcAchE), docking simulations were performed to gain insight into the recognition between the AChE and the ligands. These experiments indicated that recognition occurs in a deep, narrow groove approximately 20 degrees Celsius long on the surface of TcAchE. In TcAchE, this groove contains both the catalytic active site (CAS) and the peripheral anionic site (PAS). Reversible inhibitors bind to either the CAS or the PAS. Dimeric (dual) inhibitors, including Dr. Yan's class of novel compounds, bind simultaneously to both of the sites thereby enhancing the desired therapeutic outcomes in AD treatment. Docking, 2D QSAR and pharmacophore studies indicated that at least six compounds should be reasonable inhibitors of AChE. Three of these six compounds had attractive values, indicating they are excellent candidates for AChE inhibition. Dr. Yan plans to use these three candidates as a starting point for developing even more potent analogues for the treatment of AD.

Benefits:
AChE has been shown to play a key role in 1) the acceleration of amyloid beta-peptide deposition, and 2) promoting the formation of amyloid beta plaques.

Why It Is Better:
Preclinical studies suggest that these AChEIs are safe and effective in the treatment of AD with enhanced bioavailability - including ability to cross the blood-brain barrier - over those on the market today. However, they also attenuate neuronal cell death from neuronal cytotoxicity and, therefore, provide not just a new AD treatment paradigm, but hope for actual symptom improvement.

Other Applications:
Other diseases whose pathogenesis involves amyloid accumulation.

Inventors:
Shirley Yan, KoteswaraRao Valasani