Kaleidoscope Művelődés-, Tudomány- és Orvostörténeti Folyóirat 2021. Vol. 11. No. 23.
Journal of History of Culture, Science and Medicine ISSN 2062-2597
DOI: 10.17107/KH.2021.23.143-151

History of Alzheimer's disease (AD) from the perspective of leading research theories

Az Alzheimer-kór története a vezető tudományos teóriák tükrében

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Initially submitted Oct 15, 2021; accepted for publication Oct.29, 2021

Abstract

Alzheimer's disease is the leading cause of cognitive deterioration. Alois Alzheimer decribed it the first time in 1907. In the last five decades, there were emerging numerous hypotheses about the pathomechanism of this condition. The first one, the cholinergic hypothesis resulted in important antidementia medications. Amyloid cascade theory set direction for many years in the Alzheimer research. Currently, it also contributed to te licencing of a novel pharmaceutical Aducanumab. Additionally, latest hypotheses shed light on the new aspects of the pathology of dementia. Thes study emphasizes the historical landmarks of Alzheimer's research and reveals their interactions as well.

Kulcsszavak
Alzheimer-kór, amiloid, tau, oxidatív stressz, gyógyszer fejlesztés

Keywords
Alzheimer's disease, amyloid, tau, oxidative stress, drug discoveries

Introduction

Alzheimer's disease (AD) is the leading cause of cognitive decline affecting more than 50 million people worldwide (Guerchet, Prince et al. 2020; https://www.who.int/news-room/fact-sheets/detail/dementia). Since according to the expectations, this number is going to triple in the upcoming three decades, AD became one of the greatest challenges of the scientific community of the 21st century (Abbott 2011). It is indicated by the fact that the 21st of September (celebrated since 1994) is dedicated the social recognition of the burden of AD (World Alzheimer's Day). The devastating symptoms usually occur around the age of 60-65 as episodic memory impairment, orientation difficulty and behavioural changes. As the disease progresses, the affected person loses communication and social skills and impairment of self-sustaining abilities also become evident.

The major pathologic hallmark of AD is the accumulation of neurotoxic proteins, the extracellular amyloid plaques, and intracellular tau neurofibrillary tangles (Castellani, Lee et al. 2006). As their amount reaches a critical threshold, symptoms occur, and the pathologic process exponentially accelerates. Unfortunately, despite the continuous and remarkable efforts of the medical experts and leading neuroscientists, curative therapy is not available. While there are drugs authorized in the therapy of AD, they have limited effect and cannot modify the disease progression. This is the major reason why novel

DOI: 10.17107/KH.2021.23.143-151

theories appear on the scientific horizon to illuminate the potentially leading mechanism and solve one of the most complicated puzzles of our age. In the current article, we summarize the dominant theories from a historical viewpoint. Furthermore, we describe how these concepts resulted in drug discoveries. Finally, we provide a short opinion on the lessons we could learn from the history of AD.

Discovery of dementia

The concept of age-related mental decline is almost as old as written human history. However, it was considered as a normal but miserable epiphenomenon of ageing. Since the life expectancy was quite short in most of the history of human species, concept of dementia is a relatively new direction. As the human life span has started to increase with the industrial revolution, the presence of cognitive disorders had started to become more evident. The scientific breakthrough took place in the early years of the 20th Century in Germany.

Alois Alzheimer (1864-1915) and the worldwide known psychiatrist, Emil Kraepelin (1856-1926) (Engstrom and Kendler 2015) examined a patient at the main neurological hospital in Frankfurt called the "Städtische Anstalt für Irre und Epileptische" (in free translation, the Municipal Hospital of Insane and Epileptic Patients). The patient was Auguste Deter, a 51-year-old lady with prominent short-term memory loss and personality changes. The core feature of these changes was the paranoid delusions. While similar symptoms were known previously, Alzheimer had an idea that the rapid decline of cognitive function might relate to progressive brain pathology (Cipriani, Dolciotti et al. 2011). Auguste died in April 1906 and the medical team led by Kraepelin executed a histological examination using Bielschowsky silver impregnation. The surprising findings were clearly visible under the lens of the microscope: tangle shaped accumulation in the neural cell bodies and stamp shaped accumulation between the neurons. The novel results were published soon, Alzheimer presented the images on the psychiatric congress of Tubingen, West-Germany in 1907 and published the data under the title as follows: "*Uber eine eigenartige Erkankung der Hirnrinde*" (Alzheimer 1907). In 1910, the colleague and supervisor of Alzheimer, Emil Kraepelin (1856-1926) published the 8th Handbook of Psychiatry and dedicated a long paragraph for dementia disorders (*Presenile and Senile Dementia*) (Kraepelin 1910). The case report of Auguste Deter was also described with the pathologic hallmarks and the curious case was named after the describing person as Alzheimer's disease. Interestingly, there is still a debate on the exact disorder which has been discovered by Alzheimer. Our opinion is that Auguste Deter had a relatively rare frontal variant of AD or another devastating dementia disorder, called frontotemporal degeneration. While it goes without any questions that the discovery of Alzheimer is one of the leading scientific breakthroughs of the modern medical history, society needed to wait more than 60 years for the deeper understanding of AD. Since the entire world was suffering from dictatorships, wars and poverty in the upcoming decades following 1910, research behind AD pathology was not in the scientific spotlight till the 70's.

The cholinergic hypothesis

Acetylcholine (ACh) is an organic chemical serving as a crucial substance in the communication of neurons. The information transports between neural cells relies on electric and chemical mechanisms. Chemical substrates of transmission are called neurotransmitters. ACh (acetylcholine ($CH_3COOCH_2CH_2N^+(CH_3)_3$)) is the firstly described and one of the most abundant neurotransmitters of human neural system. Its role has been discovered by Henry H. Dale (1875- 1968) in 1913 and he received a Nobel prize honouring his work on ACh together with Otto Loewi (1873-1961) in 1936 (Tansey 2006). ACh has a crucial role in the control of parasympathetic reactions (mechanisms activating in resting periods

2021. Vol. 11. No. 23.
ISSN 2062-2597
DOI: 10.17107/KH.2021.23.143-151

to fill up the energy resources of the body), in the muscular activity and in cognitive functions including arousal, memory, attention, control of sleep (induction of rapid eye movement sleep), learning, reward and motivation. In the brain, three major sources relate to the production of ACh: mesopontine tegmentum (pons and mesencephalon of brain stem), basal nucleus of Meynert and medial septal nucleus (Van der Zee, Platt et al. 2011). Effect of ACh is also influenced by the acetylcholine-esterase (ACh-E) enzyme working in the synaptic cleft and reducing the amount of ACh. Function of ACh has been associated with memory formation by numerous studies showing that depletion or disruption of ACh lead to severe learning difficulty and amnesia like symptoms (Hasselmo 2006).

The cholinergic hypothesis of AD was conceptualized by AJF Maloney and Peter Davis (1948-) in 1976 (Davies and Maloney 1976). They studied various types of enzymes linked to the production of neurotransmitters in different regions of brain slices derived from control subjects and AD patients. The major finding of their study is that only ACh production is reduced in cortical and subcortical areas among AD patients in comparison to healthy controls. Further studies confirmed their results showing that the basal nucleus of Meynert degenerates in the early phases of AD leading to decreased ACh production corresponding to impaired memory functions (Whitehouse 1998). While these observations were not able to generate compounds slowing down the degenerative process, they resulted in important drug discoveries. Inhibition of ACh-E generates an increased concentration of ACh in the synaptic cleft, so the depletion of ACh production could be partially compensated. In 1995, the Food and Drug Administration (FDA) approved the ACh-E inhibitor tacrine as the first therapeutic drug against AD. While tacrine had positive effect on cognition, side effects was too strong to stay on the market for longterm (Summers 2006). The second generation of inhibitors were released and rivastigmine was authorized in 2000, galantamine in 2004 and donepezil in 2010. They are prescribed in the mild and moderate phases of AD and donepezil and rivastigmine are available in Hungary as well. Decrease in the amount of ACh is a consequence of the neural loss, therefore these drugs are not able to modify the disease process but can alleviate the cognitive symptoms (Hampel, Mesulam et al. 2018). Their exact impact on the cognitive functions is still under a heated scientific debate and the world needed to wait 15 years for a new hypothesis following 1976.

The amyloid cascade theory

A novel idea has been published in 1991 by John Hardy (1954-) and David Allsop (1954-2021) based on the genetic profile of AD patients (Hardy and Allsop 1991). At that time, Allsop was already a pioneer in the field of AD research. In his early career, he determined the amino acid composition of amyloid isolated from brain plaques of AD patients (Allsop, Landon et al. 1983). He has been also demonstrated that monoclonal antibodies against amyloid peptides react with plaque cores but not with neurofibrillary tangles (Allsop, Landon et al. 1986). In a further study, Allsop isolated the amyloid precursor protein on the 21st chromosome of a patient with Down-syndrome (Allsop, Haga et al. 1989). As it is well known, patients with Down-syndrome have shorter life expectancy partially due to the higher risk of Alzheimer-like dementia. His findings supported that changes in genetic background can lead to the appearance of amyloid pathology and AD. The idea was summarized in a highly cited review paper written together with John Hardy showing that the pathologic process of AD starts with the aggregation of amyloid-beta (Aβ), it generates changes in the phosphorylation of tau leading to deposition and finally to the neural injury appearing in the symptoms of AD (Hardy and Allsop 1991). The entire process is similar to the slope of the dominos, resulting in the name of cascade theory. Seemingly, the misfolding of Aβ is the major step of the cascade terminating in the production of Aβ plaques since otherwise normal Aβ has a vital role in the integrity of neural networks. It stabilizes synaptic connections, protects neurons from oxidative stress,

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ISSN 2062-2597
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enhances recovery from neural injury, blocks leaks in the blood-brain barrier and has antimicrobial activity (Morley, Farr et al. 2010).

Following this paper, the crucial role of misfolded Aβ in the pathomechanism of AD has been highlighted in many studies. Genetic experiments revealed that patients with the mutation of Aβ and its cleaving enzymes show severe familial forms of AD (Zheng and Koo 2006). Neuropathologic studies demonstrated that Aβ plaque is neurotoxic, degenerates the synaptic connections, reduces neural survival, increases oxidative stress, leads to inflammatory changes, and generates epileptic seizures (Mucke and Selkoe 2012). Due to these observations, Aβ was in the focus of drug trials in the recent decades with various targeting strategies: production inhibitors, aggregation inhibitors and antiamyloid antibodies. Production inhibitors target the secretase enzymes related to the production of Aβ (BACE1 inhibitor drugs) (Vassar 2014). Many of these proved to be efficient in the reduction of Aβ burden; however, cognitive symptoms did not improve or in some studies, they were even associated with accelerated cognitive decline. Similar results were shown with monoclonal antibodies: while antibodies were able to reduce Aβ accumulation successfully, it was not followed with the improvement of cognitive performance (Gold 2017). Only one drug got an FDA permission: Aducanumab (developed by Biogen Idec) has been approved recently, in June 2021 (Padda and Parmar 2021). Seemingly, amyloid cascade theory can address the core initial steps of pathologic process in AD; however, most of antiamyloid clinical trials have failed. While there are likely various reasons behind, other theories might serve novel directions for proper understanding of AD. Currently, many scientists believe that the revision of classic "tau or amyloid" question might reveal novel insight to the pathology.

The oxidative stress hypothesis and hyperexcitability theory

In 2004, a new idea was introduced by Russel Swerdlow (1965-) and Shaharyar Khan (1934-) suggesting the key role of mitochondrial dysfunction in the development of AD (Swerdlow and Khan 2004). Mitochondria (MC) are cellular organs having mandatory role in the energy production of the cells and protection of oxidative stress. Oxidative stress is caused by reactive oxygen species (ROS) mainly produced by MC. Between normal conditions, there is a balance between oxidative and antioxidative processes. The core idea of oxidative stress theory is that function of MC in highly defined by inherited factors and aging has a modifier effect as well. In AD, MC function is genetically altered leading to increased ROS production which stimulate the misfolding of amyloid plaques. It is confirmed by many studies showing the AD patients have altered MC enzyme expression and it generates larger oxidative stress (Zhu, Perry et al. 2006). Finally, it associates with the reduction of neural survival and increased amyloid load.

Seemingly, there is a bidirectional connection between amyloid and oxidative stress. While MC dysfunction and oxidative stress clearly relate to amyloid burden, neurons close to the amyloid plaques also show increased calcium influx, augmented stress-related signaling pathways, larger ROS concentration and increased excitotoxicity (pathologic release of glutamate terminating in neural damage) (Cheignon, Tomas et al. 2018). Molecular observations were further supported by neurophysiological animal studies demonstrating that the genetic rat models of AD show frequent occurrence of epileptic seizures due to the high calcium load and glutamate outflow (Scharfman 2012). It might be a consequence of amyloid-related changes in the neural milieu where oxidative mechanisms change the permeability of neural membranes resulting in frequent and large depolarization of the neurons. The idea was summarized by Jorge G. Palop and Lennart Mucke in 2010 as the hyperexcitability concept, describing that amyloid strongly changes the regulation of excitatory transmission, finally leading to increased oxidative stress, destabilization of the neural network and generation of epileptic discharges (Palop and Mucke 2010). The concept motivated many human observations demonstrating similar findings: epilepsy is a frequent comorbid condition of AD;

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patients frequently have epileptic discharges and hyperexcitability, generating radical alterations in the neural networks (Friedman, Honig et al. 2012). While all these findings seem to be quite novel, it should be addressed that the link between epilepsy and amyloid pathology has been described already in 1892 by George Marinescu (1863-1938) and Paul Blocq (1860-1896) (Blocq and Marinescu 1892).

The importance of these studies is that the amyloid-related oxidative stress and hyperexcitability can be diagnosed and might be treated (Horvath, Csernus et al. 2020). The hyperexcitability theory also revealed a novel insight on the use of Memantine. Memantine was approved by FDA in 2003 and its major effect is the antagonism of glutamate receptors showing beneficial impact on the behavioral and cognitive functions in moderate and severe AD (Winblad, Jones et al. 2007). While it has been authorized 18 years ago, the possibly modified pathophysiology as glutamate excitotoxity was linked quite recently to AD. The idea also generated many novel therapeutic trials with the use of antiepileptic drugs. Together with the drug studies targeting MC function, these trials account approximately 20% of the entire spectrum of phase 3 studies of AD.

The tau propagation theory

Similarly to Aβ, tau is also mandatory in the integrity of neural cells due to the stabilization of neural cell skeleton, the microtubules. Normal phosphorylation process is important for the proper function of tau. Hyperphosphorylation could lead to changes in protein structure resulting in misfolding and intracellular aggregates. The pathologic tau protein decreases the efficacy of signal transmission across neurons, decreased neural survival and has direct neurotoxic effect (Trojanowski and Lee 2005). Its presence as intracellular tangles in the samples of AD patients have been demonstrated already by Alois Alzheimer (1864-1915) (Alzheimer 1907). The exact mechanism in the pathogenesis of AD was introduced in 2009 by Bess Frost, Rachel L. Jacks and Marc I. Diamond (1965-) as the tau propagation hypothesis (Frost, Jacks et al. 2009). Based on this concept, tau appears is specific areas of the brain having the strongest neural activity since they are in the center of neural networks (hub areas). From the first appearances, they spread to various directions following the neural routes similarly how prion proteins spread in the neural tissue. The idea was reinforced by many studies showing that the injected tau particles can “infect” neural tissue specimens (Lasagna-Reeves, Castillo-Carranza et al. 2012,). Studies also demonstrated that the speed of tau propagation is highly interfere with the changes of amyloid metabolism, leading to an agreement stating that amyloid and tau are both important in the pathologic process of AD and their relation might be a bidirectional connection where both accumulated proteins can generate overproduction of the other (Ittner and Götz 2011). Drug developments focusing on the modification of tau show high scientific interest especially phosphorylation inhibitors and immunotherapy. While some studies have been stopped in the first clinical phases by similar reasons as antiamyloid therapies (reductive effect on protein load but no impact on cognitive functions), some of them are already in the last phases representing a hopeful direction for novel drug discoveries (Ceyzériat, Zilli et al. 2020).

The inflammation hypothesis

Inflammatory response is a secondary reaction in the body on potentially harmful events as injuries, bleeding, infections, or cellular death. In acute form, it protects the body from further damage and induces the healing processes of the organisms. However, if the initial stimulus persists or the acute reaction become uncontrollable, reaction could continue in chronic phase and finally could generate immense damage of the tissues (Lawrence and Gilroy 2007). In 2013, Dimitrije Krstic and Irene Knuesel introduced the inflammation hypothesis with the summary of previous results showing that chronic inflammation has crucial role in the development of AD (Krstic and Knuesel 2013).

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According to the theory, local neural damage or systemic injuries might trigger long-lasting changes in the balance between proinflammatory and anti-inflammatory molecules. Local neural damage such as decreased tissue oxygenation, neural invasion of viruses or bacteria, rapid changes in the glucose metabolism of neurons or toxic protein accumulations (e.g., tau or amyloid) might lead to an immediate activation of microglial and astrocyte cells (first responders) generating an acute neuroinflammatory reaction (Salminen, Ojala et al. 2009). While the acute activation of microglia and astrocytes help to isolate the injuries and initiate the repair of the damaged tissue, chronic response participates in the neurodegenerative process. Based on the current literature, amyloid plaques can alter the membranes of the surrounding astrocytes resulting in increased calcium influx and dramatic changes in the glia- neuron interactions (Frost and Li 2017). The affected astroglial cells show dominant morphological changes as well: enlarged cell bodies form nests around the amyloid plaques (astrogliosis) (Osborn, Kamphuis et al. 2016). Interestingly, the structural alterations have been described already in the first report of Alois Alzheimer (Alzheimer 1907). Finally, these changes compromise the neural functions dependent on the astrocytes such as energy metabolism, neurotransmitter production and release, or the level of glutamate in the synaptic cleft. All these prominent alterations result in neural death via oxidative stress and excitotoxicity. Amyloid and tau aggregations also cause long-term activation of the microglia cells leading to a prominent and constant increase of inflammatory cytokines (interleukins, tumor necrosis factors, etc.) (Lee and Landreth 2010). While these mediators are essential of the repair of neural damage, if their production remains constant, they also trigger long-lasting proinflammatory changes including the production of ROS agents. The consecutive oxidative stress terminates in accelerated neurodegenerative process.

Currently, the inflammatory hypothesis is one of the leading concepts of AD generating numerous animal and human trials targeting astrocytes, microglia and proinflammatory molecules (Ozben and Ozben 2019). It also serves as a basis for observational and cross-sectional studies analyzing the link between infections, chronic inflammation, and neurodegeneration. It also serves as an engine for the renewal of previous observations showing the potentially pathologic role of certain viruses or dental bacteria in the pathogenesis of AD (Ashraf, Tarasov et al. 2019).

Perspective

AD is a devastating condition caused by many different factors including genetic and environmental causes. In our paper, we summarized the most dominant theories behind the pathogenesis of neurodegeneration from the 1970's until the last decade. Obviously, there are many others (e.g., vascular, metal ion, lymphatic hypotheses, etc.) but they did not generate intensive changes in the directions of drug development and the current paper cannot aim to highlight all of them (Liu, Xie et al. 2019).

The important message of our work comes from the comparison of different ideas. While traditional concepts (cholinergic and amyloid cascade theory) assumed linear pathology with a central element starting the entire process, novel ideas utilize bidirectional connections between the toxic protein production and changes in the metabolism of the neural tissue. Seemingly, the new hypotheses reveal a better insight for the entire process bringing all the possible mechanisms (infections, inflammation, oxidative stress, excitotoxicity, and amyloid-tau cascades) under one roof. Thus, it seems to be feasible that these concepts could lead to patient-tailored individualized therapeutic approaches resulting in better outcomes than the traditional antidementia medications. Furthermore, these ideas could generate novel observations linking interdisciplinary areas to the research of AD including virology, dentistry, preventive medicine, or network sciences. However, revisiting of traditional concepts and reports is also crucial. Fascinating examples are that the link between excitotoxicity and amyloid has been proposed already in the end of the 19th century

(Blocq and Marinescu 1892) or the changes in astrocytes around amyloid plaques was already mentioned in the first report of Alois Alzheimer (Alzheimer 1907). Furthermore, the classic ideas can also lead finally to successful drug discoveries as we have seen recently. Aducanumab is the first disease modifying drug of AD which has received the FDA approval recently, in June 2021. Its development was highly motivated by the traditional amyloid cascade theory. In the current paper, we show our respect to all the researchers of Alzheimer's disease dedicating their life for the better understanding and treatment of dementia. With our report, we also admire the great work of David Allsop who had a pioneer role in the understanding of amyloid pathology. His research had a triggering impact on the development of monoclonal amyloid antibodies (including Aducanumab) giving hope for many families around the world. Professor Allsop passed away recently, in March 2021.

Funding
Our study was supported by National Brain Research Program I, II (KTIA_NAP_13-1-2013-0001; 2017-1.2.1-NKP-2017-00002), Hungarian Scientific Research Fund 2019 of the National Research, Development and Innovation Office (PD- 132652), Janos Bolyai Research Scholarship of the Hungarian Academy of Sciences (bo_78_20_2020). This is an EU Joint Programme- Neurodegenerative Disease Research (JPND) project. The project is supported through the following funding organization under the aegis of JPND-www.jpnd.eu (*National Research, Development and Innovation, Hungary,* 2019-2.1.7-ERA-NET-2020-00006).

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