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EC PHARMACOLOGY AND TOXICOLOGY
Letter to Editor

Stop the Aggregation of Antimicrobial Peptides AMPs, Aβ, Amylin, Insulin and More Unknowns

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Received: November 27, 2017; **Published:** December 18, 2017

The oligomerization of the AMPs is a process that takes place in the neuronal membrane. Conformational and structural modification, like N-methylation [1], cause the retarding effect needed to prevent such oligomerizations [2]. It is evident that N-methylated short AMP mimics can disassemble aggregates and fibrils [3]. Sato, Feix, and collaborators have suggested a route for the penetration into the membrane [4].

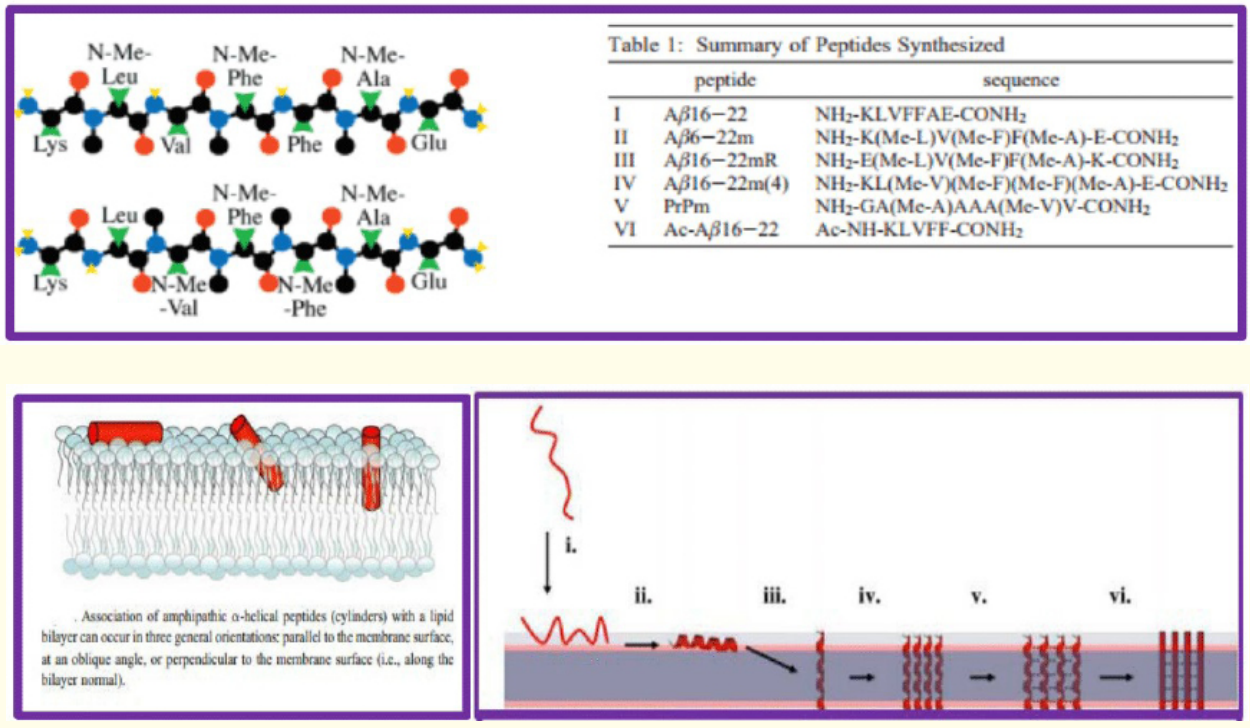

Table 1: Summary of Peptides Synthesized

	peptide	sequence
I	Aβ16−22	NH_2-KLVFFAE-$CONH_2$
II	Aβ6−22m	NH_2-K(Me-L)V(Me-F)F(Me-A)-E-$CONH_2$
III	Aβ16−22mR	NH_2-E(Me-L)V(Me-F)F(Me-A)-K-$CONH_2$
IV	Aβ16−22m(4)	NH_2-KL(Me-V)(Me-F)(Me-F)(Me-A)-E-$CONH_2$
V	PrPm	NH_2-GA(Me-A)AAA(Me-V)V-$CONH_2$
VI	Ac-Aβ16−22	Ac-NH-KLVFF-$CONH_2$

. Association of amphipathic α-helical peptides (cylinders) with a lipid bilayer can occur in three general orientations: parallel to the membrane surface, at an oblique angle, or perpendicular to the membrane surface (i.e., along the bilayer normal).

Figure 1: *Oligomerization of AMPs [2-4].*

The accumulation of The AMPs in the brain, Aβ and others. Insulin, Amylin and many unknown more that are the digestion products provided by the aspartyl proteases, the secretase complex, are themselves a sort of "Cinquième cologne" and damage the neuron by typical AMP cell membrane disruption, drilling holes in the phospholipid membranes, in particular, damaging the synaptic cleft [5,6].

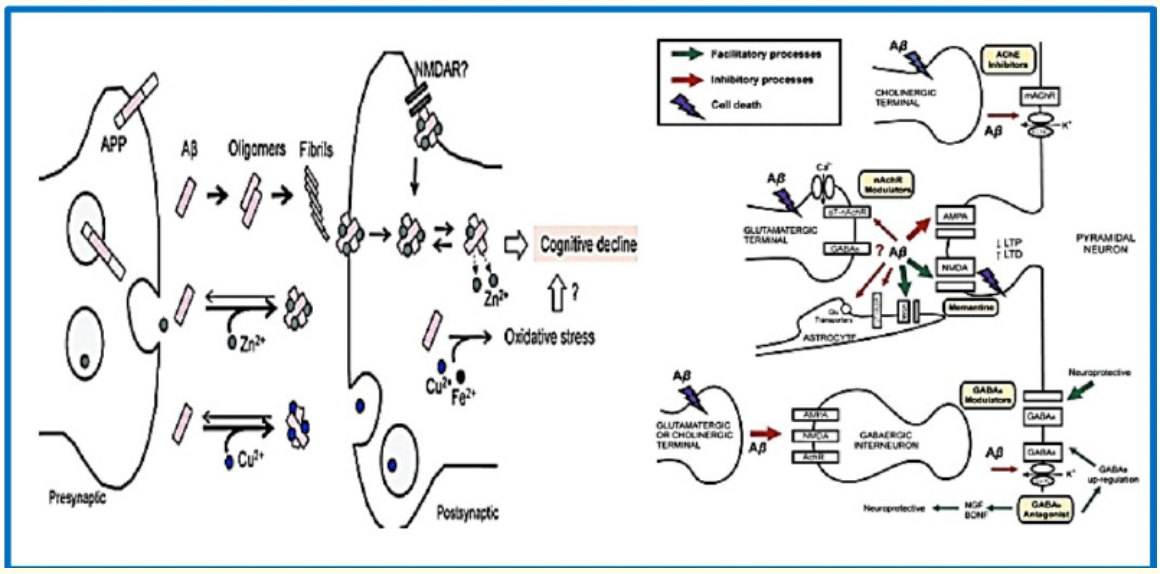

Figure 2: *Fibrils disrupt synapse in the synapse cleft [5,6].*

Alzheimer's disease (AD) is the most known progressive neurodegenerative disease characterized by cognitive decline, brain atrophy due to neuronal and synapse loss, and formation of two pathological lesions: extracellular amyloid plaques, composed largely of amyloid-beta peptide (Aβ), and neurofibrillary tangles formed by intracellular aggregates of hyper- phosphorylated tau protein.

The events that trigger the main pathological changes in AD take place in regions of the temporal lobe, including the medial septum, hippocampus, amygdala, and entorhinal cortex. The early onset of the AD is manifested as an inability to form new memories. However, the multiple structural and biochemical changes which are documented in the mid-to-late stages of the AD (such as synapse loss, plaque accumulation, tangle formation, and neurodegeneration) do not explain the memory deficits observed in the initial stages of the illness [7]. For example, the loss of synapses appears to be the best morphological correlate for functional deficits observed in the middle and late stages of the AD, but many patients in early stages do not show a significant decline in some synapses.

Based on these findings, attempts have been made to find an explanation for cognitive deficits observed at early stages of the disease when no significant decline in the synapse and cell number was detected. Scientists proposed that misfolded oligomeric forms or small Aβ aggregates that still free in the tissue might induce an initial state of synaptic dysfunction in early AD patients.

A major problem in this area is that the oligomers are ill-defined. These aggregation intermediates, often referred to as prefibrillar oligomers, oligomers, protofibrils, intermediate-sized toxic amyloid particles, or amyloid oligomers, have been studied extensively *in vitro*. It was suggested at an early date that they are inserted into the cell membrane, wherein they form functioning ion channel-like structures. This pore-forming capacity has been proposed to be a universal cytotoxic mechanism for all amyloid proteins, and analyses of the composition of pores recovered from artificial lipid bilayers have revealed oligomeric complexes of trimers up to octamers, depending on the amyloid protein. For IAPP the major inserted complexes were of the trimeric and hexametric type. Suggested mechanisms by which IAPP may permeabilize membranes are either through formation of toroidal (doughnut-like) pores or by nonspecific membrane disruption due to excessive negative curvature strain [8].

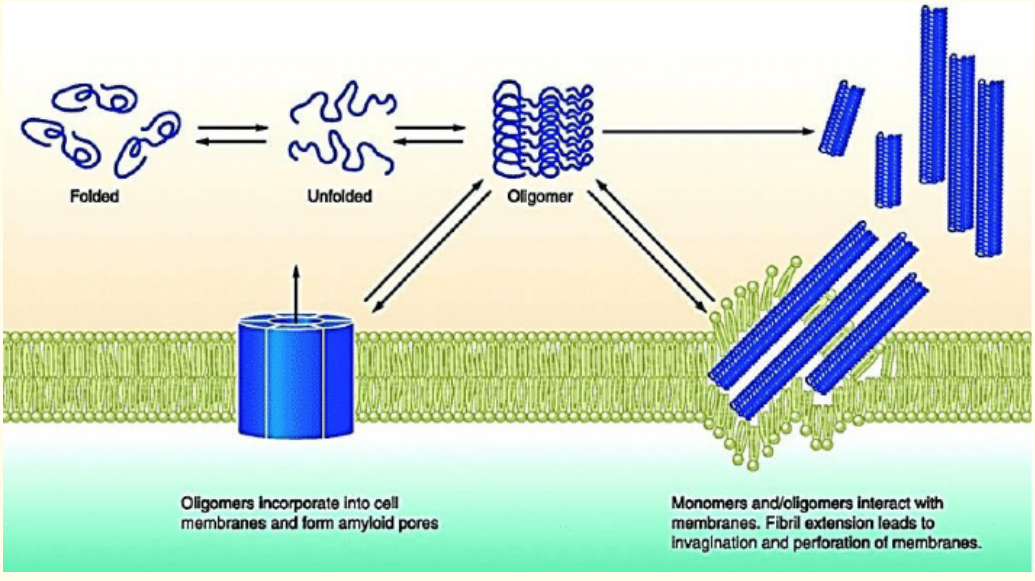

Figure 3: *Fibrils damage neuronal outer cell membrane [8].*

The action of fibrils. Plaques, tangles problem, the destroyers of synapses, is the last strike on the neurons. This is one of the major events of neuronal death. There are chemical compounds that disassemble these supramolecular structures. Polyphenols are the focus of efforts directed in fibril disassembling. Resveratrol Selectively Remodels Soluble Oligomers and Fibrils of Amyloid Aβ into Off-pathway Conformers [9]. Inhibitors of Aβ peptide aggregation ore considered as a basis towards new drugs against the AD [10]. The focus of this quest is based on the observation that castalagin, vescalagin, SEN304 and inh3 are promising molecules to prevent the amyloid- beta peptide aggregation, and to reduce the cellular toxicity of the peptide.

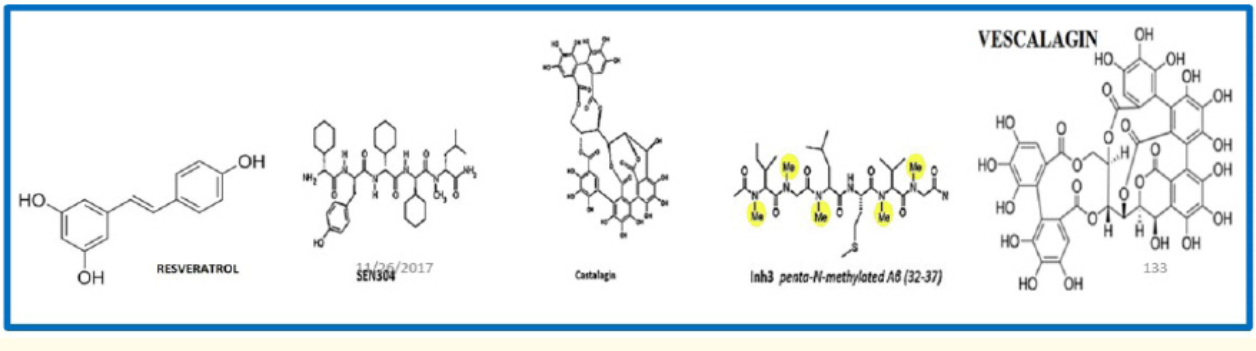

Figure 4: *Agents that disassemble fibrils and aggregates [10].*

Curcumin is known to interact with AMP fibrils. Curcumin-conjugated magnetic nanoparticles for detecting amyloid plaques in Alzheimer's disease mice using magnetic resonance imaging (MRI) [11]. Gazit and coworkers explored the Inhibition of Amyloid Fibril Formation by Polyphenols: Structural Similarity and Aromatic Interactions as a Common Inhibition Mechanism [12]. Folk medicine recommends the application of curcumin [13] to retard the developing neurodegenerative diseases.

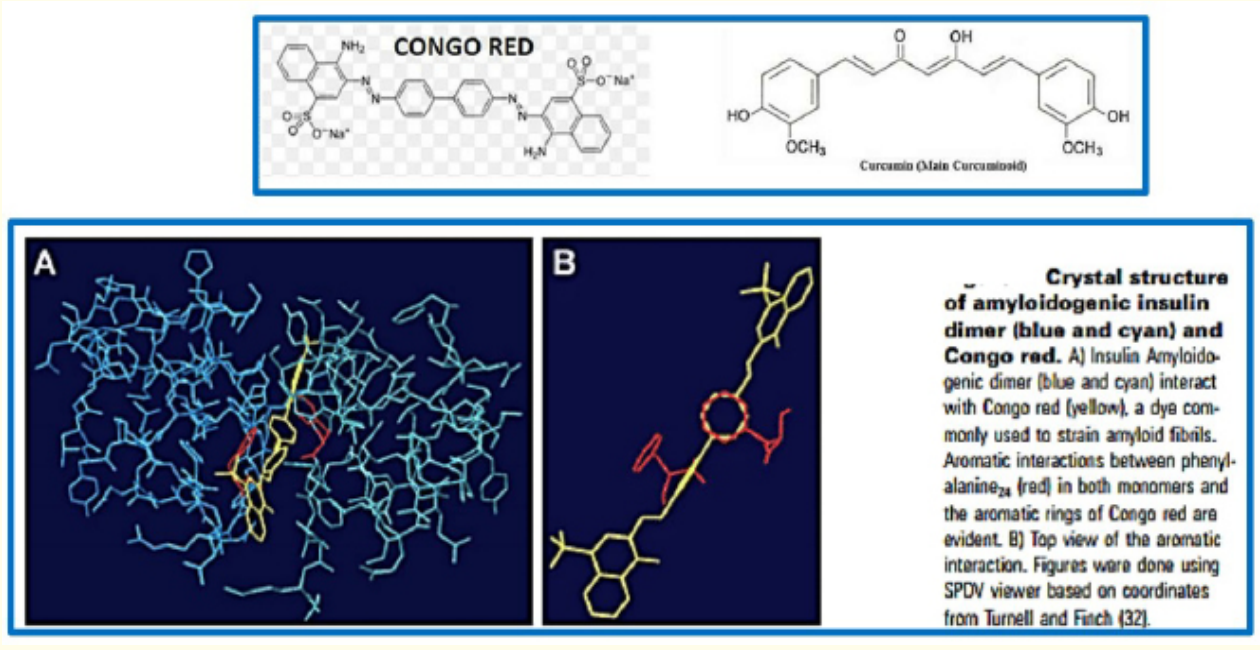

Figure 5: *Congo Red conglomerate with insulin [12].*

The current perception on neuron-degradation is based on the early damage of the BBB. This allows the infiltration of microbes and proteins, all of which were forbidden to penetrate when the healthy BBB in operation.

These intruders cause inflammation and infection. The available immune system is in combat with these "unwanted" and sets in motion the best available agent: antimicrobial peptides by digesting many proteins using the γ-secretase aspartyl membranal enzyme.

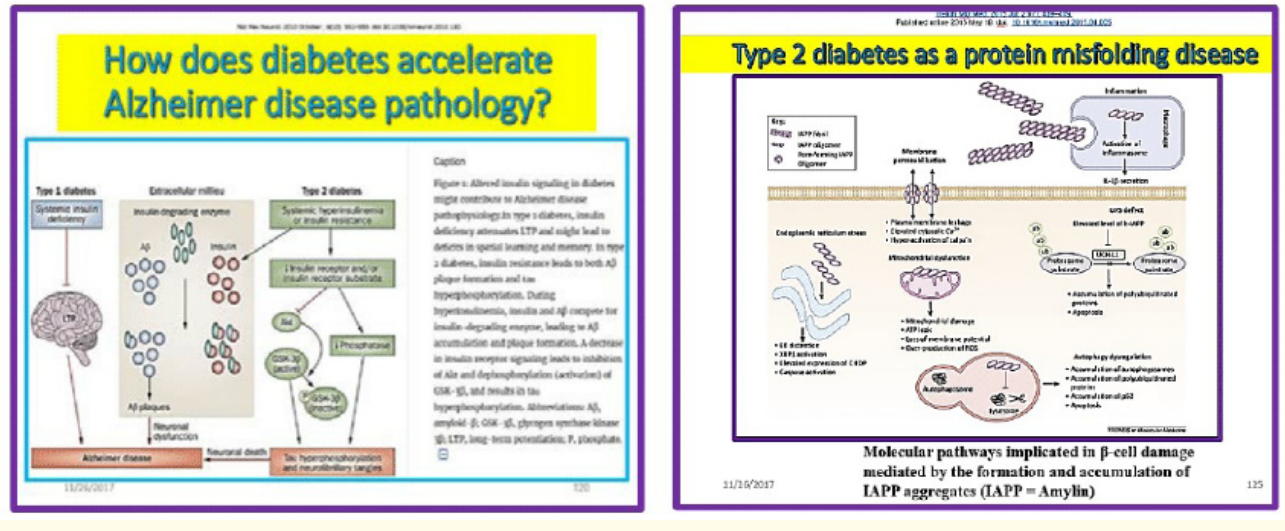

Figure 6: *Aggregates with insulin [14,15].*

Insulin and Amylin are regular peptide hormones that applied to the brain. However, the acute situation is causing the involvement of these into oligomers and fibrils that infiltrate the neuronal system of the injured brain (BBB) and eradicate synapses and with it the neurons [14,15].

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Volume 5 Issue 3 December 2017