Role of Acetylcholinesterase in Alzheimer’s Disease Resulting from Concussion

1. Three forms of Acetylcholinesterase (AChE) (Soreq and Seidman, 2001)
   a. E4-E6 – has Cys residue that forms dimers – found in synapse (AChE-S)
   b. E4-E5 – also has Cys residue to form dimers – found on erythrocytes (AChE-E)
   c. E4 readthrough - no cys, rare soluble form that is soluble, expressed in high stress or brain injuries (AChE-R)

2. AChE kinetics involves two separate binding sites
   a. Peripheral binding site at neck of gorge
   b. Catalytic site at base of gorge
   c. Regulation of acetylcholinesterase activity is partly based on concentration
      i. At high concentration, when acetylcholine is at BOTH peripheral and catalytic sites, enzyme activity is inhibited
      ii. At low concentration, substrate binds to peripheral site, causes conformational change in omega loop that sucks substrate down gorge to catalytic site; with no additional binding of acetylcholine a peripheral site, enzyme breaks down substrate

3. Peripheral binding site has additional function
   a. Peripheral binding site has a cell adhesive function during neural development (Bigbee et al. 1999)
      i. Similar structure to other proteins involved in laying down a neural network
      ii. Possibly involved in cell-cell interactions by connections with neurotactin and neuroexin (Soreq et al, 2001)
   b. AChE expressed in neurons during periods of axonal outgrowth prior to synaptogenesis (Bigbee et al. 1999)
      i. AChE is even expressed in high levels in non-cholinergic neurons during neurite outgrowth
      ii. Display a dose-dependent reduction in outgrowth in presence of anti-AChE drugs that bind peripheral binding site (but not catalytic site); removal of inhibitor resulted in normal outgrowth
         1. Not just length, but branching of neurons

4. Role of AChE in formation of plaques in Alzheimer’s Disease (AD)
   a. AchE co-localized with amyloid-β peptide deposit of Alzheimer’s brains.
   b. Inhibitors that block Ache active site don’t impair this function, but those that bind at peripheral binding site (propidium) inhibit interaction with amyloid-β peptide
   c. Ache is deposited with Aβ early in the development of senile plaques
   d. Ache increases the rate at which Aβ fibrils form, but does not change the morphology of the final fibrils
      i. Mutations in Aβ that bind to Ache form fibrils faster when Ache present
      ii. Mutations that don’t bind Ache have no change in rate of fibril formation when Ache is present
   e. Use of propidium inhibits almost 75% of enhancement of amyloid formation by Ache [binds peripheral site]
   f. Appears that Ache comes from deterioration of Ache containing neurons, and that its presence stimulates growth of senile plaques

5. Brain trauma
a. Unconscious for >30 min – significant risk for AD
b. Boxing- senility has both Aβ fibrils and plaque associated with AD
6. Antisense destruction of AChE mRNA using protected oligonucleotides –
   a. Improves survival and recovery from closed-head injury

