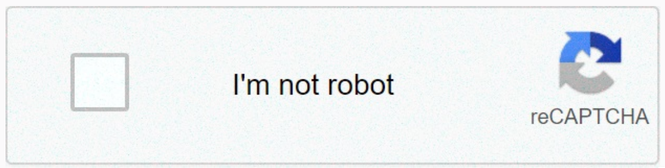

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Alzheimer disease review article pdf 2018

Started loading M2TW on Steam. I'm sure I can play the game. I've played STW, MTW, ETW and NTW. But I usually see a guide to the sticky guides at the top of the forum. I want to read the differences before I start playing. Post edited by bubblehead in August 2012 0 · Alzheimer's disease (AD) is a neurodegenerative and prominent disease of conformational protein (PCD)1,2 mainly caused by aberrant processing and polymerization of normally soluble proteins.3 When deployed, Soluble neuronal proteins reach altered conformations due to genetic mutation, external factors or aging, and aggregated, leading to abnormal neuronal functions and loss.4 The discovery of a drug is attributed to Alois Alzheimer , a German neurologist who examined a 51-year-old woman named Auguste Deter, who suffered from memory loss, language, disorientation and hallucinations. The autopsy revealed plaques and tangles in the cerebral cortex,5 which convinced him that this went beyond typical dementia. His discovery was followed by other studies that revealed the presence of neuritic amyloid β (Aβ) plaques in patients with dementia.6 The young onset of the disease is attributed to the predisposition to the genetic mutation of PS1, which is a rare but potent cause.7 Other neurodegenerative diseases associated with abnormal protein conformations are Parkinson's disease, Creutzfeldt-Jakob disease , Huntington's disease and Machado-Joseph disease, which are caused by abnormalities in α-synuclein, Cellular Prion Protein (PrPc), Scrapie pririon protein (PrPSc), Htt and Ataxin 3 proteins, respectively. When understanding the causative factors and the mechanism of pathogenesis of the disease, it is extremely important to approach fields such as AD mechanisms, pathogenesis and diagnosis, and finally how to design new therapies against it (Figure 1). Figure 1 Overview of the fields of research that need to be elucidated to understand the pathophysiology of Alzheimer's disease and develop therapeutic strategies against it. Diagnostic and imaging techniques include nanoparticle-based early-phase sensitive detection (NP) of AD biomarkers such as Aβ and τ in cerebrospinal fluid (CSF) samples from patients. Nanomaterials can also be used as contrast agents for aggregate images of Aβ plates. It is imperative to understand the role of NPs in increasing the efficacy and bioavailability of the drug through the blood brain barrier (BBB) in the central nervous system (CNS). This review includes a detailed analysis of the pathogenic pathway that leads to complete AD, addresses current diagnoses and therapies available, and emphasizes the potential role of nanotechnology in therapy against disease progression. Pathogenesis of AD The field of research to understand the pathogenesis of AD and design efficient therapies is vast. AD is a highly complex and progressive neurodegenerative disease.8 It is one of the leading causes of dementia cases worldwide. In the U.S. alone, approximately 5.3 million Americans have AD, of which 5.1 million are 65 years or older and 200,000 have younger-onset AD.9 The reported histopathological characteristics of AD are extracellular aggregates of Aβ plates and intracellular aggregations of neurofibrillary tangles (NFTs), composed of hyperphosphophoryl microtubules associated with τ. Aβ plaques initially develop in basal, temporal, and orbitofrontal neocortex regions of the brain and in later stages progress along the neocortex, hippocampus, amygdala, diencephalon, and basal ganglia. In critical cases, Aβ is found throughout the midbrain, lower brain stem and cerebellar cortex as well. This concentration of Aβ triggers the formation of τ-tangle, which is found in the areas of locus coeruleus and transentorhinal and entorhinal of the brain. In the critical phase, it spreads to the hippocampus and neocortex.10 Aβ and NFTs are considered the main actors in disease progression, and this review focuses on the cause, pathogenesis and factors associated with the progression of AD. Amyloid β and amyloid pathogenesis begins with the altered neckline of the amyloid precursor protein (APP), an integral protein in the plasma membrane, by β-secretases (BACE1) and γ-secretases to produce insoluble Aβ fibrils. Aβ then oligomerizes, diffuses in sinatic fissures, and interferes with the sinatic signaling.11,12 Consequently, it polymerizes in insoluble amyloid fibrillations that aggregate into plaques. This polymerization leads to the activation of kinases, which leads to hyperphosphorylation of the protein τ associated with the microtubule, and its polymerization in insoluble NFTs. The aggregation of plates and tangles is followed by the recruitment of microglias around plates. This promotes microglial activation and local inflammatory response, and contributes to neurotoxicity. The structure and function of APP amyp belong to a family of associated proteins that includes the mammalian amyloid precursor as proteins (APLP1 and APLP2), and the amyloid precursor protein (APPL) in Drosophila. It is an integral transmembrane protein with extracellular domains (Figure 2). In a sick state, APP generates amyloid fragments through the differential neckline by enzymes.7 The physiological functions of THEA remain less understood. Studies with transitorily transfected cell lines show that THE App moderates cell survival, growth and motility, together with growth and neurite functions, which are attributed to the release of soluble ectodomains in the normal app neckline.13,14 The importance of APP has been highlighted by studies where neuronal abnormalities have been reported in animals injected with app-ectodomina intracerebira injections , which is cut non-amyomyogenic (normal state) or amyloid (diseased state).17 APP releases several polypeptides they appear possibly due to alternative splices, glycorylation, phosphorylation or complex proteolysis.18,19 Figure 2 An overview of the aβ-pathogenesis hypothesis. Note: Amino acid sequence of the Aβ fragment and location of the action of α-β-, and γ-secretases in diseased neurons within a diseased amyloidpathic pathway. Abbreviation: Aβ, amyloid β.APP comprises 770 amino acids, of which Aβ includes 28 residues and 14 additional residues from the transmembrane domain of the APP. At the site of the neckline, α-secretase is fissure and secretes large APPsα of soluble ectodomain in the middle and the terminal fragment C83 is retained in the membrane, which is further cut by γ-secretase in the residue 711, releasing soluble P3 peptide. Alternatively, in a sick state, the abnormal neckline is made by β-secretase releasing APPsβ and C-terminal C99 fragment is retained in the membrane and further cut by γ-secretase, releasing insoluble Aβ peptides. The c83 and C99 neckline by γ-secretase releases the app intracellular domain in the cytoplasm, which is soluble and transallocates to nuclei for another function of genetic expression.5 The non-amyoloidogenic APP pathway undergoes constitutive and regulated neckline. The enzyme α-secretase cuts app into residues 16-17 of the Aβ domain and produces soluble and non-patogenous precursors. In neurons, ADAM10 and ADAM17 (metalloprotease) are considered the main α-secretases. The processing by α-secretase and γ-secretase generates the small hydrophobic fragment p3, which is soluble and has a role in normal sinatic signaling, but its exact functions must still be elucidated. It has been reported that the cell surface APP may become endocited as well, resulting in the endonomic production of Aβ, which leads to extracellular release and aggregation of Aβ. The processing α-secretase releases the large soluble ectodomain APPsα, which acts as a neuroprotective factor and also has a role in cell-substrate adtake. The presence of APPsα is associated with normal synaptic signaling and adequate synaptic plasticity, learning, memory, emotional behavior and neuronal survival. In addition, sequential processing releases the app intracellular domain, which transaldes into nuclei and facilitates nuclear signaling and the pathways of genetic expression and -regulation.20 Amyloidus pathways THE APP is cut differently in the sick state. Aβ is launched from the APP through sequential necklines by BACE-1, an aspartyl membrane protease with its active site located in lumen, and γ-secretase, an intramembrane aspartyl protease composed of four proteins: presenilin, nicastrine, anterior-defective pharynx 1 (Aph1), and Psen2 complexed together.21 This complex contributes to the activity of γ-secretase, which produces insoluble and neurotoxic fragments Aβ. β-secretase neckline is the first and limiting of rates, making a cut in the N-terminus of Aβ. It removes most of the extracellular portion of the protein, leaving app terminal C,22 it is further cracked in the C-terminus of Aβ, resulting in the formation of Aβ oligomers that polymerize even more, forming aggregate plates (Figure 3). Figure 3 Alternative amendment of APP in amyloidgenic and non-amylodogen pathways. Note: APP neckline by α and γ-secretases in normal state and alternative neckline by β and γ-secretases in sick state. Abbreviations: C83, 83-amino acids carboxyterminal; C99, membrane-bound fraction of 99 amino acids; AICD, app intracellular domain. There are two main types of Aβ polymers that have a direct role in plaque formation and induced neurotoxicity: Aβ40 and Aβ42. Aβ40 is abundant and less neurotoxic than Aβ42, which is less abundant, highly insoluble, severely neurotoxic, and more prone to aggregation and acts as a fraction of toxic construction of the Aβ assembly. The aggregation of Aβ40/Aβ42 results in blocked ion channels, altered calcium homeostasis, increased mitochondrial oxidative stress and decreased energy metabolism and glucose regulation, which contributes to the deterioration of neuronal health and, finally, to neuronal cell death. Hyperphosphorylation of τ and AD is also characterized by the presence of NFTs. These tangles are the result of hyperphosphorylation of the protein τ associated with the microtubule.23 NFTs are fragments of paired and helically injured protein filaments in the cellular cytoplasm of neurons and also in their processes. The τ protein has a domain of microtubule binding and tubulin co-assembly to form mature and stable microtubules.24,25 It has the ability to stabilize microtubules and form interconnected bridges between contiguous microtubules to form an adequate stable network of microtubules and keep them together. When the protein τ comes into contact with the released kinases, due to the abundance of Aβ in the environment, it becomes hyperphosphorylada. Its hyperphosphorylation leads to your being oligomerized. The tubule becomes unstable due to the dissociation of subunits of tubules, which break down and then convert into large pieces of filamentτ, which are further aggregated into NFTs. These NFTs are straight, fibrillar and highly insoluble in neuronal cytoplasm and processes, leading to abnormal loss of communication between neurons and signal processing and, finally, apoptosis in neurons (Figure 4).26 It has been reported that the soluble Aβ controls the neckline and phosphorylation of τ for the NFT generation.7 Figure 4 Hyperphosphorylationof τ. Note: Mechanism by which hyperphosphorylation leads to microtubule instability and, finally, microtubule subunits disband leading to the formation of tangle and large neurofibrillar scans. Abbreviation: Aβ, β amyloid. In addition, τ phosphorylation is regulated by several kinases, including glycogen Synthase kinase 3 (GSK3β) and cycin-dependent kinase 5 (CDK5) activated by extracellular Aβ. Although GSK3β and CDK5 are the main kinases responsible for hyperphosphorylation, other kinases such as Protein Kinase Protein Kinase A, ERK2, a a Kinase, caspase 3 and caspase 9 also have prominent roles, which can be activated by Aβ.27 GSK3β and CDK5 in AD GSK3β regulates the neckline of gastromine fragments app. Lithium and kenpaullone (two GSK3 inhibitors) prevent gsk3 expression and contribute to inhibition of Aβ production.28 As such, GSK3 inhibitors may indirectly interfere in the generation of aβ plaques and tangles in AD. GSK3β activity in mitochondria has been associated with increased oxidative stress.29 As such, gsk3β plays a significant role in AD pathogenesis, contributing to the production of Aβ and aβ mediated neuronal death increasing hyperphosphorylation. In addition, phosphorylation has been reported to be affected by the Aβ-CDK5 interaction. This interaction leads to the neckline of adjacent proteins, releasing clenched peptides with lower solubility and longer half-lives, which can also phosphorylate distant proteins. Substantial research focusing on the identification and classification of kinases responsible for pathogenic points of hyperphosphorylation for primary pathogenic kinesases GSK3β and CDK5, in addition to mitogen-activated protein kinase (MAPK), ERK1 and -2, MAP Kinase (MEK), microtubule affinity regulatory kinase (MARK), c-Jun NH(2)-kinases terminals (JNKs), p38 and PKA, among others.30,31 Abnormal app processing leads to the secretion of Aβ , which affects gsk3 kinases, phosphorylation leading protein τ. This leads to the aggregation of τ filaments that are insoluble and, finally, the formation of huge masses of NFTs in neurons.32 Genetic mutations: presenline mutation 1 and AD APP is not the only gene associated with AD. Gene presenilin (PSEN1 and PSEN2), which are part of the γ-secretase family, also mutate.33 In addition, pd patients may be predisposed to the PS1 mutation that leads to familial AI at a young age.34 The γ-secretase complex consists of four proteins: Psen1, Psen2, Aph1 and nicastrine. Psen, an aspartyl protease, attaches to the catalytic nucleus of the complex. Psen2 facilitates the maturation of the PSEN, while Aph1 stabilizes the complex.35 Nicastrin acts as a receptor for γ-secretase substrates. There are 179 PSEN1 and 14 PSEN2 genetic mutations that participate in early-onset autosomal ad. These mutations favor the production of more toxic forms of amyloid, for example, β42 as opposed to Aβ40, which contributes to disease progression.36 Epigenetics and EpigeneticS AD deals with the study of interactions between genes, expression of genotypes and various molecular pathways that modify genotype expression in their respective phenotypes.37 Epigenetics exploring neurological, neuroepigenetic diseases, has developed very well and has been widely studied in diseases associated with CNS. , pathologies and motor, behavioral and cognition disorders.38,39 Epigenetics is important to understand the depth of the effect of the environment or paternal genes, nutritional habits, trauma, stress or learning disabilities, exposure to chemicals or of drugs in DNA DNA resulting structural disturbances, mutations, or alterations.40,41 The involvement of epigenetics has recently been explored in one of the most complex neurological diseases related to aging — AD.42 The onset of AD and its progress involves a complex interaction of several factors such as aging, genetic mutations, metabolic and nutritional disorders, effect and exposure to environmental variables, and, more importantly, the involvement of social factors.43 There is a fair chance that factors , for example, hypertension, diabetes, obesity, and inflammatory disorders may have an effect on AD and may be inducing epigenetic changes as well, or may induce DD-like pathogenesis at a young age. Associations between DNA methylation patterns in the brain and aging are possible44 and have been reported in various regions of the brain.45 Since the epigenetic mechanisms of DNA play a role in memory formation and maintenance, as well as the decrease in DNA methylation deteriorates neuronal plasticity, leading to memory loss, it is speculated that understanding epigenetic mechanisms is important to understand aging and the complexities associated with patients with AD.46 In addition to DNA methylation. , histona modifications may also play an important role. Studies have explored histone acetylation in MUTANT APP-PSEN1 transgenic mice, where impairment in associative learning has been linked to the reduction of Histone-Acetylation H4K14.47 In addition, histone deacetylase inhibitors (HDAC) also have an effect on the production and aggregation of Aβ in AD mice. Studies involving its inhibitors, such as tricathanin A, valproic acid and vorinostat, are promising. Therefore, it is extremely important to understand the epigenetic mechanisms involved in aging in order to achieve mechanisms and complexities associated with AD.48 Microglial infiltration during plaque formation leading to neurodegeneration in addition to extracellular Aβ plaques and NFTs due to hyperphosphorylation, microglial infiltration in response to these aggregates exacerbates the pathogenesis of AD. In addition to plaques and tangles, a diversity of morphological variants of Aβ deposits is found in the brain of AD. Extracellular and intracellular Aβ and tangles cause extreme toxicity, resulting in synotic damage and increased reactive oxidative stress, which leads to microglial infiltration around the areas of the plaque. Microglia are phagocytes residing in the CNS and play a vital role in maintaining neuronal plasticity and remodeling of the synapse.49 Microglia are activated by protein accumulation, which acts as a pathological trigger, migrates and initiates innate immunizations (Figure 5).50 Aβ plaques activate toll-like receptors in microglia, leading to microglial activation and secretion of proinflammatory cytokines and chemotherapy.50 Figure 5 Neuronal damage mechanism and progression of (DA). Note: Extracellular and intracellular amyloid β and tangles cause extreme toxicity, resulting in sinatic sinatic and increased reactive oxidative stress which then leads to microglial infiltration around the areas of the plate. In AD, microglia can bind to Aβ through cell surface receptors, including SCARA1, CD36, CD14, α6β1 integrin, CD47, and Toll-like receptors.51,52 After receptor binding, Aβ microglia oligomers and NFT fibrils, which are eliminated by endomal degradation. Microglial proteases such as nepriIysin and insulin degrading enzyme play important roles in degradation.53 However, in severe cases of AD, microglial clearance of Aβ is inefficient due to increased localized concentrations of cytokines, which decrease the expression of Aβ-phagocytosis receptors and decrease clearance of Aβ.54 One of the factors behind compromised au clearance by microglia is the trigger receptor expressed in myeloid cells 2 (TREM2) mutation. TREM2 mutations are associated with increased severity of AD. TREM2 is a cell surface receptor of the superfamily Ig highly expressed in microglia and involved in mediating the phagocytic clearance of neuronal debris. It also binds anionic carbohydrates, bacterial products and phospholipids and transmits intracellular signals through the associated transmembrane adapter DAP1255 and more phosphorylation of downstream mediators.56 During D.C., a rare TREM2 mutation (R47H) has been reported to play a potent role in worsening the risk of developing AD.57 This mutation leads to the inability of cns aβ receptors to clear, contributing to the accumulation of Aβ and intensification of pathogenesis in patients with AD. Neurological disorders associated with B and HIV1 Currently, neurological disorders associated with the disease are the largest area of concern. In this era of antiretroviral therapy (ART), with the increasing number of elderly HIV patients, the incidence of dementia or other neurocognitive functions is increasing in elderly patients when compared to younger patients.58 In AD, there are neurological dysfunctions due to the abnormal accumulation of extracellular Aβ produced by alternative app neckline. This testimony of Aβ is also reported to occur in the cortices of HIV patients when compared to non-HIV controls with age correspondence.59-62 Increased indications similar to AD, with increased levels of Aβ, during HIV infection are not well understood. The hypothesis is that the deposition of Aβ may be a common aggravating factor in HIV infection1, thus contributing to neurocognitive disorders associated with HIV1. If Aβ is the common factor between AD and HIV1-disease scenarios, it is imperative to approach the direction of the Aβ pathway and end products with a single effective drug molecule. With the increase in aging in HIV patients due to the introduction of ART, a significantly higher occurrence of dementia/neurocognitive dysfunctions was observed in HIV1-infected individuals than younger patients, and the dementia associated with HIV1 in these patients is three times higher than that of younger people.58 The prevalence of neurocognitive patients associated with HIV1 is increasing because the continuation of ART medication causes subtle neurodegeneration, especially in hippocampal neurons. In addition, the increase in Aβ deposition is characteristic of HIV-infected brains1, and it has been hypothesized that cerebral vascular dysfunction contributes to this phenomenon, with a critical role suggested for BBB in the Aβ homeostasis brain. State of the art: AD therapeutics AD involves protein errors, which distorts cellular systems and neuronal death. Decompacting proteins results in toxic loss or gain of protein function. This can occur due to the aggregation of abnormal proteins, over which the protein no longer plays its normal role and cannot be cleaned by the cellular environment, leading to deleterious biological responses. There are constant studies of AD on the inhibition of the production of fold proteins and their aggregation and propagation to limit toxicity caused by abnormal proteins.63 Most therapeutic approaches to AD are focused on reducing the levels of toxic forms of Aβ and τ, the broad scope of the neurodegenerative processes underlying both the onset and late stage of AD. Several drugs have been analyzed and reached phase I, II and III clinical trials. Table 1 summarizes the specific amyloid drugs being studied and aimed at sufficiently fundamental and close degenerative mechanisms.64,65 Table 1 Amyloid-specific drugs that target fundamental and close degenerative mechanisms, however, all these current therapeutic targets (e.g., rivastigmine , galantamine and donepezil) seem secondary, and none of them are currently considered causally involved in the development of AD. Therapeutic failure often occurs due to unfavorable pharmacokinetics and drug pharmacodynamics. Pharmaconopic failure is the result of inadequate physical chemistry of drugs (such as hydrophobiity), unfavorable absorption by biological membranes, unfavorable pharmacokinetic parameters (such as intense and plasma metabolism), drug instability (oxidation, hydrolysis or photolysis), and tissue toxicity (hepatotoxicity, neurotoxicity, or renal toxicity). Several treatment strategies were proposed and attempted for the removal of Aβ. Several drugs are used for the degradation of Aβ, but most of the drugs that showed promising results in in vivo studies were not able to clean human clinical trials and failed, creating an urgent need to develop new strategies. Many of the drugs available lose their effectiveness when crossing the BBB and are minimally bioavailable in the brain. This requires a new area of study that expands on effective neuroprotective strategies specific to the CNS. PMs are intriguing candidates for this purpose due to their multifunctionalization potential, allowing them to mimic physiological transport mechanisms throughout the This barrier is an important physical fence made of cells that protect the brain from potential dangerous substances in the bloodstream; blood pressure; it also prevents the passage of 98% of the neuropharmaceuticals and available diagnoses. Diagnosis for AD: labeling and diagnostic imaging The current AD is mainly based on neuropsychological tests. A clinical diagnosis of AD requires neuroimaging and monitoring of accepted biomarkers, e.g., concentrations of Aβ peptides (aratio Aβ1-42:Aβ1-40), as well as total and hyperphospholatеτ (Thr181 and Thr231) in CSF. Amyloid oligomers and plaque accumulation may also be images with 18F-florbetapir (or, alternatively, 11C Pittsburgh compound B) positron emission emission tomography (PET), but the nonlinear association between Aβ content in CSF and PET tomographies remains worrisome. However, CSF sampling is relatively invasive and is not always well tolerated or feasible in several elderly patients. Noninvasive imaging methods, such as PET fludeoxyglucose, which gives insights into brain metabolism, are of great clinical utility. In fact, altered brain metabolism (hypere hypometabolism) has been associated with different stages of AD. Magnetic resonance imaging (MRI) in increasing strength and resolution of the field is another useful and noninvasive approach to identify functional abnormalities. Magnetic resonance imaging is used to detect and identify amyloid plates using iron oxide NPs as contrast agents or marked with fluorescent probes to make detection efficient.66 These iron oxide NPs are reported to bind to the N terminal of Aβ, aiding their image. In addition, non-fluorescent or fluorescent Rhodamine NPs marked γFe2O3 NPs have been reported to selectively label Aβ fibrils and remove them from solubilized Aβ, employing external magnetic field.67,68 In addition to iron NPs, there have been reports of n-butyl polystyrene cyanoacrylate (n-butyl cyanoacrilate) NPs encapsulating thioflavin T to achieve Aβ.69 Gold NPs have been used in magnetic resonance imaging as contrasting agents to study structural stages in self-assembling Aβ70 and fluorescent semiconductor nanocrystals (quantum dots) for labeling.71 For sensory soluble forms of CSF Aβ, an ultraconductor PN-based biobarcode system that specifically detects soluble oligomers with the aid of oligonucleotides (DNA barcode)-modified AuNPs and functional magnetic microparticles with monoclonal/polyclonal antibodies were used ,72, as well as electrochemical sensing using click chemistry, which involves AuNPs and monoposters assembled to interact with βtústide pep 73 and ultrasensitive electrical detection for Aβ1-42 using scanning tunneling microscopy.74 These recently achieved technological and conceptual achievements have considerably improved the diagnosis of AD. Once AD is diagnosed, the therapeutic choice concerns treatments that are only modified by the disease and offer relatively limited benefit. nanotechnology as a therapeutic strategy throughout the BBB There are promising drugs against toxicity Aβ,75, but to explore its maximum effect on CNS cells, there is a need for nanocarriers to be employed. Employees. cns is the biggest issue faced in the field of ad therapy. The main reason is the presence of a semipermeable fully functional BBB, which is placed as an obstacle to the transmigration of neurotherapeutic molecules (such as drugs, peptides, vectors and molecules) through it, in the CNS. THE BBB and its selective transport of molecules to the brain oppose the effective delivery of therapeutic agents. In addition, BBB also negatively affects the efficacy and tolerance of medications, as high doses of drugs are necessary to achieve levels above the minimum effective concentration in the brain. Nanotechnology, including nanopsarticulate systems, offers an opportunity to overcome such problems and can be used as Trojan horse systems for the transport of active molecules through BBB (Figure 6), thus reducing toxicity and improving therapeutic efficacy.76,77 Figure 6 Semipermable blood-brain barrier and nanoparticle transmigration route (NPs). The use of drugs in nanoplatforms or nanodevices results in the improvement of their pharmacokinetics and pharmacodynamics, as well as reduces toxicity. An essential aspect in the development of nanomedicine is the delivery of medicines and the controlled release of medicines in disease sites. Therefore, the effectiveness of a treatment can be increased by incorporating nanotechnology-based drug delivery systems. These new platforms aim to improve bioavailability throughout BBB, pharmacokinetics and pharmacodynamics of medications, reducing their side effects. In summary, recent advances in nanotechnology propose effective diagnostic and therapeutic options. Delivery of targeted medications with the aid of 100 nm-sized NPs can effectively increase the bioavailability of medications across the BBB to the CNS with minimal side effects or no side effects. In addition, these nanomaterials are designed to be biocompatible, thus reducing toxicity, in addition to the advance in their magnetic and optical properties, they can be efficient alternative agents for early diagnosis.78 The delivery of saxagliptin via peptidase dipeptidy 4 enzyme-inhibiting molecules is being explored for their activity in D.C. therapy, with the aid of a chitosan-L-valine valine conjugate used to prepare NPs encapsulating saxagliptin. These NPs are stable and crossed the BBB efficiently.79 In addition, one of the most efficient nanocarriers are magnetoelectric NPs (MENPs), which have been well studied for their potency in the delivery of drugs throughout the BBB in a noninvasive and on demand way to release drugs to target areas without adverse effects. The on-demand launch feature is really important because it ensures the delivery of exact quantities of medicines, which is physiologically effective without causing toxicity.80-83 Its applications in drug delivery been well reported in the field of neuroAIDS and AD.83-86 The interest of research in nanotherapeutics, that is, using nanocarriers to transport drugs through BBB, is growing continuously and positively, as these NPs help the efficient delivery of drug drugs The advantages of NPs over simple drugs or microdrug systems are many, including larger surface area (higher drug loading) and a diverse variety of biomaterials, organic compounds (natural or synthetic) and inorganic (metals) for NP production. The interaction between the drug moiety and NPs is diverse. It can be covalent binding, the presence of an ionic surface charge (ionic bonding), direct adsorption or superficial bonding, and drug trap. NP surfaces can also be modified to aid the binding of medicines, such as pegylation, which is the process of covalent/non-covalent polyethylene glycol (PEG) amalgam to the surface.87-91 In addition, they increase the specificity of the meta via ligant binding. NPs can be modified and imbued with unique physical-chemical properties, i.e., the addition of metallic or electrical attributes, such as menps, which facilitates the transport of drugs through the BBB, on demand with the introduction of externally applied electric or magnetic fields, increasing the supply of medicines several times. NPs can have their surface loads altered to interact with the BBB (negatively charged), thereby introducing ionic interaction or pulling toward the BBB. This change in load increases the drug loading capacity of NPs and assists in the on-demand release of drugs. MENPs are one of the most effective types of NP for personalized noninvasive, image-guided therapy against CNS diseases. They have a unique magnetoelectric actuation effect, which allows longitudinal noninvasive monitoring using magnetic resonance imaging,92,93 contributing to image-guided therapy. In addition, liposomal NPs are also potent candidates in the delivery of medications, as they can be easily modified by the surface, facilitating the loading of hydrophilic and hydrophobic drugs, and assisting in sustained release throughout the BBB. They can also be labeled with fluorescent lipids, which can aid in image-guided therapy and can be observed under microscopy. Plasmonic systems based on carbon nanotubes against CNS diseases have been well studied. Challenges for clinical translation With the advent of NPs, various types such as gold NPs, metal NPs, silver NPs, silica, hydrogels, liposomes and magnetic NPs, are being employed in rapid-speed drug delivery studies. NPs are being exploited for the delivery of CNS drugs at the clinical level. The U.S. Food and Drug Administration (FDA) and the National Institutes of Health are supporting the concept of personalized nanomedicine, which can trigger a revolution in drug delivery across the BBB, contributing to better health care and more opportunities to combat CNS diseases.94 The success of preclinical studies on CNS nanomedicine95-98 can act as a basis for examining clinical level strategies to test biocompatibility, toxicity, efficacy, availability at the human-patient level. The clinical translation of these NPs against CNS diseases at the patient level depends on a number of factors, for example, patient diversity, genetic and environmental effects, combination of multiple diseases, diseases, efficacy, and bioavailability in the brain. Based on the patient-disease profile, these NPs can be designed and modified to provide personalized nanomedicine, which may be more beneficial to the individual. This requires an adequate understanding of the mechanism of the disease, and even predictive methods using bioinformatics can be used to understand the progression of the disease and then design the therapeutic accordingly. Regarding cns therapy, several studies have highlighted the importance of applying nanotechnology for disease diagnosis, drug delivery and teranostic application. Although most current research is at the preclinical level, the success of these preclinical and in vivo studies provides promising potential to be translated to clinical levels. Safety, efficacy and regulation issues are the main challenges for the progression of personalized nanomedicine to treat CNS diseases clinically. New methods such as ultrasound-mediated BBB interruption by opening BBB noninvasively applying external stimulation such as focused ultrasound or electromagnetic fields may be promising, but these methods can result in side effects such as neuroabportal distortions or induced infection of the intake of unwanted molecules during the forced opening of THE.99 Therefore, controlled parameters of these stimulations are very critical at clinical levels , because not only can they modulate the intrinsic properties of introduced NPs by heating them or modifying their surfaces they can also disrupt cns homeotase, disturbing BBB permeability, causing internal flow of unwanted circulating molecules to the CNS, leading to neurotoxicity, dysfunction, immunohyperactivation, inflammation, release of reactive oxygen species, synatic damage and oxidative stress, contributing to fatal neuronal injury.96,97 Therefore , although nanotechnology-based research is promising, it has a long way to go to be translated from bench to bedside therapy. There is an urgent need to address the issues of toxicity, bioavailability, pharmacokinetics, release and metabolism of NPs for successful clinical trials. There are challenges highlighted by the FDA, focusing on biodistribution of NPs, administration modes, nps' ability to transport multiple drugs, effective transmigration throughout the BBB, risk assessments, toxicity, standards, safety, procedures and validation.100 The search to address issues of biocompatibility, surface functionalization, permage trap, enzymatic degradation and out-of-segmentation issues is underway through the introduction of superficial functionality , preservation strategies to minimize the side effects of external stimulation, and maintaining the availability of medications in the CNS for longer periods. Progression to personalized nanomedicine is challenging, but it is critical for future clinical trials make nanotherapeutics available at the patient level. Abstract and future perspectives AD is a neurodegenerative neurodegenerative affecting people all over the world. Clinically, it is characterized by the presence of extracellular amyloid plaques and intracellular NFTs, resulting in neuronal dysfunction. Amyloid aggregation occurs due to the differential neckline of the APP sequentially by β-secretase and γ-secretase, leading to the release of extracellular Aβ 40/Aβ 42. AD is also characterized by the presence of NFTs. These tangles are the result of protein hyperphosphorylation associated with microtubules τ. GSK3 and CDK5 are the main kinases responsible for the phosphorylation of τ. In addition to the aggregation of plaques and tangles, aggregation of microglial in the site also plays a vital role in triggering innate immunoresponses against aggregation. A rare mutation paralyzes the regular functioning of microglial surface receptors, contributing to the intensification of AD. Understanding all these factors and then designing specific therapies to direct them is the need for the time. The prosecution's is one of the most common neurodegenerative diseases today, but unfortunately 101 is not currently available. Several treatments are being employed to combat cognitive and behavioral deficits associated with AD. The development of an effective therapeutic approach directed against AD is still in its stage of development and, therefore, the need for the time is to look at cellular factors closely associated with the pathogenesis of the disease and direct them to improve the quality of life of patients with AD. Cellular factors discussed in this article, such as Aβ, APP, secretases, CDK5 and GSK3β, may be key targets for a therapeutic approach. It is extremely important to understand the limitations of drug

bioavailability in the CNS due to the strongly controlled permeability of THE BBB. Drugs aimed at the synthesis of Aβ or suppressing the formation of NFTs may stop or reverse AD. Nanomedicine offers an attractive approach to the supply of drugs throughout the BBB.85.86.102.103 Nanotechnology concerns nanosized drug molecules and their efficient delivery and controlled release in the brain by external magnetic fields, which can be a promising factor in therapy for AD. The need for the time is to unravel the mechanisms of ad genesis, its early detection using state-of-the-art biosening designology, specific targeting of molecules associated with disease manifestation, and efficient supply of optimal drugs to the brain using new nanotechnology approaches. In addition, studies of AD comorbidities with other diseases or viral infections are also very important for understanding and exploring therapeutic approaches. AD, Alzheimer's disease; Aβ, Amyloid β; BBB, hemocephalic barrier; CNS, central nervous system; CSF, cerebrospinal fluid; NFTs, neurofibrillary tangles; PCD, conformational protein disease. Recognitions The authors acknowledge the financial support of the NIH R01DA034547 grant and the Alzheimer's Disease Research Department of the Florida Department of Health (scholarship 8AZ04). We would also like to the Dissertation Year Fellowship 2018 awarded to ST (graduate student) by University Graduate School, Florida International University, Miami, FL, USA. Disclosure The authors do not report conflicts of interest in this work. References 1. Adav SS, Sze SK. Insight into changes of brain degenerative proteins in the pathology of neurodegeneration and dementia by proteomic profile. Mol's brain. 2016;9(1):92. doi:10.1186/s13041-016-0272-9 2. Leandro P, Gomes CM. Protein insusion in conformal disorders: rescue of folding defects and chemical follow-up. Mini Rev Med Chem. 2008;8. 9):901–911. 3. 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