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Smoking and Progression of Alzheimer's Disease: Connecting Edges

Sigara İçme ve Alzheimer Hastalığı Arasındaki İlişki

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ABSTRACT

Smoking is a practice to burn and inhale the smoke and is primarily a route of administration for recreational drugs. The combustion releases the active substances in drugs such as nicotine and make them available for absorption through the lungs.The most common form of smoking is ciggarate smoking and is associated with life threatening complications like heart diseases, lung cancer, atherosclerosis, rheumatoid arthritis, osteoporosios, immune system dysfunction, hypertension, chronic obstructive pulmonary diseases, miscarriage, premature birth and dysfunctions of reproductive system as well. Smoking affet almost every organ of the body however, compared to the volume of research on the cardiovascular, pulmonary and cancer related health consequences of chronic smoking, lesser attention has been devoted to investigation of its effects on human neurocognition and brain neurobiology. In central nervous system, it leads to deficiencies in auditory verbal learning and/or memory, general intellectual abilities, visual search speeds, processing speed, cognitive flexibility, working memory and executive functions across a wide age range. The present work makes an effort to compile the evidence to challenge the notion/myth that smoking may be neuroprotective in cases of Alzheimer's disease. The neuroprotective effects of smoking may be accredited only to nicotinic content of cigarete smoke that too in part, but smoke is a deadly mixture of thousands of chemicals that must have disastrous effect on central nervous system. The various effets of cigarrate smoke and its ingredients on pathological markers of Alzheimer's disease as oxidative stress, senile plaques, tau hyperphosphorylation, neuroinflammation, synapse loss and effects on blood brain barrier are discussed.

Key words: Alzheimer's disease, amyloid, blood brain barrier, cigarette smoking, cognition, inflammation.

ÖZET

Sigara içme; sigaranın yakımı ve sonrasında nefes çekme işlevi olup zevk veya eğlence için alınan uyuşturucuların başlıca güzergahıdır. Yanma uyuşturucuda ki nikotin gibi maddeleri serbest bırakır ve akciğer boyunca absorbe edilmesine neden olmaktadır. Duman solumanın en yaygın formu sigara içimidir ve üreme sistemi işlevsizliği, premature doğum, düşük yapma, KOAH, hipertansiyon, bağışıklık sistemi işlevsizliği, kemik erimesi, eklem iltihabı, damar tıkanıklığı, akciğer kanseri ve kalp hastalıkları gibi hayatı tehdit eden komplikasyonları ile ilişkilendirilmiştir. Sigara içimi kardiyovasküler, akciğer ve kanser araştırmaları hacmine oranla hemen hemen vücuttaki tüm organları etkilemektedir. Fakat sigaranın beyin nörobiyolojisinde ve insan nörobilişsel sistemlerine etkiside daha az oranda araştırılmaktadır. Sigara, merkezi sinir sisteminde, işitsel sözel öğrenme ve hafızada, genel entelektüel yeneteklerde, görsel arama hızlarında, işlem hızında, bilişsel esneklikte, geniş bir yaş aralığında çalışan bellek ve yürütücü işlevler üzerinde aksamalara neden olmaktadır. Bu çalışma sigara içiminin Alzheimer vakalarında nöroprotektif etkisinin olabileceği efsanesi üzerine kanıtları derlemektir. Sigara içiminin nöroprotektif etkisi yanlızca sigaradaki nikotin miktarına bağlı olabilir ama sigara merkezi sinir sistemine zarar verebilecek binlerce ölümcül kimyasalları içermektedir. Burada, sigara içiminin oksidatif stres, senil plaklar, tau hiperfosforilasyon, nöroenflamasyon, sinaps kaybı gibi Alzheimer hastalığı patolojik belirtilerine neden olan katkı maddeleri ve kan beyin bariyerlerinde ki etkisi tartışılmaktadır.

Anahtar kelimeler: Alzheimer hastalığı, amiloid, biliş,inflamasyon,kan beyin bariyeri, sigara içimi

Introduction

The older population is undergoing a continuous expansion in the whole world as a result of prolonged life expectancy and reduced natality because of better medical care and increased awareness regarding several disorders. The increasing life expectancy is likely to result in an increase in age-related disorders and dementia is a major cause of disability in people aged over 60 which encompasses symptoms of a chronic progressive cognitive decline usually affecting memory, judgment, decision-making and socio-behavioral skills.

Alzheimer disease (AD) is the most common form of dementia. AD is a chronic, progressive, untreatable multifactorial, most common neurodegenerative disorder characterized by apraxia, aphasia, agnosia and severe cognitive deficits. Accompanying behavioral changes like anxiety, hallucination and depression may complicate the problem. AD have a serious impact on families, caregivers, and the healthcare system in general. Although many theories and treatments have been proposed targeting pathophysiology of AD yet, current treatments

(acetylcholinesterase inhibitors) are merely palliative and do little to slow the progression of the disease. The increased incidence of AD appears to be rising faster than the population is aging and such an increase cannot be due to any genetic cause as human genome does not change rapidly enough to trigger them so frequently. The rise in AD population may be due to changed "harmful environments" and compromising life style. More recent research and demographic studies have shown that use of tobacco products or exposure to tobacco smoke damages the human body with deadly consequences and is one of the largest risk factors for AD. The present work studies the relationship between tobacco smoke and resultant consequences on the progression of AD.

Smoking, Dementia and Alzheimer's disease

Tobacco and its ingredients are the main cause of morbidity and mortality from conception to the late age[1]. Worldwide, there are 1·1 billion smokers[2] and more than 5 million deaths are directly attributed to tobacco consumption[3]. Tobacco consumption accounts for a shortening of disease free life by 14 years[4]. More than 1.1 billion people (one-third of the global adult population) use tobacco regularly[5] and 48% of men and 12% of women smoke cigarettes. Cigarette smoking reduces life span by an average of 7 years[6,7]. Tobacco use in the form of cigarettes is a main preventable cause of death and disability[8,9]. Annually, about 5 million deaths are attributed to tobacco smoking contributing the second leading cause of mortality among adults worldwide[10,11]. Smoking harms almost every organ of the body. More than 1,000 people are killed every day by cigarettes, and one-half of all long-term smokers are killed by smoking related diseases[12].

A cigarette is an efficient, well-engineered nicotine delivery device that has proved to be deadly when smoked regularly. Nicotine from a smoked cigarette will reach the brain in as little as 7 seconds after inhalation[13]. A typical cigarette contains approximately 0.5 to 1.0 g of tobacco and on average, 10 mg of nicotine[14,15]. A cigarette is typically smoked in 10 puffs and within 5 minutes. A typical smoker will absorb 1 to 2 mg of nicotine, but absorption can range from 0.5 to 3 mg[16,17]. The elimination half-life of nicotine is 2 to 3 hours, meaning that the level of nicotine in the blood decreases by one half after a smoker stops smoking for that length of time[17].

Cigarette smoking increases the risk of heart diseases, lung cancer and microbial infections[18-21]. It is also associated with delayed recovery from injuries, atherosclerosis, chronic obstructive

pulmonary disease, Crohn's disease, rheumatoid arthritis and cancers of the lung, mouth, larynx, esophagus and bladder[22,23]. In addition, female smokers have a greater propensity for miscarriages, low-birth weight babies, adverse menstrual symptoms, osteoporosis and transmission of HIV-1 from mother to child[24,25].

Each cigarette smoked, induces significant changes in brain systems[26]and is associated with biomedical conditions that compromise brain neurobiology and neurocognition[27,28]. However, compared to the substantial volume of research on the cardiovascular, pulmonary and cancer-related health consequences associated with chronic smoking, surprisingly little research has been specifically devoted to the investigation of its effects on human neurocognition and brain neurobiology[29].

Cigarette smoking has been linked to common causes of death in the elderly and contributes to death and disability associated with chronic illnesses in this age group[30]. Beside several complications, cigarette smoking doubles the risk of developing dementia[31]and it also accelerate the rate of cognitive decline in elderly without dementia[32].

Dementia is a major cause of disability in people aged over 60. It contributes 11.2% of all years lived with disability, more than stroke (9%), musculoskeletal disorders (8.9%), cardiovascular disease (5%) and all forms of cancer (2.4%). The WHO 2012 Report "Dementia: a public health priority" estimates there are at present 35.6 million people living in dementia worldwide. Every four seconds, a new case of dementia occur somewhere in the world. This epidemic has enormous implications for society, in terms of both human suffering and monetary cost[33,34]. This condition had been known by the Greeks as morosis, and as oblivion and dementia by the Romans. In Middle English it was known as dotage, in French it was called démence, and in 18th century English it was categorized as fatuity[35].

Dementia is a progressive debilitating syndrome of dysfunction in several intellectual domains including memory, language, visuospatial ability, praxis, gnosis and executive functioning. As the world population ages, the frequency is expected to double by 2030 and triple by 2050[36]. Dementia can be divided in to cortical and subcortical forms. AD is a form of cortical dementia, as is Creutzfeldt-Jakob disease (CJD). In subcortical dementia, structures below the cerebral cortex are affected or damaged, such as occurs in Parkinson's disease. In multi-infarct dementia both the cortical and subcortical parts of the brain are affected. Dementia can also be divided into reversible causes such as hypothyroidism, normal pressure hydrocephalus,

vitamin B12 deficiency, hypothyroidism, normal pressure hydrocephalus and irreversible causes such as AD. Of those, AD is the most common affecting 35 million people worldwide[37-39] and cases are expected to increase 3-fold over the next 40 years[40].

Death is said to occur within 3 to 9 years after the diagnosis of AD is made[38]. AD incidence appears to be rising faster than the population is aging. The aetiology of sporadic AD is not well known, but several risk factors have been shown to increase the probability of developing the disease[41]. Although the main risk factor for AD is aging, various others factors include, gender, ApoE polymorphism, the coexistence of other disorders (such as cardiovascular diseases, brain injury, diabetes and Down's syndrome). Several lifestyle conditions, including physical activity, education, diet and smoking[42,43] are other factors that may escalate progression of AD.

Smoking as a Major Risk Factor for AD

A detailed risk assessment study concluded that 14%of AD cases are potentially attributable to smoking, and thus a 25% reduction in smoking frequency could potentially lower AD prevalence by many hundred thousand cases worldwide[41].

Generally, smoking habit develops in adolescence[44] and gradually consumption of cigarettes increases and probability of quitting it decreases with age[45]. More recent and complete demographic studies have shown that smoking represents one of the largest risk factors for AD[41,46]. Smoking is also a risk factor for the cardiovascular disease, diabetes and stroke which are in turn are underlying risk factors for dementia[47]. The risk of developing dementia may be up to 70% higher in current heavy smokers than in non-smokers[48] beside this smoke also accelerate age related cognitive decline[49] .There is Significant correlations between whole brain volumes and smoking history. Smokers' brains have smaller cortical grey matter volumes and/or lower densities compared with non-smokers[50]. People smoking more than two packs a day were twice as likely to suffer from dementia than nonsmokers, even after controlling for age, sex, education, race, marital status, hypertension, alcohol use, body mass index and various other factors[51-53] .

Noting that an average smoker might smoke 10 cigarettes in a day, common sense might suggest that the nicotine delivered by a single cigarette is negligible, and that it is implausible that one cigarette could have a permanent impact on the brain. Yet, a PET study revealed that

nicotine obtained from 2 puffs of cigarette smoke was sufficient to occupy 50% of the brain's high affinity α4β2 nicotinic receptors (nAChR), while the nicotine from a whole cigarette occupied 88% of nAChRs[54]. This lends plausibility to the idea that one cigarette might have an important impact on brain physiology and animal behavior[55] by increasing oxidative stress and effect on cerebrovascular events[56] .

Lethal Ingredients of a Smoke and Brain Functions

One-third of people who have ever tried smoking become daily smokers. When individuals inhale cigarette smoke, either directly or second hand, they are inhaling more than 7,000 chemicals: hundreds of these are hazardous, and at least 69 are known to cause cancer. The chemicals are rapidly absorbed by cells in the body and produce disease causing cellular changes[9]. These compounds comprise five known human carcinogens and many toxic agents.

Cigarette smoke include deadly ingredients like Ammonia (Household cleaner), angelica root extract(known to cause cancer in animals), arsenic (used in rat poisons),Benzene (used in making dyes and synthetic rubber), butane gas (used in lighter fluid), Carbon monoxide (poisonous gas), Cadmium (used in batteries), cyanide (deadly poison, may cause nerve damage in cigarette smokers with optic neuropathy), DDT (A banned insecticide and a chemical used to destroy mosquitoes), Ethyl Furoate (causes liver damage in animals),Lead(Poisonous in high doses), formaldehyde (used to preserve dead specimens), methoprene (insecticide), Megastigmatrienone (chemical naturally found in grapefruit juice), Maltitol (sweetener for diabetics), Methane (It is a chemical coming out when the lighter is lit up), Napthalene (ingredient in mothballs), Methyl isocyanate (its accidental release killed 2000 people in Bopal, India in 1984), Polonium (Cancer-causing radioactive element).

These ingredients work synergistically and independentally as well to alter the normal brain physiology to escalate the progression of AD and seem far away from any beneficial effect on our system. It look apparent and obvious that the harmful effect of smoke are hundred times higher than the beneficial effect of a single ingredient nicotine, if there is any.

CO is one of the key ingredients present in the cigarette smoke and a cigarette smoker is exposed to an estimated 400 to 500 ppm of CO while actively smoking[57]. The pathophysiology of CO poisoning is due to cellular hypoxia imposed by replacing oxyhemoglobin with CO-Hgb and producing a relative anemia[58]. CO binds to hemoglobin with an affinity more than 200

times that of oxygen[59]. CO binds to many heme containing proteins other than hemoglobin, including cytochromes, myoglobin, and guanylyl cyclase. CO binds to cytochrome a3 in vitro[60], and the disruption of oxidative metabolism may lead to the generation of oxygen free radicals[61]. In the setting of smoke inhalation, concomitant cyanide toxicity may occur with CO poisoning[62]. Evidence indicates that exposure to carbon monoxide leads to birth weight deficits and may play a role in neurologic deficits (cognitive and neurobehavioral endpoints) in the offspring of smokers[12] .

Cigarette smoke also contains residues of pesticides. Tobacco is a sensitive plant prone to many diseases. It therefore requires high chemical inputs: up to sixteen applications of pesticide are recommended during one three month growing period. Some of the chemicals are absorbed by the plant and residues remain in the final tobacco product. A large community based study identified that occupational exposure to organochlorine pesticides was associated with dementia and AD[63]. Other pesticides that have not been used for years, such as DDT, may be found in tobacco due to the persistence of these chemicals in the soil where tobacco is grown[64]. The Environmental Protection Agency banned the use of DDT in the United States in 1972 because of concerns regarding its environmental persistence and potential effects on wildlife[65].

Serum levels of DDE, the metabolite of the organo-chlorine pesticide DDT, are associated with AD diagnosis and AD severity[66] as Serum levels of DDE were significantly higher in patients with AD [66], and that there was a significant association between DDE levels and a diagnosis of AD[67]. Further, a wide range of toxic metals are also found in tobacco, depending largely on the soil content where the tobacco was grown. The use of fertilizers has been blamed for high concentrations of arsenic, mercury, lead, cadmium, chromium, polonium, and beryllium in tobacco[68] .

Nicotine is the primary pharmacological agent in tobacco, with numerous complex actions[69]. Nicotine from the tobacco smoke influences the blood vessels causing vasoconstriction (due to increased quantity of released catecholamine). In addition to nicotine, tobacco smoke contains other vasoactive substances: endothelin, corticotrophin releasing factor, sodium-nitropruside, cadmium and prostaglandin[70] .When a person inhales smoke from a cigarette, nicotine is distilled from the tobacco and carried in the smoke particles into the lungs, where it is absorbed rapidly into the pulmonary venous circulation. It then enters the arterial

circulation and moves quickly to the brain. Nicotine diffuses readily into brain tissue, where it binds to nicotinic acetylcholine receptors (nAChRs), which are ligand-gated ion channels. Nicotine has been reported to be the highest and most toxic compound of aqueous extract of tobacco leaves[71,72] and has been shown to be the psychoactive substance in cigarette that accounts for both self-administration and reinforcement of drug taking behavior[73,74].

Research published in 2012 in the journal Neurology[75] suggested that wearing a nicotine patch might help improve memory loss in non-smoking older adults with mild cognitive impairment and this may be because nicotine stimulates receptors in the brain which are important for thinking and memory. However, whilst the association between nicotinic acetylcholine receptor (nAChR) dysfunction and cognitive decline in AD may yet have therapeutic potential a great deal of research is still needed. Cigarettes kill half of lifelong regular smokers, and of those an average of 22 years life expectancy will be lost[76]so research into protective factors is likely to focus on nicotine rather than tobacco smoking.

The alleged cognitive benefits are attributed largely to nicotine and its effects on the cholinergicsystem[77], a system whose function seems critical to maintaining memory[78]. As there are nicotinic acetylcholine receptors throughout the cholinergic system which can bind to nicotine, the idea of nicotine as a mechanism for aiding cognitive function is entirely plausible[79,80]. In the central nervous system, nAChRs are present both pre and post-synaptically on different neuronal subtypes and have a neuromodulatory function[81]. This property of neuronal nAChRs allows nicotine to have a secondary effect on virtually all neurotransmitter/neuromodulator systems in the brain. Thus nicotine influences a wide range of cognitive processes including sensory, motor, attention,executive, learning and memory functions[82]. Nicotine increase blood pressure in mother and reduce uterine blood flow, therefore decreasing a fetus's access to all nutrients. It is found that the most common effect of nicotine exposure is low birth weight[83]. Low birth weight is independently associated with cognitive deficits[84].

However, if nicotine actually does produce some protective effect among smokers or improves cognition in patients with Alzheimer's patients it could be administered through a patch other means[85]. Given the horrible health consequences from smoking, there would be no justification for delivering the nicotine through cigarettes to get any beneficial effects.

Further, nicotine consumption, while much less harmful than smoking, is associated with serious health risks, including hypertension and cardiovascular disease[86] .

Smoking Associated Cell Injury in Brain

In vivo chronic exposure of rat brain tissue to cigarette smoke significantly decreases membrane-bound ATPases, which alters ion homeostasis, and leads to increased Ca2+ and Na+ levels in the cytosol of various cell types[87], as well as increase Ca2+ in mitochondria, which is associated with neuronal injury or death[88]. Increased mitochondrial Ca 2+ secondary to cigarette condensate exposure is associated with damage to the inner mitochondrial membrane (e.g., membrane swelling) and vacuolization of the matrix. Importantly, nicotine delivered independently of cigarette smoke does not appear to produce these adverse affects[89].

Cigarette smoking has been revealed to cause structural changes to certain regions of the brain especially the apoptotic bodies in hippocampus[90]. In the temporal cortex, it has been reported that it could causes reduction in the total number of cells (expressed as reduced DNA) with hypertrophy of the remaining cells (increased total /DNA ratio)[91]. Further, exposure to cigarette smoke could accelerate the aging of the brain through inducing changes of synaptic proteins and pre-AD-like neuropathology.

Smoking and Neurotransmitter Dysfunction

Brains of patients with AD contain less dopamine, norepinephrine, and serotonin than usual[92,93]. Sub normal production of these neurotransmitters appears to be linked to the death of dopamine receptors and noradrenergic and serotonergic neurons, in the cortex and elsewhere in the Alzheimer's brain. Loss of the D2 receptor-enriched modules in the brains of Alzheimer's patients contribute to disturbances in information processing that may be responsible for cognitive and noncognitive impairments[94].

When compared to non-smokers, smokers brain cell receptors have been shown to have fewer dopamine receptors[95]. Dopamine is normally released naturally while engaging in certain behaviors like eating, drinking and copulation[96]. The release of dopamine is believed to give one a sense of reward. One of the leading hypotheses regarding the mechanism of addiction theorizes that the initial increase in dopamine activity from nicotine results initially in

pleasant feelings for the smoker, but the subsequent decrease in dopamine leaves the smoker craving more cigarettes[97].

There is increase of DA release in the striatum in response to smoking which result in positive reinforcing effects of nicotine. A reduced DA function is observed in smokers as it has been in other types of dependence[98]. Increases in norepinephrine and p-endorphin may be implicated in these effects as well[73]. There is auto-desensitization and resultant tolerance of the receptors to nicotine exhibiting an overall decrease in DA-D2 binding. We can correlate neurotransmitter outflow with the number of receptors. The relatively small binding changes reflect large changes in neurotransmitter outflow. The phenomenon can be explained on the basis of auto-desensitization[99].

The brain serotonin (5-HT) system has been demonstrated to play a major role in central nervous system (CNS) development, cognitive (memory and learning), and personality and behavioral modulatory processes. In fact, several neuropsychiatric conditions (e.g., obsessive compulsive disorder, anxiety, depression, schizophrenia, etc.) as well as impaired brain functions (e.g., sleep disorders, appetite, etc.) have been related to an altered serotonin (5-HT) system.

Symptoms of depression, aggression, anxiety and disturbances in food intake and sleep are common in AD and serotonergic impairment is well documented in these conditions[100] . According to studies by Teaktong et al., acute inhibition of serotonin neurons, which control a wide range of behavioral and physiological processes, is primarily related to an effect on nicotine receptors[101,102]. Pregnant Rhesus monkeys exposed to environmental tobacco smoke have clearly shown specific (5-HT) receptor deregulation in the developing neonates and suggest that this may be responsible for behavioral abnormalities associated with perinatal tobacco exposure[103].

Smoking and Amyloid Beta Induced Neuroinflammation

Amyloid beta(Aβ) is a short peptide that is an abnormal proteolytic by product of the trans membrane protein amyloid precursor protein (APP), whose function is unclear but thought to be involved in neuronal development. Amyloid beta monomers undergo a dramatic conformational change to form a beta sheet-rich tertiary structure that aggregates to form amyloid fibrils. The plaques and tangles of AD are confined largely to the cortical regions of

brain and show clear cut regional differences within the cortex. The entorhinal cortex and hippocampus are affected early and severely, followed by the medial temporal, parietal and frontal cortices[104]. Smokers had more neuritic plaques in the neocortex and the hippocampus than never smokers[105] and amount of plaques are directly correlated with amount of smoke exposure. Smoke exposure exacerbates the pathology by increasing the amount of amyloid plaques, promote formation and maturation of amyloid plaques[106]. Further, oxidative stress produced by cigarette smoke can modulate the activities of beta and gamma secretases and promote the production of Amyloid beta through a JNK-dependent pathway[107,108].

Another important hallmark of AD pathology is a chronic inflammatory response in the brain associated with amyloid deposition. This neuroinflammatory process manifests as an increase of reactive astrocytes and activated microglia[109].

Animals exposed to high doses of tobacco smoke exhibit a higher inflammatory response in hippocampus and cortex, and that this neuroinflammatory process is likely the result of higher amyloid deposition induced by smoking. Further, microglial activation and astrogliosis were found to be positively correlated with smoke exposure[106].

Smoke Exposure and Hyperphosphorylation of Tau

In AD abnormal aggregation of the tau protein, a microtubule-associated protein expressed in neurons is observed and nicotine use worsens the effects of tau, responsible for the fibrous tangles that are an indicator of the AD[110].

Tau protein acts to stabilize microtubules in the cell cytoskeleton. Like most microtubule-associated proteins, tau is normally regulated by phosphorylation. In AD patients, hyperphosphorylated tau P-tau accumulates as paired helical filaments that aggregate into masses inside nerve cell bodies known as neurofibrillary tangles and as dystrophic neurites associated with amyloid plaques[111].

Presence of amyloid deposits produced as a result of chronic smoking produces an increase in cellular oxidative stress, which in turn leads to a dysregulation in the activity of serine/threonine kinases, among others[112]. These kinases are involved in tau phosphorylation, inducing its hyperphosphorylation, which presumably leads to tangle formation[113].

Effect of Smoking on Synapse Functions

Synaptic degeneration is an early event in neurodegenerative diseases particularly in normal aging human subjects and AD patients[114]. The pathological manifestations of AD beside neuritic extracellular amyloid plaques and intracellular neurofibrillary tangles include reactive microgliosis, dystrophic neurites, and loss of neurons and synapses[115].

Synaptic proteins are essential components to maintain normal synaptic function. Synaptophysin is the most abundant synaptic vesicle protein and is often used as a marker for quantifying the number of intact synapses. Synaptophysin interacts with other synaptic proteins such as synaptobrevin to control the exocytosis of synaptic vesicle, hence the release of neurotransmitters[116]. Synapsin-1 is another presynaptic protein which regulates neurotransmitter release. Through changing its state of phosphorylation, synapsin-1 controls the fraction of synaptic vesicles available for release[117]. Chronic exposure to cigarette smoke decreased the expression of synapsin-1 and synaptophysin, which are signs of synaptic degeneration[118].

Debrin, a protein which is localized at the dendritic spine. Dysregulation of drebrin expression has been found in AD patients and subjects with mild cognitive impairment[118]. Actin filaments are the major cytoskeletal component in dendritic spine. Drebrin can bind to actin and inhibit its interaction with myosin, resulting in reduction of contractile force of actomyosin and thereby inhibit spine retraction. Overexpression of drebrin has been shown to alter spine shape[119,120]. Pathological changes of spines are highly correlated to synaptic plasticity, it is possible that the increased expression of drebrin would affect normal synaptic functions. Increased expressions of drebrin may have inhibitory effects on activity-responsive reorganization of spine structure, leading to a maladaptive rigidity of synaptic structure that could affect synaptic plasticity[121]. Chronic exposure to cigarette smoke leads to synaptic changes which are related to aging and cognitive impairment through interacting with synaptophysin,synapsin-1 and drebrin[122].

Smoking and Blood Brain Barrier

The blood brain barrier (BBB) has been shown to maintain brain homeostasis. It selectively excludes most endogenous and xenobiotic blood-borne substances from entering the brain, protecting it from systemic and exogenous influences[123,124]. The BBB dynamically responds to hemodynamic disturbances(e.g., focal ischemia), through free radical release and cytokine generation. It also plays a crucial role in protecting against neurotoxicity. Dysfunction of the

BBB is involved in the pathogenesis and progression of a number of neurological disorders including Alzheimer's disease and dementia[125].

Cigarette smoke has been shown to lead to cerebrovascular vasodilation through sympathetic activation. Nicotine activates nicotine receptors, which leads to the acetylcholine dependent release of NO from the vascular endothelium[126,127] through activation of endothelial nitric oxide synthase (eNOS)[128]. NO is one of the major endothelium-derived relaxing factors, which plays an active role in regulating microvascular tone and the cerebral blood flow under normal and pathological conditions[129]. Furthermore, NO has been shown to increase vascular permeability at the BBB thus impairing brain homeostasis and facilitating the passage of unwanted substances from the blood into the brain[128,130].

Cigarette smoke itself contains high concentrations of NO[131], which may affect the viability of the BBB. Nitric oxide is a critical factor that besides affecting the vascular tone also modulates platelet aggregation and leukocyte adhesion to the endothelium. At the BBB, NO plays an inhibitory role in the dynamic regulation of BBB function[132,133] and is involved in a variety of physiologic and pathological processes as part of the inflammation process itself[134]. Cigarette smoke can also modulate the level of NO by decreasing the activity of eNOS and promoting that of its inducible form (iNOS) [135] . The result is the initiation and progression of vasculo-pathogenic diseases such as atherosclerosis, thrombosis and ischemic like insults.

Further, Nicotine contained in tobacco smoke has been shown to negatively affect endothelial tight junctions [136] and the brain-to-blood Na+ K+2Cl− co-transporter located on the luminal surface of BBB[137]. Exposure to nicotine impairs BBB function. Nicotine decreases expression of ZO1, which is a critical component of a variety of tight junctional proteins and that of the Na, K, 2C co-transporter. This can lead to impaired BBB function and altered brain homeostasis[134]. The oxidative stress produced by smoking may also induce pinocytosis, thus increasing transcytotic activity across the BBB endothelium[138]but can also cause direct BBB breakdown (especially in conditions like stroke and traumatic braininjury[139]. This occurs by tight junction modification, local matrix metalloproteinases (MMPs) activation and basal membrane degradation[139]. ROS and nicotine act synergistically with other potentially harmful systemic stimuli (e.g., hypoperfusion of the brain vessels) to further impair both BBB function and integrity and leads to secondary brain damage[134].

Smoke and Hippocampus Damage

Much of the attention of nicotine research is centered on its addiction issues and less focus is placed on its neurotoxicity[140]. The pathophysiology of AD is related to the injury and death of neurons, initiating in the hippocampus brain region that is involved with memory and learning, then atrophy affects the entire brain[141].

The range of cognitive deficits associated with prolonged smoking includes deficits in psychomotor speed[142], verbal and visual memory[143], working memory[143] and executive function[144]. Researchers support an emerging pattern, where adolescence nicotine exposure elicits hippocampal cell damage leading to abnormality of synaptic receptors and correspondingly behavior abnormalities[140]. Hippocampus is the store house of memory, emotion and any damage to the hippocampal circuitry can lead to behavioral changes. A recent report indicated that activation of nicotine receptors by low dose nicotine resulted in apoptotic cell death in primary hippocampal progenitor cells[99]. Eventually there was down gradation of cholinergic receptors at the same region. At the same time one study explained cellular deterioration and neuronal loss on the basis of oxidative damage in lipid, protein and DNA of brain cells[145].

Smoking Associated Oxidative Stress

Oxidative Stress and Smoking

Age is the most significant risk factor for AD with an incidence that doubles every 5 years after the age of 65[38] . The process of aging is associated with increased oxidative stress[146] which plays a central role in the pathogenesis of AD leading to neuronal dysfunction and cell death[147]. Level of oxidative markers is directly related to the severity of cognitive impairment in AD[148].

Cigarette smoking is an important environmental aging accelerator[149] because it induces oxidative stress in multiple organs including the brain [150] . A major exogenous source of free radicals in cigarette smoke is a heterogeneous aerosol consisting of high concentrations of free radicals, reactive oxygen and nitrogen species. These reactive radicals modify biomolecules through oxidation reaction, resulting in defective cellular signaling and accumulation of malfunctioned proteins [151] .

Tobacco smoke contains very high levels of superoxide and other reactive oxygen species causing damage macromolecules[152] including lipoperoxidation of polyunsaturated fatty acids

in membrane lipids, protein oxidation, DNA strand breakage[152,153], RNA oxidation[154], mitochondrial depolarization and apoptosis. Mutations of the nuclear protein p53 which may lead to apoptosis are also associated to tobacco smoke toxicity. Specifically to direct DNA damage from carcinogens contained in cigarette smoke[155] . In vivo and in vitro studies have shown that antioxidant supplementation prevents, to some extent, the oxidative damage and inflammation induced by cigarette smoke exposure[156,157].

Accumulation of reactive oxygen species in AD lead to mitochondrial dysfunctions and extracellular amyloid β (Aβ) deposits. Binding of redox active metals to Aβ deposits can induce a direct reaction of hydrogen peroxide formation[158]. Thus, free radicals can be produced by mitochondrial biochemical reactions, by microglial activation, generated by β amyloid plaques, but also in inflammatory reactions that have been identified in brains affected by dementia[159]. In addition, β-amyloid has the ability to destabilize lysosomal membranes, resulting in cell death. These findings show a clear link between oxidative stress and pathogenic macroautophagal processes in AD[160]. The oxidative stress lead to change of composition of neuronal fat molecules, altering membrane fluidity and permeability and disturbing some of the membrane functions, such as transport and barrier-like functions. The consequences of these disturbances are directed mainly towards the traffic of Ca 2+ ions that cross the membrane structure, with the alteration of the signal transduction processes[161]. Oxidative stress may act on genes influencing their activity. Thus, some genes, like the E4 allele gene on chromosome 19, can be stimulated in the context of increased oxidative stress, leading to in-creased expression of E apolipoprotein, with negative effects on neuronal plasticity processes, such as learning and memory, which are, of course, seriously affected in AD[162].

Antioxidant Enzymes and Smoking

The sustained release of reactive free radicals from the tar and gas phases of smoke imposes an oxidant stress, promotes lipid peroxidation and consequently perturbs the antioxidant defense system in the blood and tissues of smokers[163] .

There is increased free radical damage in the cerebral cortex in both smoker and AD patients[164] and in vivo chronic cigarette smoke exposure is also associated with decreased enzyme-based free radical scavenger (e.g., superoxide dismutase, catalase, glutathione reductase) and non-

enzyme-based radical scavenger (e.g., glutathione and vitamins A, C and E) concentrations in rat brains[165] and higher levels of oxidative stress markers (malondialdehyde)[166].

The obligatory use of the body's reserve of antioxidants to detoxify the tremendous level of these free radicals in smokers therefore results in severe antioxidant deficiency status, thereby predisposing them to the development of life threatening diseases. Further, this deficiency in smokers maybe enhanced by their generally lower intake of both supplementary and dietary antioxidants[167].

Further, the activity of ceruloplasmin, and the levels of zinc and selenium were significantly decreased exposed to cigarette smoke[165].Regarding selenium, another antioxidant, studies have noted a decrease in its serum levels correlated with cognitive decline. However, extensive analysis on the usefulness of selenium in dementia demonstrated a lack of consistent clinical evidence to support the benefit of selenium supplementation in patients with Alzheimer's, and the absence of a significant decrease in brain, CSF, or blood selenium in patients with AD[168]. Still, other studies support a critical role of selenium in disease pathogenesis, suggesting a role[169,170] .

The quinone semiquinone radicals from the tar phase of cigarette smoke are capable of reducing molecular oxygen to superoxide radicals whose excessive generation inactivates SOD, an enzyme SOD is the first enzyme in antioxidant defense that scavenges superoxide radicals to form H 2 O 2 and hence diminishes the toxic effects of the radical[171]. Catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GR) levels CAT is involved in the detoxification of high concentrations of H2O2 , whereas GPx is sensitive to lower concentration. The brain contains less CAT levels and hence GPx has a major role in quenching H 2 O 2 and other peroxides which otherwise will lead to the production of hydroxyl and peroxyl radicals in the presence of iron[172] . Inhibition of CAT activity in rat brain and liver by cigarette smoke has been reported[173] . The presence and production of the free radicals from smoke lower this enzyme, leading to accumulation ofH2O2 and lipid hydroperoxides further worsening the damage[174].

Smokers are constantly overexposed to free radicals through inhalation of long-lived carbon- and oxygen centered radicals that subsequently deplete the plasma and tissue stores of micronutrients[175]. The activity of ceruloplasmin, and the levels of zinc and selenium were significantly decreased exposed to cigarette smoke[165]. *In vitro* exposure of plasma to cigarette

smoke resulted in the destruction of tocopherols, carotenoids, and retinol. The levels of trace elements like zinc and selenium in brain were decreased upon exposure to cigarette smoke. Zinc, the cofactor for the enzyme SOD has been shown to protect the brain during ischemia or hypoglycemia[176]. Selenium functions as an important nutrient of the brain and being a component of GPx, it plays a major role in preventing free radical mediated cell damage[177]. Cadmium, the heavy metal from tobacco, decreased the bioavailability of selenium and zinc and hence depletes the antioxidant status[178].

Conclusion

Tobacco use and dependence are by products of a large, complex web of socially accepted (unfortunately) environmental and genetic influences. Neuronal function and integrity is highly affected by the toxins contained in cigarette smoke, which may have implications for long-term neuronal function and survival. The literature reviewed in the presents work suggests that smoking increases amyloid deposition, neuroinflammation, tau hyperphosphorylation and synapse loss. Smoking also exacerbates gliosis, induce microglial activation, astrogliosis through cerebrovascular mechanism including change in integrity of blood brain barrier. Majority of adverse neurobiological and neurocognitive effects of chronic cigarette smoking are a function of the direct and indirect consequences of continual exposure of the cardiopulmonary system, cerebrovascular system and brain parenchyma to the combination of non-nicotine combustion products contained in cigarette smoke. International Anti-Smoking Day celebrated on 31st of May memorize us the pledge to spread awareness regarding the disastrous and life threatening consequences of smoking on human health.

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