Microbial Inflammation and Infection as a Cause of the Onset of Neurodegenerative Diseases

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Abstract

For three decades the Amyloid hypothesis was leading in popularity compared to the oxidative stress ideas. It guided researchers in the neurodegenerative diseases area. This idea contributed a lot to the progress of the respective quest for remedy, the amyloids, amylin, insulin and other antimicrobial agents were held responsible for neuron death by their aggregates, fibrils, and plaques. However, it seems today that the culprit is not there. On the other hand, more and more evidence is accumulating to favor an idea that was almost abandoned, the microbial inflammation and infection as the onset and significant cause of neuro-degeneration and death.

Keywords: Microbial Inflammation; Neurodegenerative Diseases; Oxidative Stress; Amyloid Hypothesis

Introduction

Could Alzheimer’s patients be the result of toxic residues of the brain’s attempt to fight inflammation? (Figure 1) [1-4]. Researchers report on various infections as possible triggers of Neurodegeneration of the brain parenchyma. The researchers describe a scenario. A microbe penetrates the brain, passes through a membrane, a blood-brain barrier and is diluted with age (Figure 2) [5-8]. The brain’s defense system hastens to stop the intruder by creating a sticky cage of proteins called beta-amyloid. The bacterium, like a spider web spider, was trapped in a cage and died. What is left is the cage, a sign that it is a hallmark of Alzheimer’s? (Figure 3) [9-11].

In recent years, The Amyloid Precursor Protein-Secretase-Amyloid-β hypothesis is losing momentum. Instead, inflammation [12,13] is a defense response against various insults, designed to remove toxic substances to inhibit their harmful effects. It consists of a dazzling collection of molecular cellular mechanisms and a complex network of controls to keep them in check. In degenerative diseases, inflammation may be triggered by an accumulation of proteins with abnormal conformation or by signals arising from injured neurons. Given the number of functions of many inflammatory factors, it was difficult to pinpoint their specific roles (feto)-physiological conditions.

When the BBB [18] is damaged, gut bacteria, protein and other “prohibited” bodies can enter the inner brain and start the process, that continues for decades, of neuronal eradication, and finally interception and death [19,20]. The quest for remedy is reaching every corner. Here are some examples of agents discovered in the plants [6,21,22].

The leaks in the 400 miles of blood vessels that surround the brain, is hard to locate in the living brain, which makes a possible medicinal drugs treatment very difficult to the practically impossible today. Recently, nutritional measures suggested in many online publications on how to fix a leaky BBB [23] do not deter researchers from seeking instrumental methods, like LASER [24] based approach for the initial instrumental diagnosis of Neurodegeneration.

The Inflammatory Hypothesis

The intrinsic model

Nowadays, there are two models of the inflammatory hypothesis of the AD, an intrinsic and an extrinsic. The intrinsic inflammation model [25-27] accounts for the intact ‘blood-brain barrier’ (BBB) limits the entry of neurotoxic and systemic lymphocytes into the brain. As a result, the glial brain cells can produce a localized innate immune system when challenged by foreign agents. Neuroinflammation is mostly perceived as being a downstream result of the amyloid hypothesis, whereby the presence of amyloidogenic peptides causes the activation of progenitor microglia in pro-inflammatory waterfalls and the release of potentially neurotoxic substances resulting in degenerative changes in the neurons. A wide-ranging genome study (GWAS) now affects congenital immune genes as a risk factor and supports the primary function of AD inflammatory pathogens by an improper activation of the complement system, in combination with Aβs and neurofibrillar complex (NFT).

Curing Alzheimer’s : Is there any Potential Remedy?

New approaches in AD drug discovery

Once inflammation is active, is very winning. These inflammatory molecules travel throughout the body causing stress and oxidation. Oxidative damage is the earliest cause of Alzheimer’s disease. Destroy the fragile machines of the tissues and the mitochondria, especially. In the brain, inflammation is used to replace the use of tryptophan towards the production of anxiety-stimulating substances like quinoline, instead of toward serotonin and melatonin. For example, some AMPs alter the properties of a mammalian membrane or interact with its receptors and influence various cellular processes including cytokine release, chemotaxis, antigen presentation, and angiogenesis and wound healing. Today, we are beginning to see that much of the importance of AMPs in mammals might lie in their multifunctional role (Figure 4).

However, increasing evidence indicates that some AMPs can confer protection by an indirect mechanism and not merely because they can kill microbes. They can function as potent immune regulators, altering host gene expression, acting as chemokines and inducing chemokine production, inhibiting LPS- or hyaluronan-induced pro-inflammatory cytokine production, promoting wound healing and modulating the responses of dendritic cells or T-cells of the adaptive immune response.

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The main events in the AD early stages:

**Oxidative Damage in Alzheimer Disease**
- Increased beta-amyloid in AD brain, hippocampal atrophy, and neuronal loss
- Synapsin I expression in transgenic mice

**APP family of proteins:** similarities and differences between APP and 
- Familial Alzheimer's disease
- Alzheimer's disease with mutations in APP

Figure 1: The “OLD” look of Neurodegeneration.

**The “NEW LOOK” of NEURODEGENERATION**

1996 paper: anti-inflammatory agents as protective factors for AD.

Figure 2: The inflammation based Neurodegeneration, new “look”.

**Micro biome microbes crossing the Blood-Brain Barrier into the parenchyma and stroma of the inner brain.**

Figure 3: Microbiome microbes crossing the Blood-Brain Barrier into the parenchyma and stroma of the inner brain.
In this way, AMPs are acting as a bridge between innate and adaptive immunity. All of these functions favor resolution of infection and reverse potentially harmful inflammation, and complement the direct antimicrobial action. Here, we review some of the essential functions of AMPs that are not related to their direct antimicrobial action.

Ultrashort SMAMPs (Synthetic Mimics Antimicrobial Peptide) [28,29] can become very instrumental in neuro-medicine. We have demonstrated that SMAMPs (mimics of 5 amino acids), based on some privileged scaffolds like 1,4-DHP and Azepine cross the BBB, and enter the Stroma and Parenchymas of the living brain. There is currently an immediate need for improved biomarkers [30] and therapies for psychiatric, developmental, traumatic, inflammatory, infectious and degenerative nervous system disorders. These, in whole or in part, are a significant societal burden due to growth in numbers of affected people and in disease severity.

Role of Antimicrobial Peptides (AMPs) and Synthetic Mimics of Antimicrobial Peptides (SMAMPs) in Brain Inflammation

Most cationic peptides, such as β-Defensins, assigned initially to a microbial function are now recognized as mediators of innate immunity and adaptation. The following supporting evidence is presented for the hypothesis that neuropathological changes associated with chronic disease conditions of CNS involve abnormal expression and regulatory function of specific antimicrobial peptides. It is also suggested that these changes exacerbate the pro-inflammatory conditions in the brain, which ultimately intensify the neurogenerative process [31].

How can antimicrobial peptide surrogates contribute to Neurodegeneration research?

- Inflammation is back; AMP are anti-inflammatory.
- Foldamers as secretase inhibitors.
- Antimicrobial peptides surrogated do not aggregate.
- Immunotherapy.
- The unique mechanism of inhibition of γ-secretase. The function of Notch in γ-secretase inhibitor (GSI).
- Aib aided BBB penetration of probes and drugs.

The above-mentioned polypeptides suffer from a significant drawback, that is their ability to penetrate the BBB and that proteases digest them. Their features are far away from the LIPINSKI rule of 5 statements. In this respect, STAMPS may become useful to treat neuronal inflammation. The many drawbacks of AMP are omitted by the design and synthesis of such peptide surrogates. Antimicrobial peptides are susceptible compounds and suffer many disadvantages when intended to be applied by humans their struggle against the bacteria [3]. We would like to suggest the exploring of some leading STAMPS as Neurodegeneration retarding compounds. In addition to the role of anti-microbial, AMPs also act as essential effector molecules in Inflammation, immune activity, and wound healing. Antimicrobial peptides are needed to combat neuroinflammation [32]. Antimicrobial peptides (AMPs) are central components of innate CNS immunity which acts in the protection of brain cells by inducing neuroprotective factors.

Antimicrobial peptides in neuronal are significant players in retarding neuro-degradation diseases. β-Defensins have major tasks in defense of the Brain parenchyma and lobes. The AMPs Amylin (sugar metabolism) an Amyloid-β, and others like insulin (diabetes) have a significant role in the inhibition of the spread of inflammation and infection by their involvements in the harnessing of immune fortifying agents as follows:

Human β-defensins [33] (hBDs) are a conserved family of cation antimicrobial and immunomodulatory peptides expressed primarily by epithelial cells in response to invasion by bacteria and fungi certain viruses. To date, the most studied research members of these peptides are HBD-1, -2 and-3. Expression of HBD-1 and 2 has been demonstrated in the past microglia culturally astrocytes of both mouse and the human brain. Unlike HBD-2 and 3, HBD-1 is constructively expressed and is not felt by pro-inflammatory factors.

Anti-neurodegradation agents: Antimicrobial peptide surrogates

Recently, publications [34] deal with the potential contribution of pathogenic bacteria to AD aging. Bacteria and bacteria and other proteins enter a defective brain blood barrier (BBB) that attacks the neurons that cause inflammation in the brain. This inflammation is considered a first step in the development of fatal diseases: Alzheimer’s, Parkinson’s, and dozens of other known brain diseases.
Natural immune systems apply microbial peptides, β-defensins and other agents like amylin, β-amyloid (Aβ) are “harnessed” to protect the neurons, to stop inflammation. These microbial materials bring with them a lousy trait: they form aggregates, fibrils, tangles and other supramolecular structures. Theses in the brain and inflammation have caused the bodies to hit the most sensitive areas of neurons in the brain, the synapses. To bring about degeneration and death by damaging the synapse membrane in microbial form; digging (Figure 5).

Antimicrobial polypeptides are useful in the cure of neuronal injuries. An example is Antimicrobial peptides and complement in neonatal hypoxia-ischemia induced brain damage [35]. It is well established that HI (hypoxia-ischemia) brain injury associated with infiltration of inflammatory cells into the brain. Neutrophils are the most prolific type of leukocytes and are an integral part of the innate immune system. Although tests in adult rodent of ischemic insult show that neutrophils are known to accumulate in the inner brain as early as 4–6 h post injury, and lasting up to 48 h [36,37]. This does not look to be the case for neonatal HI injury, where neutrophil infiltration into the damaged brain is less marked, with a smaller number present at 42 h post-insult. However, this study showed that P7 neutropenic rats had a 70% reduction in brain swelling at 42 h after HI compared to littermate controls. Therefore, in contrast to the suggestion that neutrophils do not accumulate in the undevolved brain following HI, they still play an important role in worsening of neonatal brain damage.

"Here, we synthesize research behind the emerging hypothesis that inflammation—which can the result, for example, from viral or by entering the parenchyma through a leaky BBB to initiate a microbiome induced infections—can initiate and propagate chronic neuronal dysfunction, an event that precedes the clinical onset of many neurodegenerative diseases. Therapeutic approaches that target immunological pathways in the prodromal phase of diseases might decrease the incidence of neurodegenerative disorders and increase the therapeutic window for neuroprotection.”

DHP penetrates BBB through DHP receptors

We Investigate L-type calcium channel blockers of the dihydropyridine class for association with Parkinson's disease because these drugs traverse the blood-brain barrier, are potentially neuroprotective, and have previously been evaluated for impact on PD risk.

Calcium signaling in Parkinson's disease [38]

Calcium (Ca^{2+}) is a universal two messenger that almost regulates essential activities of all eukaryotic cells. It is of essential importance to neurons, which have developed comprehensive and complex pathways to pair Ca^{2+} signal to their biochemical machines. In particular, Ca^{2+} participates in transmitting the depolarizing signal and contributes to synaptic activity. During aging and in the processes of neurodegenerative diseases, the ability of neurons to maintain an adequate energy level can be treated, thus impacting on Ca^{2+} homeostasis (Figure 6).

Reached Phase III Candidate for the Treatment of Parkinson's Disease

The agent ISRADIPINE

This new study, based on the Phase III trial of ISRADIPINE in early Parkinson’s disease (STEADY-PD III), investigates ISRADIPINE as a potential neuroprotective agent in PD based on robust preclinical data and reliable epidemiological data [39,40].

The study design STEADY-PD III is unique in assessing the effect of ISRADIPINE over 36 months, at a time when all participants will be on ST, which allows us to determine whether the benefit is sustained “on” traditional symptomatic therapy (ST). Also, research design allows us to determine whether effects on motor function are corroborated by important Secondary outcomes evaluating clinically relevant measures of ST use, motor complications, non-motor functioning, global disability, quality of life, ambulatory capacity, and cognition. This design is innovative and innovative and enables the determination of long-term benefits on a number of clinically relevant results in a relatively small group on the derived ST benefit.

It is reported that Some Calcium Channel Blockers May Protect against Parkinson's disease. L-type channel: Studies [41-44] on short Aβ peptides provided an early indication of involvement of calcium channels in the Aβ pathology. Application of Aβ25–35 to cultured neurons caused cell degeneration, which was prevented by nimodipine.

Overall, the current data suggest that use of calcium channel blocker antihypertensive, significantly slows the rate of progression of subjects to dementia compared to those subjects who do not use CCBs.
Dihydropyridine derivatives regulate heat and shock responses and have a neuroprotective effect in the transgenic mouse model of Alzheimer’s disease [43]

Heat shock proteins (Hsps) have accompaniment activities that play a significant role in the homeostasis of proteins by preventing misfolding, by clearing the accumulated and defective proteins from the cells, and by keeping the proteins in an active state. Alzheimer’s disease (AD) is believed to be caused by amyloid-peptide that activates tau hyperphosphorylation, which is neurotoxic. Although proteostasis capacity decreases with age and facilitates the manifestation of neurodegenerative diseases such as AD, the upregulation of chaperones improves prognosis. Our research goal was to identify potent HSP co-inducers that enhance protein homeostasis for the treatment of AD, especially 1, 4-dihydropyridine based AMP mimics optimized for their ability to modulate cellular stress responses (Figure 7).

Brain infections and the crossing of the blood-brain barrier BBB

The adequate handling of Central Nervous System (CNS) infections requires that antimicrobial agents penetrate the Blood-Brain Barrier (BBB) and reached concentrations in the CNS adequate for the eradication of the infecting pathogen.

1,4-Dihydropyridine cationic peptidomimetics with antibacterial activity [34]

We synthesized new broad-spectrum antibacterial cationic peptidomimetics centered on a hydrophobic 1,4-dihydropyridine (1,4-DHP) scaffold. The synthesis of the scaffold in a three-step Hantzsch reaction followed by simultaneous coupling of the 1,4-DHP scaffold to two dipeptides bearing cationic side chains. The prepared peptidomimetics were found to have no measurable toxic hemolytic effect against mammalian red blood cells. The compounds were found to have antibacterial activity against Gram (-) and Gram (+) bacteria with MICs in the range of 35-100 LG/mL. These cationic antimicrobial peptidomimetics will lead to more effective antibacterial drug candidates based on a synthetically accessible scaffold. In addition to their antimicrobial activity, AMPs also serve as essential effector molecules in inflammation, immune activation, and wound healing (Figure 8).

Targets: Based on the Lys-Ala-Ala-Ala-Lys active pentapeptide isolated as a fragment of Dermaseptin S4 (Figure 9) [3].

Diazepam based smamps

Since the findings of Sternbach, Librium, Valium and many more AZEPINE based neurological Drugs, the AZEPINE unit has become most applied in the area (Figure 10).

Many agents directed at inhibition of g-secretases are based on AZEPINE units. It might be a wish to mimics features present in the phase III candidate semagacestat. There is a potential role of antimicrobial peptides in the early onset of Alzheimer’s disease. In fact, one of the promising natural products, the semagacestat is a modified peptide compound. It is one of the most advanced candidates with respect to the therapy of Alzheimer’s. Semagacestat is a γ-secretase inhibitor for the potential treatment of Alzheimer’s disease. γ-Secretase modulators do not induce Aβ-rebound and accumulation of β-C-terminal fragment.

Our synthesis of diazepam based STAMPS are as follows:
The diazepine unit integrates 2 amino acid rests of the Lys-Ala-Ala-Lys (a unit of DermaseptinS4) tests. Since very potent compounds were identified in this series, we would like to extend this work to more analogs that will be tested as AMP surrogates on both G+ and G- bacteria and then as secretase inhibitors in the Neurodegeneration field. The sound supported synthesis will produce many compounds libraries for biological activity tests (Figure 11).

The Pentapeptide will be converted to the diazepine based molecule where constraints are introduced by the diazepine b-turn mimic as a moiety. A robust supported synthesis may provide many analogs to be...
Figure 9: The suggestion of novel DHP bases SMAMPs.

Figure 10: AZEPINE based bioactive agents.
tested for biological activity. Poly N-methylated peptide surrogates as selective antimicrobial agents (Figure 12).

N-methylation [45-48] is an essential structural change since it changes some of the main features needed for biological activity. The architecture and micro-Structural features of antimicrobial activity in Synthetic antimicrobial [49-51] peptide surrogates (SMAMPs), which mimic AMP include charge, amphipathicity [52,53], hydrophobicity [54], flexibility [55,56] and H-bonding capacity (Figure 13) [57,58].

We have published [59] on the preparation and conferring modified Friedinger lactams (β-turn mimics) N-H and N-CH₃ analogs to short peptide sequences altering their ability to eradicate Gram-positive (Staph. Aureus) and gram-negative (E. coli) bacteria (Figure 14).

The effect of the one N-Me modification showed in a comprehensive study a selectivity in eradication mainly expressed in the Gram-positive bacteria eradication. Poly N-methyl peptides were examined as aggregation Inhibitors of Amyloid-β (Aβ) (Figure 15) [60].

Experimental and theoretical means [61] have demonstrated that the most common forms of the peptide, Aβ (1-42) and Aβ (1-40), self-assemble into amyloid fibers by a nucleation-condensation polymerization mechanism. The aim of this is to reveal the modes of action of three potential inhibitors at an atomic level of detail, with the ultimate goal of discovering new therapeutic agents reducing Aβ 42 toxicity. Methods: Thioflavin T (Thu) fluorescence assay, Atomic Force Microscopy (AFM), nuclear magnetic resonance (NMR), MTT assay is a colorimetric assay for assessing cell metabolic activity. (MTT: The assay for cytotoxicity). Results: castalgin, its enantiomer vescalagin, SEN304 and inh3 show a substantial decrease in the fluorescence-i.e. lower amyloid peptide aggregation-than for the peptide alone. These results have been confirmed by AFM imaging (absence of fibers with the inhibitors, while plaques of fibers were seen otherwise), while computational simulations combined with NMR allowed determining the binding sites of this molecule within the peptide structure (Figure 16).

The N-methylated [62] short peptide Inh3 (see above) is an effective inhibitor of Aβ aggregation. The short poly-N-methylated Inh3 is more effective than the complex polyphenolic natural products VESCALAGIN and its enantiomer Castalagin. It was found that many biologically active agents that affect positive effects on the aggregation of neuropeptides like Aβ and Amylin are also antibacterial. Both Aβ and Amylin, the fibril forming polypeptides active in the brain, are antibacterial as well (Figure 17).

Investigations into other natural products and synthetic peptide libraries have further emphasized the importance of cyclization and N-methylation for pharmacological properties to some of these properties that reduce flexibility and excellent proteolysis resistance, and provide the ability to penetrate biological membranes by reducing the number of hydrogen and hydrogen bonds using N-methylation [63]. Both cyclization and N-methylation support the formation of intramolecular hydrogen bonds which further decreases flexibility and solvation. Interestingly, most studies of passive membrane perfusion by cyclic peptide libraries have further demonstrated that the impact of N-methylation on membrane permeability was highly position dependent and not necessary correlated with increasing N-methyl content [64]. We therefore turned to new alternatives, seeking first to improve selectivity via short (truncated) analogs of natural dermaseptins. This strategy also turned out to be disappointing although not devoid of some interest. Thus, elimination of flexible peptide domains indeed led to short a-helical derivatives with reduced hydrophobicity but with improved selectivity [65,66].
Design and structure of SMAMs.

Figure 12: Suggested azepine based SMAMPs.

Figure 13: Peptides in Neurodegeneration.
N-methylated Aβ(16-20)m peptides can:
1) prevent the aggregation of full length Aβ peptide
2) disassemble existing fibrils and possibly small oligomers.

Aβ40: DAEFRHDSGYEVHHQKLVFAQEDVGSNKGAIIGLMVGGVV

Figure 14: Modified Freidinger lactam based STAMPS.

Figure 15: N-methylated peptide inhibitors.

Figure 16: Aβ aggregation Inhibitors.

Figure 17: (A) Synthetic Amylin (also antibacterial) and (B) Amylin and Aβ (forming fibrils, antibacterial).
The challenge

The introduction of N-Me units on a short peptide based on b-turn mimics as building blocks can improve selectivity in Gram-positive vs. Gram-negative bacterial eradication. The changes in the flexibility of these agents can also be expressed in selective hindering of fibril-forming peptides (Aβ and Amylin for example). The building b-turn mimics in this work will be based on Freidinger lactams (Figure 18) [67-69].

Foldamers are a very prominent class of α-helix mimetic peptides [70]. They are composed of β-amino acid αβ-amino acid oligomers, or N-substituted glycine residues (peptoids). Such foldamers have been shown to inhibit the proteolytic activity of γ-secretase, an enzyme that is involved in the processing of amyloid-β (Aβ) in Alzheimer's disease, by blocking the initial substrate binding site of γ-secretase.

There is a possibility that these octapeptide surrogates will mimic α-helix [71] which is an active form that might interrupt the formation of the self-assembly Aβ-fibril aggregates. Antimicrobial chemokines interact with receptors to realize chemotactic functions. They share a similar fold consisting of a three-stranded sheet followed by one α-helix at the C-terminus. The N-terminal region is frequently disordered (Figure 19) [72-75].

Protective Properties of Autophagy in Neurodegenerative and Infectious Diseases

Contribution of antimicrobial properties to anti-neurodegenerative agents (deters self-devouring apoptotic processes) [76]

Autophagy or “self-devouring” is the natural, regulated, destructive mechanism of the cell that disassembles unnecessary or dysfunctional components. It allows the orderly degradation and recycling of cellular components. Autophagy was initially been considered to be a nonselective bulk degradation process, accumulating data now supports the concept of selective macroautophagy, where the cell uses receptor proteins to enhance the incorporation of specific cargoes into autophagosomes.

The canonical model for this process involves these receptors binding to cargoes, typically via interaction with ubiquitin motifs, and the receptor binding to the autophagosome membrane protein via interacting domains. However, some classical receptors, may not require the binding to be incorporated into autophagosomes. Although systematic studies have not yet been performed, many of these receptors appear to be able to assist autophagic capture of both neurodegenerative disease-causing proteins and infectious agents. In their antimicrobial role, these receptors are referred to as a new class of pattern recognition receptors termed sequestosome. The ability of receptor proteins to recruit substrates to autophagosomes can also be modulated by posttranslational modifications. Although systematic studies have not yet been performed, many of the receptors, including p62 and optineurin, appear to be able to assist autophagic capture of both neurodegenerative disease-causing proteins and infectious agents.

Autophagy also regulates inflammation. As recently reviewed, the anti-inflammatory functions of autophagy in principle involve:

(a) Prevention of spurious inflammasome activation and down-regulation of the response once inflammasome is activated and

(b) Inhibition responses. The underlying processes include autophagic elimination of endogenous damage-associated molecular patterns (DAMPs) e.g., depolarized mitochondria leaking ROS, mitochondrial DNA, and oxidized mitochondrial DNA, which lowers the threshold for inflammasome activation, or direct targeting and degradation of inflammasome components and products.

This, in turn, tapers the intensity and duration of inflammasome activation. However, the engagement of autophagy with cellular outputs of a prototypical unconventionally secreted protein is more complicated. Autophagy assists secretion of a cytosolic protein that lacks a signal peptide and is unable to enter the conventional secretory pathway vs. the ER and Golgi. Thus, autophagy also plays a decisive role in delivering the protein and possibly other proinflammatory substrates, once they are activated correctly in the cytosol, to the extracellular space where they perform their signaling functions (Figure 20).

In this project the effect of chirality N-methylation and α-helix will be studied. Inhibition of Aβ fibril formation will be studied as well.

Similarities in structure and function antimicrobial peptides (AMP) and fibril-forming peptides

There is accumulating evidence [78-80] that microbial components differentially induce the transcription, by microglial cells, of both antimicrobial peptide genes, the products of which accumulate rapidly at sites in the CNS undergoing regeneration following axotomy. The interactions between peptides and lipids are of fundamental importance in the functioning of numerous membrane-mediated cellular processes including antimicrobial peptide action, hormone-receptor interactions, and drug bioavailability across the blood-brain barrier and viral fusion processes [22]. Cerebral aggregation of amyloid-β (Aβ) is thought to play a significant role in the etiology of Alzheimer’s disease. Host biomolecules that target and combat these pathogens, for instance, antimicrobial peptides (AMPs) such as Aβ itself, are an exciting option for the detection and diagnostic follow-up of such cerebral infections.

In this work, we will demonstrate improved antimicrobial activity (Antimicrobial activity against a microorganism is measured in vitro by a peptide's minimal inhibitory concentration (MIC), which is defined as the lowest concentration able to visibly inhibit growth overnight) of β-hairpin mimics of the naturally occurring membrane-lytic host-defense peptides. Such peptide surrogates were based on an N-methylated moiety, aimed at reducing flexibility and stabilizing the conformation of the peptide surrogate. This may trigger Aβ overproduction and aggregation. Host biomolecules that target and combat these pathogens, for instance, antimicrobial peptides (AMPs) such as Aβ itself, are an attractive option for the detection and diagnostic follow-up of such cerebral infections. Studies suggest that the deleterious effects of Protegrin-1 (PG-1) on Gram-negative bacterial membranes are primarily dictated by the abundance of lipid A and anionic phospholipids in microbial outer and inner membranes. Just as the insertion of PG-1 into lipid a monolayers can explain its ability to expand and permeabilize the outer membrane of E. coli, similar effects on phosphatidylglycerol-rich monolayers could contribute to its ability to permeabilize the inner (cytoplasmic) membrane. This inherent ability to “recognize” and interact with structures or structural patterns that are intrinsic to microbes and absent in eukaryotic cells may augur well for the development of protegrins and other antimicrobial peptides as future therapeutic agents [81]. Models of Toxic β-Sheet Channels of Protegrin-1 Suggest a Common Subunit Organization Motif Shared with Toxic Alzheimer β-Amyloid Ion Channels [82]. Damage in the Blood-Brain-Barrier (BBB) can also become a source of neuroinflammation (Figure 21) [2,83].
**Conformation of the peptide surrogate**

Furthermore, these synthetic peptide mimics (SMAMPs) in the protegrin 1 [84-86] case were shown to interact with the bacterial β-barrel protein Lipopolysaccharides-assembly protein (LptD) [87], which sets them apart from other antimicrobial peptides, whose effect is mainly based on a membranolytic activity (Figure 22).

**Into The Practice Guidelines**

The foldamers will be prepared in the synthesis lab based on...

Figure 21: Role of Inflammation in Neurodegenerative diseases [24].

Figure 22: Peptide surrogate conformation.
and destruction of Aβ fibrils [33].

Conclusion

“There is currently no cure or adequate clinical treatment for AD, and it remains unclear how AD originates and propagates through the brain and central nervous system (CNS). Results from recent genome-wide association studies (GWAS) indicate that a sizable portion of AD-related gene signals is not located within gene coding regions suggesting the contribution of epigenetic or environmental factors to AD risk. The potential contribution of pathogenic microbes to aging and AD is becoming increasingly recognized” [88].

Hopes

We hope to find an antibacterial activity (preferred Gram Selective) and destruction of Aβ fibrils [33].

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