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Review

Nicotine Effects on Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most common neurodegenerative disorder that affects millions of people worldwide causing massive economic burden and the number of cases is expected to rise dramatically. Currently, there is no treatment that can stop or reverse the effects of AD. This review attempts to present the current status of research, biopathological approach mechanisms, and nicotine as a therapeutic method in AD. Nicotine has been related to recovery of memory in humans and animal models and some observational studies have been compatible with a protective effect of nicotine inhalation against Alzheimer's disease. At present, there is great controversy over this possible effect of tobacco use, and evidence is inconclusive.

Keywords: Nicotine, Alzheimer's disease, Anxiety, Depression, Diagnostic

INTRODUCTION

Alzheimer's disease (AD) is characterized by successive degradation and destructive neuro human brain structure and affect over 37 million people worldwide (Mount and Downton, 2006), with a loss of over $ 600 billion in 2010 (Wimo and Prince, 2010). Overall, 5 million new cases of AD are reported annually (Alzheimer's Association, 2015). The risk of developing AD is strongly age, ending in a deterioration in mood, behavior, in performance, knowledge and memory, therefore (Alzheimer et al., 1995), AD is becoming a crisis increasing social with growing life expectancy. Despite this, there is no current treatment that can stop or reverse the effects of AD (Citron, 2010). Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia (V. Echeverria, R. Zeitlin., 2012). It has been shown that the progressive nature of neurodegeneration in AD leads to synaptic failure and neuronal damage in brain cortical areas (A. Magini et al., 2015). In particular, many findings support the hypothesis that the memory failure in AD results from synaptic dysfunction and loss of synapses is a key event in early cognitive decline (K. Gylys et al., 2004).

The disease is closely related to brain pathology involving (a) extracellular amyloid aggregates (known as senile plaques) (SP) formed by Aβ amyloid and (b) neurofibrillary tangles (NFTs) of tau protein (p-tau) (Belluti et al., 2013; Saido, 2013). Accordingly to amyloid cascade hypothesis, Aβ is primarily responsible for many of the pathological features of the disease, its oligomers representing the most toxic species (Sakono and Zako, 2010). Accumulation of Aβ (1-42) plaques inflammatory reactions starts by microglial activation due to pro-inflammatory cytokines in the brain areas that are the most representative: the right neocortex and hippocampus (Radu I, Lucian H., 2015). Moreover, disturbances of the kinase and phosphatase which results in hyperphosphorylation of tau protein, which leads to deterioration and loss of neurons (Thota et al., 2007). Despite existing strong genetic links, including APP and PS-1 mutations, the PS-2 mutation (Bothwell and Giniger., 2000) is the dominant form of sporadic AD. In this regard, AD research deals with mechanisms for early onset of disease with a wider range of factors that lead to sporadic forms, which could be one reason for the failure of the majority of therapeutic trials and lack of preventive measures by more 20 years from proposal amyloid hypothesis (Hicks et al., 2012).

Factors Influencing the Initiation and Progression of AD

The factors influencing the initiation and progression of the disease that have a role in the pathophysiology of AD are Aβ (1-42)/Aβ (1-40) oligomers, oxidative stress, proinflammatory cytokines produced by activated glial cells, changes in cholesterol homeostasis and changes in the cholinergic nervous system (Allam et al., 2008).

As with other age-related diseases (cardiovascular disease, diabetes cancers, and so on), there are likely to be behavioural, dietary and other environmental factors that may affect the risk of AD. However, this area of research has not yet matured to a point where clear recommendations can be made. Epidemiological findings suggest that a low education level, history of head trauma, consumption of high-calorie, high-fat diets and a sedentary lifestyle may each increase the risk of AD (Mayeux R., 2003; Mattson MP., 2003) When rodents are maintained in a cognitively stimulating environment or on a dietary restriction regimen, neurons in their hippocampus are more resistant to death and neurogenesis (the production of new neurons from stem cells) is increased. Similarly, regular physical exercise enhances hippocampal synaptic plasticity and neurogenesis, and is neuroprotective (Bush Al et al., 2003).

Specific dietary components may affect the risk of AD. Individuals with low dietary folate intakes are at increased risk of AD, as an apparent consequence of increased levels of homocysteine; studies of mouse models of AD have demonstrated adverse effects of low dietary folate levels and high homocysteine levels on the disease process (Mattson MP., 2003). Other dietary factors implicated as risk factors for AD include lipids and metals such as copper and iron9,14. However, despite accumulating data suggesting that dietary factors may influence disease risk, a causal relationship between caloric intake, or any specific dietary component, and AD has not been established (Allam et al., 2008).

General aspects of nicotine

Tobacco smoke consists of thousands of compounds including nicotine. Although tobacco smoking is a widespread and historic addiction of long standing, interest in brain nicotinic acetylcholine receptors (nAChRs) began to grow only some 15 years ago, when genetic studies revealed the amazing possible diversity of this type of receptor (Lucian H et al., 2008). Tobacco smoke is a very complex mixture of more than 4,700 ingredients (without their metabolites) including nicotine (Zeidler R et al., 2007; Swan G.E et al., 2007). Combined electrophysiological, pharmacological and genetic studies allowed characterizing the structure and properties of brain nicotinic acetylcholine receptors (nAChRs), but despite a vast amount of work dedicated to this area, the roles of these receptors in brain functions remain largely unknown (Lucian H et al., 2009).

A. nicotinovorans is a Gram-positive aerobic soil bacterium able to grow on nicotine as its sole source of carbon and nitrogen (Sperling RA et al., 2011). The initial steps of nicotine catabolism are catalyzed by nicotine dehydrogenase, the L – and D-specific 6-hydroxy-L-nicotine oxidase and 6-hydroxy-D-nicotine oxidase were expressed in *Escherichia coli* and obtained in a state of high purity and crystallized (Decker K et al., 2009). Nicotine is a cholinergic agonist that also has a presynaptic effect in releasing acetylcholine. Nicotine is considered to be an agonist of nAChR (Lucian H et al., 2015). It has been shown to reverse spatial memory deficits produced in rats by lesions of the medial septal nucleus of their brains, and, in aged monkeys, nicotine administration improves memory and alertness to visual stimuli. Observational studies have suggested a protective effect of smoking against Alzheimer's disease, but recent studies have called this into question. Smoking is a risk factor for stroke and so, possibly, for vascular dementia. Because nicotine has adverse effects, it is important to conduct a systematic review to assess its clinical efficacy and safety for people with AD (Jess L et al., 2001). The neuronal nicotinic acetylcholine receptors (nAChRs) in the brain are important for functional processes, including cognitive and memory functions. The nAChRs acting as neuromodulators in communicative processes regulated by different neurotransmitters show a relatively high abundance in the human cortex, with a laminar distribution of the nAChRs of super high, high, and low affinity in the human cortex (Agneta N., 2001). The regional pattern of messenger RNA (mRNA) for various nAChR subtypes does not strictly follow the regional distribution of nAChR ligand-binding sites in the human brain. Consistent losses of nAChRs have been measured *in vitro* in autopsy brain tissue of AD patients, as well as *in vivo* by positron emission tomography (PET) (Jess L et al., 2001; Agneta N., 2001).

Nicotine and alzheimer’s disease

Published studies in humans have reported the effects of intravenous or subcutaneous nicotine administration on people with Alzheimer’s disease. Significant improvements were reported in several cognitive tasks such as free recall, visual attention and perception, and in moodalthough not on memory (Gentry 2000). These results suggest that central nicotinic cholinergic stimulation deserves further investigation as a possible treatment for Alzheimer’s disease. There is also the possibility that nicotine might have a preventive action on Alzheimer’s disease, delaying the onset of clinical dementia by reducing the rate of neuronal loss or

mitigating its functional consequences.

The effects of smoking on dementia in general and Alzheimer's disease in particular are controversial, and the issue is inevitably tinged by ideological considerations (Boyd 2000, Calinas 2000) that might hinder objective investigation. Nicotine readily crosses the blood-brain barrier, and some studies support the notion that smoking reduces the risk of Alzheimer's disease. Some other studies show opposite results (Launer 1999) and yet others find no statistical association between smoking and dementia (Doll 2000). The balance between nicotine neuroprotection and toxicity depends on dose developmental stage and regimen of administration. Therefore, a full understanding of the molecular and cellular effects of nicotine on signaling pathways relevant to neuronal survival is critical for informed drug discovery of nicotinic compounds to combat human neurodegeneration (Lucian et al., 2009).

Clinical and laboratory studies indicated the involvement of nAChRs in complex brain functions such as memory, attention and cognition, but also in the pathogenesis of several neuropsychiatric afflictions such as Alzheimer's (AD) and Parkinson's diseases (PD) (Mihailescu S et al., 2000). Various studies indicated that tobacco smoking may represent a form of self-medication in some psychiatric diseases. However, the use of nicotine in therapy is severely limited by its carcinogenic and cardiovascular side effects. This negative effect is nearly overcome due to synthesis of selective nAChRs agonists (Lucian H et al., 2009).

Effect of nicotine on anxiety and depression

Anxiety and depression increase the severity of cognitive decline in AD patients. Anxiety is more common in individuals with dementia than in individuals without dementia and it is associated with worse quality of life, problem behaviors, limitations in activities of daily living, nighttime awakenings, and poorer neuropsychological performance, even after controlling for depression (Lucian H et al., 2015). Depression is one of the most prevalent and lifetime threatening forms of mental illnesses, whereas AD is a neurodegenerative disorder that affects more than 37 million people worldwide. The current symptomatic treatment of patients with mild-to-moderate AD is based on drugs such as donepezil, rivastigmine, galantamine and memantine which are associated with side effects. These drugs are able to reduce the signs of the disease but have not the potential to treat it. There is currently a high demand for natural therapies to treat AD and reduce the side effects of drugs used in the clinic. Tobacco smoke is a very complex mixture of more than 4,700 ingredients (without their metabolites) including nicotine (Lucian H et al., 2015). Nicotine has been shown to have e¡ects on anxiety and depression in both human and animal studies. Studies in both human and animals have shown that nicotine treatment can affect many aspects of emotionality (Marina et al., 2002). The large variety of nAChR subtypes expressed in areas of the brain involved in stress response suggest that cholinergic innervation of these pathways is critical in modulating mood and anxiety. Following nicotine administration, however, the route of administration, dose, and time course of administration can result in differential activation of pathways involved in emotionality, such that, depending on the behavioral study, nicotine can be either anxiolytic or anxiogenic (Irvine et al., 2001).

Local infusion and pharmacological studies have suggested that serotonergic pathways may be particularly important for the anxiogenic properties of nicotine, while peripheral stress hormones and gabaergic pathways have been identified as potential sites for nicotine's anxiolytic actions (Fu et al., 2001). In addition, the mesolimbic dopamine system may be critical for the effects of nicotine on stressrelated behaviors (Ferguson SM et al., 2000). The ability of nicotine to affect the level of neurotrophic factors may also be critical in the antidepressant actions of nicotine. In addition to its acute effects, chronic nicotine treatment also results in molecular and cellular adaptations in the brain such that withdrawal from nicotine can result in both increased anxiety and the onset of depressive symptoms (Kuryatov A et al., 2000). One active area for future research will be the identification of the molecules and brain regions that are involved in these adaptations to nicotine. Ultimately, an understanding of the nAChR subtypes involved in the ability of nicotine to modulate mood and anxiety could be useful in drug development to combat depression, while identification of the sites where adaptation to nicotine use can result in anxiety and depression upon withdrawal could aid in development of therapies for smoking cessation (Fu Y et al., 2001; Kuryatov A et al., 2000).

Diagnostic

Certain DNA diagnosis can only be done a postmortem. However, today, specialized clinics, using a combination of tools that include taking a history of the disease on patients and their families, as well as evaluating cognitive function by neuropsychological tests in combination with neuroimaging (CT, MRI and PET) to rule out other causes of dementia (Blennow et al., 2010) can diagnose AD with accuracy greater than 95%. Neurological tests, which are still the gold standard for diagnosis of AD are largely accurate in identifying people with dementia already developed. It provides structural MRI brain atrophy measures, reflecting the loss of dendrites, synapses, and neurons (Kosicek and Hecimovic, 2013).

CONCLUSIONS

Despite general progress in knowledge of the structure and functions of brain nAChRs, the mechanisms of their involvement in the pathogenesis of neuropsychiatric disorders remain unclear. AD is a devastating age-related neurodegenerative disease, which has a serious impact on an economic development system and healthcare worldwide. Although AD has been studied for over 100 years since the 1906, its exact pathogenity and mechanism remain to be clarified. Also, up to now there are no discovered treatments or diagnostic methods ideal for AD. It is commonly believed that stress, anxiety and depression are interrelated phenomena. Stress is typically implicated either in the etiology of depressive and anxiety disorders or as consequence of it.

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Conflict of Interest Disclosure

The authors declare that they have no potential conflicts of interest to disclose.

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