Chapter 10

QSAR Models towards Cholinesterase Inhibitors for the Treatment of Alzheimer's Disease

C. Gopi Mohan
Amrita Institute of Medical Sciences and Research Centre, India

Shikhar Gupta
National Institute of Pharmaceutical Education and Research, India

ABSTRACT

Alzheimer's Disease (AD) is a multifactorial neurological syndrome with the combination of aging, genetic, and environmental factors triggering the pathological decline. Interestingly, the importance of the Acetylcholinesterase (AChE) enzyme has increased due to its involvement in the β-amyloid peptide fibril formation during AD pathogenesis. In silico technique, QSAR has proven its usefulness in pharmaceutical research for the design/optimization of new chemical entities. Further, QSAR method advanced the scope of rational drug design and the search for the mechanism of drug action. It is a well-established fact that the chemical and pharmaceutical effects of a compound are closely related to its physico-chemical properties, which can be calculated by various methods from the compound structure. This chapter focuses on different Quantitative Structure-Activity Relationship (QSAR) studies carried out for a variety of cholinesterase inhibitors for the treatment of AD. These predictive models will be potentially used for further designing better and safer drugs against AD.

INTRODUCTION

Alzheimer's Disease (AD) is a multi-factorial syndrome with the combination of aging, genetic, non-genetic causes, and environmental factors triggering the pathological decline (Butters, Deliss & Lucas, 1995). It is a most common form of dementia, with chronic, irreversible and progressive neurodegenerative disorder.

AD usually begins after the age of 60, and the risk increases as the age progresses. Younger people in their 30s to 50s may get AD, but it is rare. Approximately, 10% of all the cases of AD are believed to be hereditary in nature. In familial cases, symptoms usually appear within the age range of 30-60 years and known as early-onset AD. This type of AD results from specific genetic mutation of the individual. The late-onset sporadic AD, representing 90% of patients result from multifactorial environmental factors and genetic events, caused due to the inheritance of the apolipoprotein Eε4 allele and other acting polymorphic genes (Rosenberg, 2000). The non-genetic factors are also playing an important role in AD, as the only one third of the identical twins is concordant of the disease (Jin, Gatz, Johansson & Pedersen, 2004). Still the role of the environmental risk factors has remained mysterious, but progress in finding genes causes of AD, as well as increasing risk for it has been firm and impressive.

Several evidences showed that reactive oxygen species (ROS) are involved in most of the neurodegenerative pathologies. ROS is the most dangerous reactive species, and which can spoil most of the biological molecules. Hence, it is crucial to maintain the oxidative balance and control in the brain. This is known as the oxygen paradox-oxygen, which is an absolute necessity for our energy-economical aerobic life style. However, it is a potential toxin and our brain is most aerobically active organ, which required ~20% of total oxygen in a resting individual. Normally, these free radicals quickly detoxified by the body's defense mechanism and firmly regulated by antioxidants. Hence, modifications in normal oxidative metabolism as observed in AD brain suggest that oxidative stress has a crucial role in AD pathogenesis. In general, chemical origin of the bulk of ROS is the reaction of the molecular oxygen with the redox active metals Fe and Cu.

Two distinct histological changes occur in the nerve cells of Alzheimer brain are the formation of extracellular amyloid ('senile') plaques developed between neurons and intracellular neurofibrillary tangles developed within neurons, which lead to neurotoxicity. Plaques, which are composed of β-amyloid polypeptides (Aβ) formed by the mutations in the amyloid precursor protein (APP) gene on chromosome 21q and of the presenilin 1 (PS1) and presenilin 2 (PS2) genes on chromosomes 14q and 1q, respectively (Tanzi, Kovacs, Kim, Moir, Guenette, & Wasco, 1996). Amyloidogenesis are responsible for almost one half of the early-onset forms of autosomal dominant inherited disease. An increased synthesis of Aβ in the AD brain is a central point in the amyloid hypothesis and suggests that increased amyloidogenesis and/or decreased amyloid clearance with increased amyloid fibrillation are primarily causal of the pathogenesis of AD (Naslund, Haroutunian, Mohs, Davis, Davies, Greengard, & Buxbaum, 2000). Neurofibrillary tangles are secondary important histological abnormalities, which are composed of hyperphosphorylated tau protein and links together to form filaments. Increased density of tau deposition within neurons in the brain facilitates Aβ toxicity. APP processing involves 3 classes of enzymes: α-, β-, and γ-secretase (Mullan, Crawford, Axelman, Houlden, Lilius, Winblad, & Lannfelt, 1992). APP is first enzymatically cleaved by γ- or β-secretase, and which in turn was cleaved by γ-secretase. The segment of the molecule produced by α- γ cleavage yielded a soluble fragment and a self-aggregating fragment (β amyloid 40–42) from the portion of the molecule produced by the β-γ cleavage.

Cholinergic hypothesis targeting acetylcholinesterase (AChE) enzyme are one of the major therapeutic strategies adopted for symptomatic relief on AD (Bartus, Dean, Beer & Lippa, 1982). It is a substrate-specific essential enzyme in the family of serine hydrolases, and which degrades the neurotransmitter acetylcholine (ACh) in the nerve synapses. An optimum level of ACh should be maintained in the hippocampus and the cortex region of the brain for its proper function (Stahl, 1999). This hypothesis is proven to be successful today by the effective use of cholinesterase inhibitors, to augment the surviving cholinergic activity for the treatment of AD.

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