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Molecular Mechanisms Associated with Neurodegeneration in Alzheimer's disease

Rubén Rangel Rodríguez*[1], Luis Enrique Ruiz Estrada[2], Frida Michelle Salazar Mendoza[3], Christian Aaron Torres Hernandez[4], Matt Partida Garcia[3]

[1] Universidad Michoacana de San Nicolás de Hidalgo

[2] Universidad Autónoma de Guadalajara

[3] Universidad de Guadalajara

[4] Universidad Autonoma De Durango, Campus Laguna

ABSTRACT

Alzheimer's disease (AD) is a progressive and irreversible pathology in which there is a continuous neurodegeneration process, clinically characterized by decreased cognition, memory and behavior alterations. Currently, the mechanisms behind AD progression are more clear, redefining it as a multifactorial disease on which aging, genetics, metabolism and environment play an important role on the onset. The complex molecular mechanisms interplay and generate a state of inflammation. Thus, creating neurodegeneration.

Objectives: This review focuses on recopilating and describing the molecular mechanism behind neurodegeneration in AD. Furthermore, the relation between risk factors and the mechanism will be encompassed.

Methods: A bibliographical review was carried out. Databases such as Pubmed, MDPI, sciencedirect, Termidia publishing house, scielo and the National institute of aging were used. Articles in English and Spanish between 2004 and 2023 were included. The keywords used were: Alzheimer's disease, neurodegeneration, beta-amyloid, tau protein, neuroinflammation, cognitive disorder, tangles, biomarkers.

Results and discussion: Millions of people are exposed to multiple risk factors for AD. In every one of them, there are molecular mechanisms involved, which will eventually lead to AD´s main pathological changes, Beta amyloid deposition and tau pathology, causing neurodegeneration.

Conclusions: Alzheimer's disease is an international public health problem that is affecting the lives of millions of people.To address this, we have to fully understand the molecular base of its development, in order to approach new treatments.

KEYWORDS: Alzheimer's disease, neurodegeneration, beta-amyloid, tau protein, neuroinflammation, cognitive disorder, tangles, biomarkers.

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INTRODUCTION

Alzheimer's disease (AD) is a progressive and irreversible pathology in which there is a continuous neurodegeneration process, clinically characterized by decreased cognition, memory and behavior alterations (1-2). It represents a problem to public health, since there is an uprise in the average human lifespan, and therefore more people will be living to develop AD; furthermore, it is vital to understand the mechanisms involved in the progression of AD. With broader understanding, new treatments could be developed.

Throughout the years, many researches have correlated different genetic, metabolic and environmental factors with the onset of Alzheimer's disease. Even though AD is considered a multifactorial disease, a strong connection between AD and aging, family history and presence of APO gene has been found. However, there are other remarkable risk factors such as PSEN genes, level of education, history of head trauma, metabolic diseases and exposure to metals (1,3).Considering all the possible etiologies for dementia, AD is by far the most common, representing nearly 60-80%.

The people with AD will progressively experience deficits in all kinds of cognitive domains, such as behavior, memory, language, orientation or executive capacity, being the affected neuronal population the main factor that will determine the clinical manifestation (1-4).The cornerstone of AD´s neurodegeneration is the functional abnormalities in Beta-amyloid and Tau proteins. Along with it, oxidative stress, inflammatory responses and changes in mitogen-activated protein kinases (MAPK) interplay with risk factors, leading to a loss in neuronal connections and cellular death.(3-5).The objective of this review is to describe both the classic and recently discovered molecular mechanisms associated with development of Alzheimer's Disease as well as to give a general review on clinical manifestations and new approaches in treatments.

METHODOLOGY

This bibliographical review was made using meta -analytic studies, theoretical reports, and other bibliographical reviews about Alzheimer's disease and the underlying molecular mechanisms of it. The clinical manifestations of AD, and treatments were also topics included in this review article. Many databases such as Pubmed, MDPI, sciencedirect, Termidia publishing house, scielo and the National institute of aging. Articles in English and Spanish between 2010 and 2023 were used for this manuscript. The keywords searched for in this article are the following: Alzheimer's disease, neurodegeneration, beta-amyloid, tau protein, neuroinflammation, cognitive disorder, tangles, biomarkers. A total of 34 articles were included in this review.

RESULTS AND DISCUSSION

Epidemiology

Throughout the world, AD is the most common form of dementia, representing about 50%-75% of all the dementia cases in Australia. Only in America, about 5.3 millions of people are currently diagnosed with this ailment. (2,6-7).

The incidence of AD increases with age, specifically after the age of 65, when it starts doubling every 5 years. At this point, the prevalence rates can get up to 10% and keep increasing until they reach about a 40% after the 85 years old.(6) It has been estimated that about two thirds of the people living with AD are women and only one third are man, which could be related to women's longer lifespan. (6)This incidence variation becomes more significant afterprone to develop AD are hispanics and african americans, with one and a half times more risk.(8-9)

RISK FACTORS

Aging

It is undeniable that aging is one of the main risk factors associated with AD, as its prevalence increases significantly above the age of 65 with a 3% and more importantly above the age of 84 with a 32% and possibly even up to 50% (8).

This late onset is a direct consequence of all the complex and irreversible changes related to aging, such as the loss of brain's matter, a decrease in the number of synapses and dendrites and an enlargement of ventricles alongside the deposition of both neuritic plaques and neurofibrillary tangles (NFTs) (10-11). While these are all normal findings in older patients, they are far more severe in AD and thus there exists the possibility that AD is nothing but an accelerated and more severe progression of normal aging (11). Hence, in the study of Bergeron et al, it was found that 60% of the normal elderly patients had neuritic plaques, but in a less significant concentration than those with AD. Also, in Miller's et al cross- sectional study, results showed that in 60 normal elderly patients, 32 had no neuritic plaques, 13 had neuritic plaques in the hippocampus and 12 in the temporal cortex. In regards to the presence of neurofibrillary tangles, NFTs in the medial temporal lobe and in the cortical association areas of non-demented individuals (11).

Additionally, it is possible for other pathologies to emerge while aging, like depression, diabetes, hypercholesterolemia and mitochondria dysfunction. All of which will aggravate the neurodegeneration.

Genetics

Alzheimer's disease has a strong relation with genetics, since modern research has studied the repercussion of mutations in the onset of the disease. It is well known that first-degree relatives of a person with AD, has an increased risk of developing dementia throughout his life.(12)

AD has been classified according to its etiology into two main categories, the autosomal dominant class and the sporadic class. The first one is a minority in the cases of AD, representing up to 5% of all the diagnosis, characterized by an onset under 65 years old (early onset). This group of AD is related to mutations in the PSEN1, PSEN2 and APP genes. On the other hand the sporadic version represents 95% of all the cases, it has a late onset (above 65 years old) and it's associated with APO gene mutations. (1,12-15)

Up to this date, nearly 400 mutations related to AD have been found in the PSEN family. This leads to altered proteins that impede the proper fusion of the y-secretase complex, a group of enzymes which main function is to cleavage in order to produce amyloid β-peptide. (13)Other mutations produced in the PSEN family increase the Aβ42/Aβ40 ratio by altering the APP gene, this translates into an early disposal of

Beta-amyloid protein. The APP gene is relevant in the development of AD since it plays an important role in nervous system and synapse function and signaling, therefore, an alteration in APP´s signaling tasks may contribute to neural dysfunction. Also, dysfunctions in APP lead to increased Aβ42/Aβ40 ratio and Tau pathology. The sporadic presentation of AD is a result of a complex interplay between other risk factors such as sex, trauma, metabolic syndrome and genetics. The latter is associated with mutation of 19q13.32 in the APOE gene(1) . The influence of APOE is so strong that having mutations can eightfold the risk of developing AD in the future. APOE promotes AB deposition

by binding to AB receptors on the surface of the astrocytes, affecting the uptake and clearance of AB. (1,12-13,16)

Education and intelligence

Another way of approaching AD is by comparing it to intelligence or cognitive capacity. Intelligence can be measured by tests or more effectively, by measuring brain volume with RMI, since this is one of the best biomarkers for intelligence(4). In literature it has been reported the relation between higher level of intelligence and a lower risk of developing AD. This reduction in the risk of AD could be explained by an increased brain efficiency than can implement compensatory processes or use the available neural circuits more efficiently. (17). Other studies found having a higher intelligence one standard deviation above, reduced the risk of dementia significantly. (4).

Its not only intelligence that matters, since there has been reported that cultural or extracurricular activities play a big role in AD prevention. The people that did more activities during highschool years, tend to have lower risk of a dementia diagnosis. Also, in early or middle adulthood, participating in cultural activities reduced the risk of AD in further years.(4,17-18).

There may be an indirectly proportional relation between AD and the level of cognition required for a specific job, since the people with more cognitive demanding jobs have a lesser cognitive deterioration, in comparison with the people with less cognitive demanding jobs. However, more studies are necessary to fully understand the role of intelligence in the mechanisms behind AD (18).

Head trauma

Head trauma is an important risk factor for AD, since a preceding history of traumatic brain injury has been a common factor between many AD patients. The mechanisms behind the onset of AD in patients with head injury may be related to the activation of the APP gene, generating AB that will constantly deposit in hippocampus, temporal and parietal cortex. The excess of AB will relate to an increased number of neurofibrillary tangles, leading to the onset and progress of AD(18,20).

When the Blood-brain barrier is damaged by the result of trauma, plasma proteins will leak causing the immune system to activate a response to brain antigens that are isolated from the rest of the body. APP is increased significantly in acute stages of brain trauma, the overexpression of this gene relates to a higher deposition of AB in neurons that suffer from trauma.(11,18,21).

In patients with chronic traumatic encephalopathy (CTE) a tauopathy was found. CTE is characterized by a neurodegeneration process with a reduction in gray matter, secondary to repetitive trauma. It can be presented in boxers, football players, soldiers, rugby players and any chronic practitioner of sports where brain trauma is a common thing. The symptoms of CTE are similar to the ones in AD , however, more studies needed to be made in order to discover more associations in the pathophysiology of both diseases.(11,22)

Metabolic diseases

Obesity: Obesity is strongly related to AD, due to the fact that an increase in the body fat can reduce the brain's blood supply, potentially causing brain ischemia, memory loss and even vascular dementia. Furthermore, the adipose tissue secretes

(pro-inflammatory cytokines that activate macrophages and lymphocytes, inducing a local and systemic inflammation. This inflammation will then promote insulin resistance, hyperinsulinemia and hyperglycemia. obesity is a well known risk factor for diabetes, cardiovascular disease. (10,23)

Diabetes: Hyperinsulinemia and hyperglycemia can lead to an elevation of amyloid beta accumulation, oxidative stress, neuroinflammation and mitochondrial dysfunction. This can be explained by two possible mechanisms: One is that the neuroinflammation increases microglia and their activity affects insulin receptor substrate 1 (IRS-1), compromising intracellular insulin signaling. The other is that the elevated levels of insulin oversaturate and then downregulate the uptake of insulin at the blood-brain barrier. Either way, less insulin signaling diminishes the sensitivity of insulin

degrading-enzyme, which plays an important role in amyloid clearance, and also intensifies enzyme glycogen synthase kinase 3 activity, which could promote tau and neurofibrillary tangles formation. It is also believed that insulin competes for the insulin degrading-enzyme and this affects the clearance of amyloid. What is clear, is that the disruption of insulin action can provoke amyloid accumulation and reduce tau degradation.(23-25)

Hypertension: The complete relation between AD and hypertension is still unknown. The data suggest that hypertension leads to thicker blood vessels and a smaller lumen. This will cause cerebral hypoperfusion that may be risk-related to AD. However, other studies suggest that this might be a compensatory mechanism instead of a pathological change.(10,22,25)

MOLECULAR MECHANISMS

A complex interplay between different molecular mechanisms lead to AD´s onset. The two main determinant processes are the accumulation of abnormal Tau proteins, which later form cortical and subcortical neurofibrillary tangles (NFTs). The formation of neuritic plaques (NPs) due to the extracellular deposition of amyloid-beta peptide is the other important process for AD development. (26,27)

Although NPs and AD are the two main pathognomonic hallmarks in AD, they lead to many other mechanisms such as oxidative stress, synaptic alteration, neuroinflammation and alterations in the blood-brain barrier, which directly affect the homeostasis of the neurons and produce their destruction.(26)

Amyloid-beta plaques

The Amyloid precursor protein (APP) is a transmembrane protein, known by being a beta-amyloid protein precursor, establishing an important role in plaque formation. In normality APP helps in neuroplasticity and neuronal growth and repair.(APP has a close relationship with a family of proteases called secretases. There are 3 main members of this family, the alpha, beta and gamma-secretase. These enzymes have the role of cleaving the APP in order to produce beta-amyloid peptides. In a physiological normality, both the alpha and the beta secretase are the ones in charge with APP cleavage. This produces non-toxic fragments. However, in AD´s pathophysiology, the gamma and beta secretase are the ones cleaving the APP, producing a 40-42 peptide called the beta-amyloid 42. When the cleaving process is not regulated, this peptide accumulates in cortical vessels and gray matter causing toxicity and formation of multiple extracellular lesions, the plaques. The latter is characterized by an spherical shape, an beta-amyloid peptide core and in the pheryperia, growth axonal endings.(1,6,8,24,26,28)

Tau protein and neurofibrillary tangles

The microtubules are an intracellular structure, and a basic component of the cytoskeleton. They have an important role in cell stability, help with the transport within the cell, allow cellular movement and migration (27). Microtubules have a family of proteins which bind to it in order to give stability to the structure, these are the microtubule associated proteins (MAPs). In AD there is an alteration in one specific MAPs, the tau protein. (26) This protein function is to bind the microtubule and support stability, help in the axonal transport and in signaling modulation. In normal conditions, tau protein is regulated by a phosphorylation process. However, in AD this molecular mechanism is altered, causing a state of hyperphosphorylation leading to inability in the tau protein to bind successfully to the microtubules. This hyperphosphorylated tau protein aggregates intracellularly causing neurotoxicity and binds with other tau proteins to create twisted filaments, the neurofibrillary tangles . The consequences of NFTs formation are unstable microtubules, blocked nutrients transportation and malfunction of other proteins, causing neurodegeneration. (26-27).

The NFTs can be first seen in the hippocampus and as the disease progresses, they can be found in the cortex. The relation between the NFTs and the Beta-amyloid plaques have been studied, concluding that hyperphosphorylated tau protein can create a pathological loop, where it stimulates the aggregation of Beta-amyloid peptide and the latter stimulates hyperphosphorylation. (6,8,26-27).

As mentioned previously, the secretase Beta cleaves the APP into a soluble form, the Amyloid Precursor Protein beta (sAPP β). The sAPP β will then interact with the death receptor-6, activating neuronal death and apoptotic pathways via the caspase-6. (26)

The APP that didn´t interact with beta secretase will do it with the gamma, which will end in the production of beta-amyloid peptides.This will eventually conclude in the formation of insoluble plaques. The peptides (between 40-42 amino acids) will cause malfunction of amino acids, nicotinic, muscarinic and glucose transporter receptors, by altering calcium regulation causing blockage in ion canals and transmitters, leading to dysfunctional synapsis 8.26.

Oxidative stress and microglia

The microglia constitute the unique immune system of the central nervous system . It is constituted by phagocytes that have important tasks in tissue stability, dysfunctional neural pathways elimination and defensive response against injuries or microorganisms (29)

In AD, microglia interact with the Beta-amyloid plaques producing an immune response, whose first action is to produce chemokines and cytokines that will eventually lead to reactive oxygen species (ROS) formation. Thus, creating oxidative stress in the mitochondria and releasing caspases such as p53, Bad and Bax. The latter will induce neurodegenerative processes like neuronal death, lipid peroxidation and direct damage to the membrane. The NFTs and Beta-amyloid plaques will also stimulate the microglia into producing inflammation due to Interleukin-6, Tumor necrosis factor and neurodegenerative molecules like Nuclear Factor Kappa B.(29-30)

ROS has an important role in the previously mentioned loop between Beta-amyloid plaques and abnormal tau proteins. Once the ROS is formed, after the first interaction between microglia and the plaques, a family of enzymes called the protein kinases over-stimulates the phosphorylation process required in Tau proteins, creating the abnormal version of it that will form NFTs. The tangles will induce more oxidative stress and lipid peroxidation, repeating the loop. (26,29-30)

In physiological conditions, the body has its own mechanisms to eradicate ROS. This antioxidant system is constituted by enzymes like catalase, superoxide dismutase and peroxidases that have the ability to neutralize ROS. The problem is when these enzymes are surpassed by excess ROS or when they reduce their levels. The fact that the brain has a weaker antioxidant system compared to other organs.In addition to this, the high presence of cerebral lipids makes it more vulnerable to peroxidation.(26,29-30)

The mitochondria is the powerhouse of the cell, with the processes realized inside it can proportionate energy to the cell by Adenosine triphosphate (ATP) production. If the production of ROS beats the antioxidant mechanisms, a state of mitochondrial dysfunction and oxidative stress is perpetuated. When Beta-amyloid deposit starts entering the mitochondria, free radicals will be produced inducing membrane damage, reduction in the oxidase activity, altered intramitochondrial transport and inhibition of ATP production.(26,29-30)

TREATMENT

Lifestyle changes

Several studies have shown that exercising regularly has a positive impact on the brain's health, since it activates the brain vascularization, neurogenesis, plasticity and reduces Aβ production and the neuroinflammation related. In patients of age, regular physical activity could improve cognitive function and reduce neuropsychiatric symptoms and their care requirements(10). Moreover, it has been found that patients with genetic predisposition to AD who exercise regularly have less brain atrophy than those who don´t (31).

Along with this,other lifestyle changes like implementing a Mediterranean diet and doing cognitive training may reduce AD's progression and memory loss, and even prevent new cases of AD in aging patients (10).

Additionally, it is highly suggested that vitamin D deficiency could be a risk factor for developing dementia, so its supplementation is recommended in patients whose levels are lower than normal. In two randomized, controlled, double-blinded studies, the patients with mild cognitive impairment who took fish oil supplements, which mainly contains omega-3 fatty acids, improved their memory and thinking (31).

Pharmacological symptomatic treatment

Currently, the only drugs approved for AD's treatment are the inhibitors to cholinesterase enzyme and the antagonists to N-methyl d-aspartate receptors (NMDAR), both targeting the symptoms, since it is theorized that the cognitive impairment of this disease is caused by the destruction of acetylcholine - producing cells and thus the brain's cholinergic transmission pathways. (10,31-32).

Acetylcholinesterase inhibitors (AChEIs): The acetylcholinesterase is an enzyme with the function of cleaving acetylcholine (Ach) and preventing the chronic stimulation of its receptors. In a healthy individual that process helps to keep the equilibrium in Ach activity . However, since there is a progressive destruction of Ach-producing cells and pathways in AD, it's convenient to block the Acetylcholinesterase activity in order to increase Ach levels in presynaptic neurons and preserve cognitive function. The most remarkable members of this family are donepezil, rivastigmine and galantamine. (10,33)

NMDAR antagonist: NMDAR is essential for synaptic transmission, neural plasticity and memory. When it is stimulated, there is an increase in Calcium influx which eventually triggers signaling pathways and transcription, necessary events for

long-term potentiation. However, if there is an extended stimuli applied to NMDAR, calcium and glutamate levels will increase abnormally producing an pathological excitatory state that will end in synaptic dysfunction and neuronal death. Memantine is the only approved drug belonging to this family.(10,33)

Future treatments: The actual researchers are trying to approach new ways on how to treat AD. The molecular mechanisms are getting more relevant since these new treatments focus on molecular processes, like the ones mentioned during this manuscript. For example, monoclonal antibodies and anti-tau drugs. The monoclonal antibodies are being used in order to target Beta-amyloid plaques and facilitate its removal. In addition to this, a drug that focuses on APP has been develop. However, more research needs to be done, since there is little literature that suggests a significant improvement in patients that take these drugs. And the data that shows improvement concludes that both drugs work mildly just in early onsets of AD.

In regard to anti-tau drugs, early stages of trials suggest a good immune response in patients by decreasing tau levels. Although it's promising, more research needs to be done and the complete results are yet to be published.(10,33)

CONCLUSION

Alzheimer's disease is an international public health problem that is affecting the lives of millions of people. The understanding of the disease is increasing due to the scientific advances in molecular science. Thus, we are now more conscious on what its really causing the disease, and with this new approach, more technologies are arising. Although it's promising, more research needs to be done.

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