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RESEARCH ARTICLE

NEW TREATMENT POSSIBLE AGAINST DEMENTIA

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ABSTRACT

The leading chronic neurodegenerative ailments in the world is Alzheimer's disease (AD).The pathophysiological basis of Alzheimer's disease (AD) comprises aberrant tau protein phosphorylation, abnormal beta-amyloid protein (Aβ) deposition, reduced cholinergic content activity, glutamate toxicity, autophagy, inflammation, mitochondria-targeting, and multi-targeting.(1)There are already a few symptomatic medications for the treatment of Alzheimer's disease (AD), however these compounds can only momentarily enhance patients' memory retention when given to those with the initial phases of the disease. The understanding of this challenging illnesses has advanced recently, and it has recently been identified as a multifactorial disease. As therefore, researchers are currently concentrating more on the development of molecules that may function on multiple pathogenic aspects all at once.(2)Important emerging knowledge about the etiology and underlying variables of AD is being provided by epidemiological and genetic studies. These studies are also highlighting areas of focus for future research into mechanisms and medical treatments.The broad use of genome wide association studies has generated strong evidence of the genetic complexity of AD, relating genes linked to lipid metabolism and immunology, among other physiologic processes, to the pathophysiology of the disease.(3) The pathological hallmarks of AD include the accumulation and aggregation of hyperphosphorylated Tau as neurofibrillary tangles (NFT) and neuropil threads.In a variety of animal models, both active and passive immunizations targeting the Tau protein have demonstrated the ability to reduce or prevent Tau pathology and enhance either motor or cognitive impairment.In this review, we discuss results from both human and animal studies and provide an overview of current developments in active and passive immunization targeting pathogenic Tau protein. Together, we give a brief overview about problems being encountered in these immunotherapies.(4)

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INTRODUCTION

Alzheimer's disease (AD) is a long-term, progressive, chronic illness with an unclear origin and hidden onset. It is primarily defined by mental symptoms including delusions, hallucinations, and abnormal conduct, as well as cognitive problems like aphasia and agnosia. These symptoms considerably lower older people's quality of life. The etiology of AD is complicated, and its pathology is still unknown despite substantial research. The main theories include aberrant beta-amyloid protein (Aβ) deposition, aberrant tau protein phosphorylation, and inflammation of the brain system, among others. Unfortunately, there aren't any medications on the market yet that can stop AD from progressing.(1) The primary issue surrounding AD is the complete lack of efficacious medications.

Numerous approaches have been put forth in recent years to address the pertinent pharmacological treatments to combat this neurodegenerative disease and to comprehend its pathophysiology. These factors suggest that four out of the five symptomatic medications that have been tried as AD treatments are AChE inhibitors (AChEIs). These compounds go by the names Tacrine, Galantamine, Rivastigmine, and Donepezil (the first was approved in 1993 but is currently off the market due to hazardous consequences).(2)As the amyloid-protein precursor (APP) and the enzymes that cleave it (-and-secretasess) into toxic amyloid (A) were discovered, numerous mutations in important regions of these proteins, such as APP, Presenilin 1 (PSEN1), and Presenilin 2 (PSEN2), have been linked to early onset AD (EOAD) or familial AD. Thanks to developments in genome sequencing and bioinformatics, additional genetic risk factors, like those related to

immunological function and lipid metabolism, have now been found.[3]The tau gene, often referred to as microtubule associated protein tau (MAPT), is a key player in AD and is found at chromosome 17q21.31. Tau is mostly located in the somatodendritic compartment and axons, while it has also been observed in the neuronal nucleus and dendrites.[4] A brief overview of the clinical and physiological causes of AD: The physiological and pathological underpinnings of AD consisted of nine primary processes, including Aβ deposition.aberrant tau protein phosphorylation, lowering the action of acetylcholine toxicity of glutamate, autophagy, inflammatory reaction, The theory of mitochondria and neurovascular process, in addition to "multi-target" agents. [1] In order to test the ChEs activities, we used a modified protocol of Ellman's spectrophotometric assay that was adapted to a 96-well plate system. We also used the DPPH (2,2-diphenyl-1-picrylhydrazyl) method to measure the antioxidant effect, and we used a spectrofluorimetric assay to measure ThT fluorescence in the presence of the peptide to measure the inhibition of A aggregation. Following the previously mentioned process, a modified protocol of Ellman's spectrophotometric test was applied to a 96-well plate setup.0.5 mM 5,5-dithiobis(2-nitrobenzoic acid) (DTNB; Sigma-Aldrich, Milan, Italy) was added to phosphate buffer (pH 8.0) either as the chromophoric reagent alone or in combination with the inhibitor (10 M) for AChE from electric eels or BChE from equine serum (eeAChE, 463 U/mg, and esBChE, 13 U/mg, respectively).[2]Originally identified by Jean-Martin Charcot in 1869 as a disease effecting only motor neurons, amyotrophic lateral sclerosis (ALS) is present-day understood to be a multisystem neurodegenerative sickness with clinical, genetic, and neuropathological variability.[5]

EPIDEMIOLOGY

The pathophysiology of AD is complex and does not stem from a single set of basic molecular interactions that develop with aging in those with genetic predispositions to the disease. attitudes toward the illness itself. Over the last ten years or so, significant progress has been made in our understanding of the epidemiology of AD, including its incidence, risk factors, and potential treatment strategies. According to estimates from the Centers for Disease Control, the population over 65 would rise from 420 million to over 1 billion between 2000 and 2030.The world economy is facing enormous challenges as a result of the expanding geriatric population, as are the relatives and caregivers of individuals experiencing illnesses related to old age. A fairly recent study found that the prevalence of dementia has actually reduced between 2000 and 2012, challenging the widely held belief that rates of dementia will only rise as people ages. Up until the age of 85, there is an inflection point at which the incidence of AD rises roughly exponentially with age.[3]In those in the age range most concerned of developing ALS (45–75 years), the incidence is 4–8 per 100,000 people annually. The average age at which symptoms appear varies: 40–60 years for familial ALS (fALS) and 58–63 years for sporadic ALS (sALS) . The total lifetime chance of developing ALS is estimated to be 1:350 for males and 1:400 for women.[5]

Failure of proteostasis: Normal protein homeostasis is disrupted and cellular stress is induced by protein aggregates or, most likely, their oligomeric complex progenitors. Accumulation of proteins and defective degradation are critical components in the pathophysiology of ALS, according to many genes linked to the disease. It is true that ubiquitin-2 (UBQLN2) plays a part in getting ubiquitinated proteins to the proteasome. Since they encode proteins which interact with the broken down cargo or the phagophore membrane, several more alterations are discovered in genes that affect cargo identification for the autophagy process: The protein p62, which directs ubiquitinated proteins to the phagophore, is encoded by SQSTM1, The autophagy receptor optineurin (OPTN), valosin-containing protein (VCP), TANK binding kinase 1 (TBK1), and the C9orf72 protein phosphorylate OPTN to activate it.[5]

Active immunisation: Early on in the development of tau-targeted active immunity, immunogen was injected into a variety of mice models and then manipulated with various adjuvants.Various immunogens have been incorporated into mouse models recently, and several of them generated encouraging outcomes in the preliminary phases of clinical studies. The immunogens utilized in active immunization will be further classified and described in this chapter.In 2006, wild-type mice (C57BL/6) were given an injection of a vaccination consisting of full length recombinant human Tau protein that was originally emulsified in complete Freund adjuvant (CFA) in conjunction with pertussis toxin (PT).[4]
Clinical Features:

Clinical presentation: Muscular atrophy, fasciculations, cramping, slowness of movement, and stiffness are all signs of ALS, which manifests by increasing muscular weakening. The impairment of muscles in ALS normally starts in one area of the body and then extends to nearby areas. The observed pattern is consistent with neuroanatomic propagation across the motor cortex and spinal cord categories as well as the spread of disease pathology within the motor system. The condition often manifests as asymmetric distal muscular weakness and atrophy in the muscles of the upper or lower limbs (approximately two thirds of patients with spinal ALS) or the bulbar muscles (about one third of patients with bulbar ALS). The dominant hand is where upper limb onset occurs most frequently.

BBB disruption and inflammation: The only immune cell population in a healthy central nervous system (CNS) is made up of parenchymal microglial cells, in contrast to most other organs. Because microglia in a healthy central nervous system are not regenerated from bone marrow and do not come into touch with plasma proteins, the central nervous system is able to maintain an immunosuppressive environment. Immune cell penetration into the perivascular space is strictly regulated by the central nervous system (CNS) and is often restricted. The BBB plays a major role in limiting leukocyte extravasation, or diapedesis, across the endothelium, which facilitates this "CNS immune privilege."Multiple sclerosis and other autoimmune ailments can be brought on by excessive leukocyte extravasation into brain regions. Interactions between leukocytes and adhesion molecules on ECs are necessary for leukocyte extravasation. P-selectin, E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 are the various LAMs that are expressed by ECs (VCAM-1).Selectins link themselves to P-selectin glycoprotein ligand (PSGL-1), although leukocyte α4-integrins are linked by ICAM-1 and VCAM-1. Immune cells roll along the vessel wall following the first binding event, releasing chemokines that reinforce their binding contacts. Immune cells are able to crawl along the artery in search of a location for

extravasation since this significantly inhibits cell motility. The majority of transmigration happens through a paracellular pathway that is dependent on interactions with JAM-A and platelet endothelial cell adhesion molecule (PECAM).It can also occur transcellularly, usually as a result of the leukocyte's high level of activation and inability to locate an endothelial connection. [1]

Preventing Aβ-1-40 Aggregation: The spectrofluorimetric experiments were carried out according to the prior instructions and detected ThT fluorescence in the presence of A**β**.In 96-well black, non-binding microplates (Greiner Bio-One GmbH, Frickenhausen, Germany), co-incubation samples were prepared by diluting A **β**1–40 (EZBiolab, Carmel, IN, USA) either in the absence or with the inhibitor to a final concentration of 30 M and 100 M, correspondingly, in PBS (pH 7.4) that included 2% HFIP and 10% DMSO. Following two hours of incubation at 25 C, a 25 M ThT solution in phosphate buffer (pH 6.0) was added, and an Infinite M1000 Pro multi-plate reader (Tecan, Cernusco S.N., Italy) was used to read the fluorescence. The inhibitor's IC50 was calculated for the majority of active compounds (inhibition > 80%) using seven concentrations (from 1 M to 1000 M) that were made by diluting a stock DMSO solution (10 mM) with PBS. There were three assay runs. Values are presented as mean SEM.[2]

GENETICS: The main AD genes that were initially linked to AD strongly support the validity of the classic amyloid cascade theory, even if a more comprehensive and nuanced consensus has risen since this idea was originally put out. It was found that certain mutations in these genes are almost certainly responsible for EOAD, which is caused by an increase in the accumulation of toxic amyloid species. The genes APP, PSEN1, and PSEN2 are all actively involved in amyloid production or cleavage. The distinguishing conditions of LOAD, however, appear to be far more sophisticated; they all develop more slowly, apparent much later, and are all free of genetic abnormalities in APP, PSEN1, or PSEN2.Therefore, given the very comparable diseases, but much slower pace of advancement, the question of whether or not the same pathologies underlie these seemingly separate forms of AD has long persisted.[3]

Phosphorylated tau peptide: PHF development and the destabilization of the neuronal cytoskeleton may result from elevated levels of phosphorylated Tau. A tiny peptide (Tau260–264 [pSer262]) has been injected into JNPL3 P301L mice in one of the trials. The dentate gyrus region's PHF-1 and Tau levels dropped, and following immunisation, motor performance also improved, according to the results.[1] Most research teams concentrated their efforts over the past ten years towards developing multi-target medicines with different actions to address the classical characteristics acknowledged as crucial at the start of AD.The intention was to increase the therapeutic efficacy through synergistic effects. The most often studied targeting to date comprises NMDA receptor antagonistic effects, antioxidant activity, and the inhibition of cholinesterase (ChEs) and beta-secretase (BACE), as well as the suppression of the aggregation of Aβ plaques.[2]

Apolipoproteins: One of the main genetic risk factors for AD is the APOEε4allele, which accelerates the start of the disease. The pathological correlation between these symptoms and increased cortical amyloid deposition is demonstrated by enhanced binding of the imaging agent Pittsburgh Compound B (PiB) labeled with 11C. With APP, PSEN1, and PSEN2 being in charge of familial or EOAD, APOE was the first significant risk factor for LOAD that was identified. In addition to AD, APOE has been linked to hypertension and atherosclerosis, an illness caused by inflammation of the arteries.

Additional genetic elements affecting neurodegeneration and memory: Synaptic zinc levels are regulated by the zinc transporter-3 (ZnT3) protein; mice with double KOs for ZnT3 have cognitive impairments that are phenotypically analogous to AD.Due to decreases in hippocampus proteins involved in learning and memory as shown by western blot, ZnT3 double KO mice show age-related cognitive abnormalities in learning and memory starting at 6 months. Due to decreases in hippocampus proteins involved in learning and memory as shown by western blot, ZnT3 double KO mice showed age-related cognitive abnormalities in learning and memory starting at 6 months. Because of such analogies, ZnT3 double KO mice may be a viable option for an AD phenotypic model. The regulation of NMDA and NMDA ligand internalisation, which involves Aβ, is governed by Striatal-enriched phosphatase (STEP). The NMDA-mediated internalisation of Aβ may play a significant role in the synaptic dysfunction seen in AD.[3]

Clinical trials[5]: A clinical trial is research that compares the outcomes and values of an intervention with a control group of people. The active and passive immunization therapy strategies that have encouraging pre-clinical or animal testing outcomes are the interventions discussed in this study.

Important differential diagnoses: The identification of upper and lower motor neuron degeneration symptoms, together with a steadily deteriorating spread of indications or symptoms within an area or to other regions, is the basis for the relatively simple diagnosis of ALS in individuals exhibiting a typical clinical pattern. Since a delay in therapy may have a negative impact on the prognosis, certain ALS-like disorders should be checked out.[5]

Active immunization: A small number of immunogens with promising preclinical results were chosen to participate in clinical studies. The two vaccines currently being studied for the treatment of AD are AADVac1 and ACI 35.An antibody called DC8E8 can target three or four distinct epitopes in the 3R and 4R-Taure microtubule-binding regions, respectively. Early (pre-tangle), middle (intracellular tangle), and late (ghost tangle) stages of Tau disease were also recognisable with this antibody. The purpose of this vaccination was to target AD patients' misfolded Tau. Rats used in preclinical AADvac1 testing produced large amounts of antibodies against tauopathy and triggered a TH2 immune response. Because preclinical tests showed no serious adverse effects, a clinical study was started. AADvac1 was evaluated on thirty individuals with mild to moderate AD as part of a Phase 1 clinical study that began in May 2013. Two of the thirty individuals in this experiment stopped participating because of side symptoms. To evaluate the tolerability, immunogenicity, and safety of a single dosage of AADvac1, phase 2 clinical studies were started in March 2016.According to Axon Neuroscience's news release from September 2019, 98.2% of patients produced antibodies against tau. This clinical trial will examine the safety, effectiveness, and tolerability of several dosages of ACI-35.030.

As of March 2020, neither the US clinical trial database nor the WHO International Clinical studies Registry have any clinical studies for ACI-35.030 listed.

Passive immunization: The Phase I clinical study for C2N-8E12 (ABBV-8E12) was initiated as a result of the preclinical studies' favorable results. Owing to the positive safety results of Phase I clinical trials on patients with progressive supranuclear palsy (PSP), a Phase II research has been carried out to assess the long-term safety and tolerability of AD patients. Numerous clinical trials for AD passive immunization were started as a result of the promising results of various pre-clinical studies. One of the first Tau antibodies to be investigated as a therapy option for tauopathies and AD is RG7345, a monoclonal antibody that selectively targets the Tau phosphorylated epitope pSer422, which is abundant in neuronal dendrites.[4]

DISCUSSION AND CONCLUSION

Alzheimer's disease is a neurological condition that is becoming more common every year. But the aetiology of AD is still unclear, and its pathophysiology is complicated. Treatment research and development for AD is still continuing. Clinical studies are now being conducted on anti-Aβ amyloid medications; however, the majority of these trials have been stopped due to adverse events and ineffectiveness.[1]Important motifs that may continue to suggest a primary pathophysiology around amyloidosis via its generation (from APP processing) and accumulation (from poor metabolism and clearance) have surfaced in both genetic and epidemiological investigations of AD. Other hereditary and epidemiological risk variables, such as tau neurotoxicity, lipid/protein homeostasis, innate immunity, and lifestyle choices, have also been discovered and discussed in this study as having an impact on the Aβ pathway.

According to epidemiological research, leading an active, healthy lifestyle that includes moderate exercise and well-maintained mental health may help postpone the onset of LOAD. [3]One plant metabolite and five naturally occurring secondary metabolites of fungi have been discovered as promising scaffolds for the synthesis of novel AD-treating medications.

The biological activities of these compounds were examined on many targets, including antioxidant activity, AChE, BChE, and Aβ 1–40 aggregation inhibition, as well as copper (II) and zinc (II) interaction. Compound 6 was the only one that could inhibit both AChE and BChE, although compound 2 produced the best AChE and A 1–40 aggregation inhibitor with an IC50 in the low micromolar range. [2]When anti-amyloid treatments for AD failed to meet their expectations, researchers and pharmaceutical firms turned their focus to anti-tau in recent years.[4]

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