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Review

Cigarette smoke and related risk factors in neurological disorders: An update

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ABSTRACT

Cigarette smoking is known to be harmful to health, and is considered the main cause of death worldwide, especially in India. Among the well-distinguished diseases related to smoking are, chronic obstructive pulmonary disease, oral and peripheral cancers, and cardiovascular complications. However, the impact of cigarette smoking on neurocognitive and neuropathological effects, including anxiety, Alzheimer's disease, Parkinson's disease, ischemic stroke, and blood-brain barrier dysfunction, still remains unclear. Cigarette smoke consists of more than 4500 toxic chemicals that combine to form free radicals, which lead to oxidative stress-associated neurological disorders. Herein, we discuss the role of antioxidant agents in delaying or attenuating disease complications. In addition, in this review, we discuss the neuropathological effect of cigarette smoke and its interference in neurodegeneration.

Contents

1. Introduction

The predicted correlation relationship between smoking and the development of neurological diseases has always been controversial for years. Finally, at the end of 1980s, researchers proved and reached a conclusion that smoking definitely confers the risk of ischemic stroke. More recently, other neurological diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD) have also been studied in relation to smoking. Smoking is practiced by using flaming tobacco and inhaling the smoke. Smoking has been broadly studied in association to diverse neurological disorders (NDs), mainly vascular and degenerative diseases such as AD, Parkinson's disease, anxiety, and stroke [1]. The detailed epidemiological study of Ezzati and Lopez [2] showed

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a positive correlation between cigarette smoking and the risk of ND [2]. Recently, many researchers have investigated the effects of smoking on cognitive functions. Most of these studies showed a decline in cognitive function that is attributed to the effects of cigarette smoke exposure [3,4].

Reports worldwide suggest that about 16 million people experience serious poor health issues caused by smoking. Indeed, each person who dies from smoking-related causes creates a health issue that about 30 more people have at least one serious smoking-related illness (http://www.cdc.gov/tobacco/data_statistics). A recent statistical data from the World Health Organization on the percentage of cigarette smoke exposure revealed that India is the second leading country (14.6%) in the world in terms of habitual smoking. Literature allied to tobacco-related illnesses suggest that these diseases remain the foremost cause of avertable death, with approximately 430,000 annual deaths in the United States and roughly about 4 million annual deaths worldwide. Up-to-date projections imply that tobacco use threatens 10 million lives every 12 months by 2030, especially in developing countries with 70% mortality [5,6]. A recent statistical report published in *Hindustan Times* revealed that 1 million people die because of cigarette smoke exposure in India every year. Cigarette smoke mete out huge damage to the health of Indian people, which could be increased up to 1.5 million by the year 2020 (Sanchita Sharma, *Hindustan Times*, New Delhi Updated: Apr 01, 2015 12:43 IST) [7].

2. What does cigarette smoke consist of?

Cigarette smoke generates a complex mixture of chemical compounds produced by the burning of tobacco pieces inside the cigarette. Cigarette is made up of more than 7000 lethal compounds that are harmful to active and passive smokers [8]. The chemical composition of cigarette smoke consists of both organic and inorganic compounds (Fig. 1), which is collectively known as tar. Tar is a harmful complex gas composed of carbon monoxide (CO), hydrogen cyanide, nitrogen oxides, acetaldehyde, benzene, aromatic amines, formaldehyde, benzo[α]pyrene, beryllium (a toxic metal), ethylene oxide, 1,3-butadiene (a hazardous gas), cadmium (a toxic metal), vinyl chloride, chromium (a metallic element), cumene, nickel (a metallic element), polonium-210 (a radioactive chemical element), polycyclic aromatic hydrocarbons, tobacco-specific nitrosamines, and a wide range of other chemicals present in cigarette smoke that condensate quickly in the lungs. Earlier reports suggest that these chemicals have long- and short-term effects on health. The most important inflammation pathway was reported to be the generation of high levels of reactive oxygen and nitrogen species (ROS/RNS) and other toxic metabolites [9].

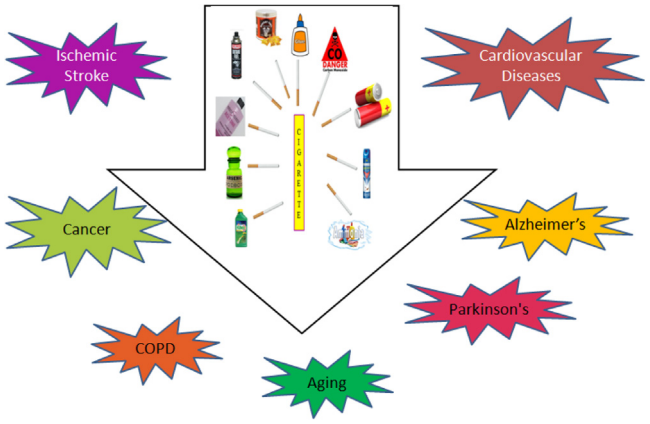

Fig. 1. Toxic components of cigarette smoke-induced disorders.

Among these compounds, nicotine is well known to be the primary compound in cigarette, which is responsible for addictiveness. Once the person inhales the smoke, nicotine provides an immediate "kick" due to the discharge of epinephrine. This quick expulsion triggers the central nervous system (CNS) to release glucose in the body. Although nicotine was first recommended as a medical drug for the treatment of rodent ulcer and constipation, each puff of smoke contains over 10 trillion free radicals, which results in degeneration [10] due to initiation and repeated attacks of ROS on cellular macromolecules. Besides, cigarette smoke contains a dozen gases, including carbon monoxide, nicotine, and tar. Carbon monoxide is reported to have an effect on the CNS and people with cardiovascular diseases. When cigarette smoke is inhaled, CO will combine with the blood cell to form COHb and circulate in the body system much faster than oxygen. Therefore, the amount of oxygen in the blood is reduced drastically, causing a hypoxic state. Furthermore, CO binding also alters the dissociation curve of oxyhemoglobin, resulting in the low rate of oxygen release in the cell. Thereby, many tissues that require large amounts of oxygen, including the brain and heart, are more severely affected by CO poisoning [10]. The brain is particularly vulnerable to oxygen, more specifically the hippocampus. Hence, persons with the habit of cigarette smoking may experience memory loss and other cognitive impairments. Apart from the binding to hemoglobin, it also activates a biochemical cascade that can contribute to cell damage even after termination of CO exposure [11,12].

3. Impact of cigarette smoke on general health

Smoking has long been known as hazardous to health. Several recent research communities claim that smoking is a major risk factor of the killer brain disease and a host of other chronic conditions. Cigarette smoke causes significant human health issues and economic burden worldwide. Chronic obstructive lung disease is the most important lung disease caused by cigarette smoke. In addition, cigarette smoke is also associated with respiratory bronchiolitis, interstitial pneumonia, buildup of poisonous substances in the lungs, permanent damage to the air sack, increased blood pressure, increased heart rate, risk of stroke and cardiac arrest due to blockage of blood supply and type 2 diabetes mellitus [13]. To date, smoking is supposed to be the most certain cause of death in India. Moreover, smoking is also reported to enhance the risk of NDs such as ischemic stroke, AD, depression, cognitive impairment, and vascular dementia [14]. These pathological and physiological changes of the brain are suggested to be possibly due to the excess generation of ROS and RNS, which promotes inflammation and apoptosis. However, the pathophysiological mechanism underlying these NDs remains elusive [15–17].

3.1. Effect of cigarette smoke on depression and anxiety

Cigarettes and other forms of tobacco are readily absorbed into the blood stream while inhaled or smoked. A brief review of both active and passive smokers revealed that a typical smoker takes 10 puffs on a cigarette for 5 min. Therefore, a person who smokes 1 pack of cigarette gets 250 hits of nicotine each day. In the last several decades, an interest among researchers has increased in understanding the fundamental cellular and physiological mechanisms underlying the effects of cigarette components on behavior and cognitive functions [18]. Nicotine absorbed in the bloodstream immediately stimulates adrenal glands to release the hormone epinephrine, which is the ultimate hormone that activates the CNS. Activation of the CNS leads to an increase in blood pressure, respiration, and heart rate.

Researchers who studied cigarette smoke-induced brain damage revealed that nicotine build up an immediate sense of

relaxation that helps in the reduction of stress and anxiety. However, in reality, it increases anxiety and depression. Moreover, parallel to other addictive drugs (cocaine and heroin), nicotine releases a neurotransmitter called dopamine, in the brain. Dopamine triggers an optimistic feeling in smokers and affects the brain pathway that controls reward and pleasure [19]. As a small amount of data revealed that cigarette smoke can reduce anxiety in some smokers, the correlation between smoking and anxiety is complicated. Generally, smokers often report augmented anxiety post smoking termination, but modern data conflict with this finding. Both anxiety and smoking behaviors have significant heritability [20]. Recent studies showed that persons with smoking habits exhibited a significant high rate of anxiety disorder, and several studies support the correlation between cigarette smoking and psychiatric disorders [21].

3.2. Effect of cigarette smoke on promoting AD

Alzheimer's disease (AD) is the most familiar type of dementia, a medical condition characterized by progressive worsening of cerebral functions such as memory, language, reasoning, decision making, attention, and orientation. AD pathology is characterized by the selective loss of nicotinic acetylcholine receptors (nAChR) and elevated amyloid-β (Aβ) deposition in hippocampus and neocortex. Prominently, the cognitive and behavioral changes that occur with dementia were found to disrupt work, social activities, and relationships and impair a person's ability to perform routine daily activities [22,23]. Research findings on smoking-related NDs also bring into attention that smoking can directly induce cognitive impairment [24,25]. In a few other studies with young adults revealed that smokers were inferior to nonsmokers in terms of measures of continuous attention and impulse control [26] oral arithmetic, receptive and expressive vocabulary, auditory-verbal memory [27], information processing speed and general intelligence [28]. Besides, an experiment on behavioral measures of balloon analogue risk task revealed an increased level of risk taking in young adult smokers [28]. Furthermore, an ultimate poor performance was noted in smokers for learning and/or memory [29–32], working memory [33], executive functions [34,35], processing speed and cognitive flexibility.

AD a severe cause of dementia and affects approximately 5.2 million Americans in the year 2013. Chronic smoking is coupled with an augmented threat for various forms of dementia, specifically AD and vascular dementia. This risk may be amended through the apolipoprotein E ε4 (ApoE4) genotype, a known genetic risk factor of the development of AD [36]. It is interesting that few other studies have also reported that smokers who were not ApoE4 carriers possessed a high risk of the development of AD [37,38]. Generally, AD was characterized by the accumulation of misfolded amyloid-β (Aβ) to form senile plaques and neurofibrillary tangles (Fig. 2). For several years, smoking was considered as a protective agent for the development of AD. Acute activation of neuronal nicotinic receptors was proposed and believed to have favorable effects in people with AD [39–41]. However, more recently, aging and APOE genotype were reported to be possibly interacted with other latent genetic or amendable environmental risk factors to boost AD-related pathogenesis and increase the risk of AD [42,43].

The most important subunit of nAChR (nicotinic acetylcholine receptor) in the central nervous system is α7nAChR which was

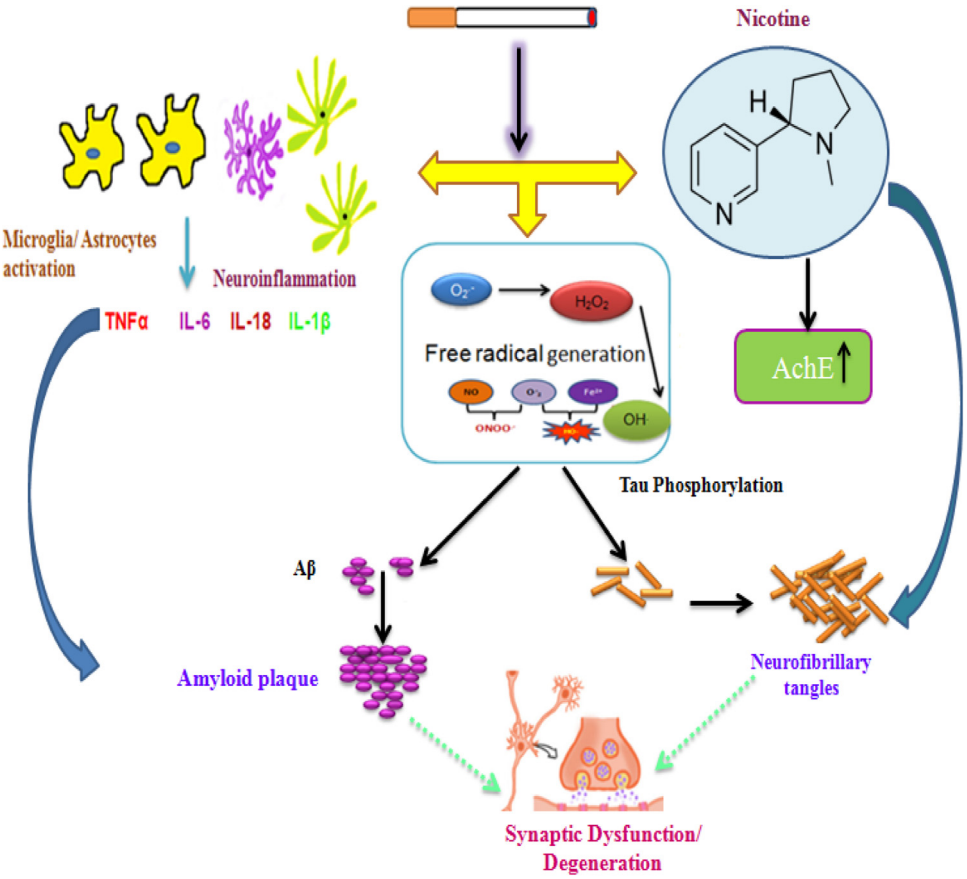

Fig. 2. Potential pathway and mechanism behind cigarette smoking-mediated Alzheimer's disease in humans and animals. Free radicals from the cigarette smoke provoke oxidative stress and inflammation that lead to synaptic dysfunction and neurodegeneration of the brain.

often co-localized with Aβ deposition in the neuritic plaques of AD cortical neurons. It plays a fundamental role in the development of dementia *via* triggering cholinergic neurotransmission. However, elevated Aβ bind s to α7nAChR with high affinity and inhibits neuroprotective activity leading to synaptic dysfunction/degeneration. α7nAChR is encoded by *CHRNA7* gene on chromosome 15q13–14, which directly connected to neuropsychiatric disorders, including bipolar affective disorder, schizophrenia, parkinsonism, several types of epilepsy, and autism (Fig. 2). Moreover, histopathological studies showed that smokers have more-severe neuropathological variation, including neurofibrillary changes and neuritic plaques, than nonsmokers [44–46]. The results of the study of Moreno-Gonzalez et al. [47] suggested that, the effect of cigarette smoke on the onset of brain alterations had proved that smoking increases amyloid deposition in a dose-dependent manner, which leads to the formation of senile plaques. Besides smoking aggravates gliosis, including microglial stimulation and reactive astrogliosis, in mice exposed to a high dose of cigarette smoke. The mechanism underlying the increased risk of AD in smokers remains unclear, but many researchers have hypothesized that this effect may be through direct induction of protein misfolding and aggregation by the toxic components in cigarettes, boosted stimulation of oxidative stress, cerebrovascular damage, inflammation, and so on.

3.3. Dysfunction of the blood-brain barrier

The lethal effects of cigarette smoking on the blood-brain barrier (BBB) have been confirmed by various experimental models. In spite of its crucial value, the effects of smoking on the BBB have been marginally addressed. Relation between cigarette smoke and BBB has been limited to a handful of substances among the massive number of substances found in cigarette smoke. Circulation of endothelial cells is an indicator of vascular damage by various stressors [48]. The scientific research by Huang et al. [49] exhibited an increase in blood circulation in a specific BBB (brain microvascular endothelial cell) after nicotine treatment. In addition, an increased cerebrospinal fluid-to-albumin ratio was found to be a sign of increased BBB permeability. Any disorder that affects the BBB function might have secondary effects on cerebral blood flow [50]. Cigarette smoking was found to lead to cerebrovascular vasodilation through an acetylcoline-dependent release of a harmful free radical such as nitric oxide. BBB dysfunction due to cigarette smoking is associated with the pathogenesis of various NDs, including stroke, multiple sclerosis, AD, dementia, and epilepsy. When a cigarette puff is inhaled, a huge amount of soluble and gaseous components contained by the smoke quickly pass through the lung alveoli into the arterial circulation and promptly reach the brain microvasculature. It is quite natural that the brain parenchyma is effectively defended from the smoke toxicants circulating in the blood by the BBB. However, chronic exposure to these substances may impact BBB viability and function overtime (e.g., chain smokers). A functionally compromised BBB can then enable the onset and/or progression of neuroinflammatory and neurovascular disorders which in turn can kick off a vicious cycle of continued BBB impairment [51].

The effect of cigarette smoke on an *in vitro* slow-based BBB showed an obvious up regulation of various proinflammatory genes and considerable increases in the levels of the serum proinflammatory mediators IL-1β, TNF-α, MMP-2, and MMP-9. In addition, Hossain et al. [52] found that coupling of flow cessation/reperfusion revealed a significant increase in the loss of BBB integrity and the individuals with the habit of cigarette smoking have been shown to possess modulated tight junction proteins in the BBB [14]. Similarly, Hawkins and coworkers confirmed that nicotine down regulated the expression of the ZO-1 tight junction protein in the BBB, the follow-on of increased permeability [53]. Furthermore, many other scientific communities revealed that nicotine alters the function of the BBB $Na^{+-}K^{+-}2Cl^{-}$ co transporter through mediation of α7nAChR [54–56].

3.4. Effect of cigarette smoke in ischemic stroke

Smoking virtually doubles the risk of ischemic stroke than nonsmokers. The more a person smokes, the greater that person's risk of stroke. Individuals who smoke around 20 cigarettes per day are six times more likely to have a stroke than nonsmokers. Approximately 50% of the population was affected by stroke due to cigarette smoke from direct or second-hand smoking [57].

The CO in cigarette smoke was found in exhaust fumes of vehicles. When inhaled, it removes the vital oxygen present in the blood vessels. CO combines with hemoglobin in red blood cells throughout the body since it carries oxygen [59]. Indian National Brain Research Center revealed that the chemical compounds present in cigarette smoke aggravates the white blood cells in the CNS to collide with healthy cells, which leads to severe neurological damage. Increased carbon monoxide level in the blood leads to damage of the artery walls and platelets there by affecting the adhesiveness of blood. Hence, the injured arteries become more narrow and "furred up," which reduces the blood flow through them and blood clots are formed, leading to atherosclerosis. A clot in an artery causes blockage of blood supply to the brain, causing ischemic stroke. In addition, smokers are more expected to develop high blood pressure, which is a major risk factor of stroke. A statistical report suggested that smokers with high blood pressure are 15 times more likely to have a subarachnoid hemorrhage than nonsmokers and those who do not have high blood pressure [60].

Vayssier-Taussat et al. [58] revealed that a high risk of stroke provoked by smoking has been attributed to both procoagulant and atherogenic effects. In particular, research by Vayssier-Taussat et al. [58] reported that smoke led to dose-dependent oxidant-mediated stress responses and cell death of vascular endothelial cells and circulating monocytes. Cigarette smoke and its harmful components affect the body's cholesterol level by reducing high-density lipoprotein cholesterol (good cholesterol) and increases low-density lipoprotein (bad cholesterol) level. Low levels of "good" cholesterol increase the risk of stroke. The report of Vikman et al. [62] also suggested that activation of the p38 mitogen-activated protein kinase-mediated inflammatory signaling pathway after the treatment with dimethyl sulfoxide-soluble cigarette smoke particles in rat middle cerebral and basilar arteries revealed an affiliated upregulation of metalloproteinase 13 (MMP13) at both transcriptional and protein expression levels [61,62]. Many research studies have been conducted on animal models exposed to cigarette smoke showed an activation of nuclear factor-κB (NF-κB), with increased release of IL-1β, TNF-α, and MMP-2/9 .On the other hand, activation of NF-κB is well known to lead to inflammation and inducing cerebral aneurysm development. Altogether, these findings suggest that cigarette smoke facilitates oxidative damage that leads to cell degradation [63,64].

Ischemic stroke is likely to induce a stronger inflammatory response in smokers than in nonsmokers. The relationship between cigarette smoke exposure and the onset of silent cerebral infraction (SCI) is well known to be comparable with that of cerebrovascular risk factors such as hypertension [52]. The risk of stroke is significantly decreased 3 years after termination of smoking and is at the level of that of nonsmokers after 5 years. Thus, we can recommend that individuals should be encouraged to quit smoking by mass media campaigns and increased cost of tobacco products. In addition, strong evidence indicates immediate

health benefits for both men and women after termination of smoking before the age of 35 years [59].

4. How cigarette smoke exposure generates oxidative stress

ROS/RNS are highly reactive in nature and can interact with molecules containing oxygen atom to proliferate the generation of other free radicals. This imbalance between free radicals and antioxidant agents is said to be an oxidative stress/insult. Each puff of cigarette smoke has 10^{15} free radicals that damage the micromolecules and macromolecules of the body systems, especially the lungs and brain. The major free radicals through cigarette smoke are O_2^- and NO, which combine to form peroxynitrite [65,66]. Owing to the accumulation of these free radicals, tissues are indented to deplete antioxidants such as ascorbic acid and protein sulfhydryl groups, causing the oxidation of DNA, lipids, and proteins. This accumulation of ROS in tissues might be due to an increase in oxidant generation, a decrease in antioxidant defense agents, or failure to repair oxidative damage [67,68]. Researchers could find heterogeneous effects of cigarette smoke in the brain through neuroimaging and neuropathological studies. In addition, smoking apparently causes damage to endothelial cells, which results in high threat of cerebrovascular disease. Even though nicotine shows a neuroprotective effect in animal models, the hazardous effect of other toxic compounds present in cigarettes cannot be ignored.

Nuclear factor-like 2 (Nrf2) is a well-studied and reported transcription factor that plays a vital role in countering oxidative stress [69,70]. Generally, it is maintained at a low level in the cytoplasm. During an oxidative stress insult, Nrf2 freely translocate from the cytoplasm to sub cellular organelles into the nucleus. However, when Nrf2 binds with an antioxidant response element, it triggers the downstream genes involved in detoxification and antioxidant processes [71–73]. The effect of cigarette smoke-induced oxidative stress might become exaggerated with aging and AD [74,65]. As mentioned earlier, a significant number of latently toxic compounds that is present in the gas and particulate phases of cigarette smoke may also directly interact with neuronal cells and thereby promote oxidative imbalance [74,75]. Carbon monoxide (CO) levels were found to be significantly higher in smokers, which ultimately associate with a lowered effect on hemoglobin concentrations and a diminished effectiveness of the mitochondrial respiratory chain [76,77]. Aβ toxicity in AD is accredited due to histidine residues at position 6, 13 and 14 which are the structural site for transition metal coordination. $Cu^{2+}$and Fe^{3+} binding produces toxic chemical effect thatalters the oxidation state of both the metals, thereby producing H_2O_2 catalytically in the presence of transition metals. Thus the reaction finally provides toxic $OH^{\bullet}$ free radicals. It is interesting to note that Aβ plaques was considered as the toxic species which is responsible for AD, but current research reports suggest Aβ is a physiological antioxidant and this property is modified due to aging. This particular property may be used as potent therapy for AD in future [78]. Where as in PD, dopamine is reputed as an excellent neurotransmitter but at the same time it is a good metal chelator and electron donor that set *in vivo* conditions for redox metal chemistry in generating toxic free radicals. It highly co ordinate with Cu^{2+} and Fe^{3+} and reducing metals to kick off

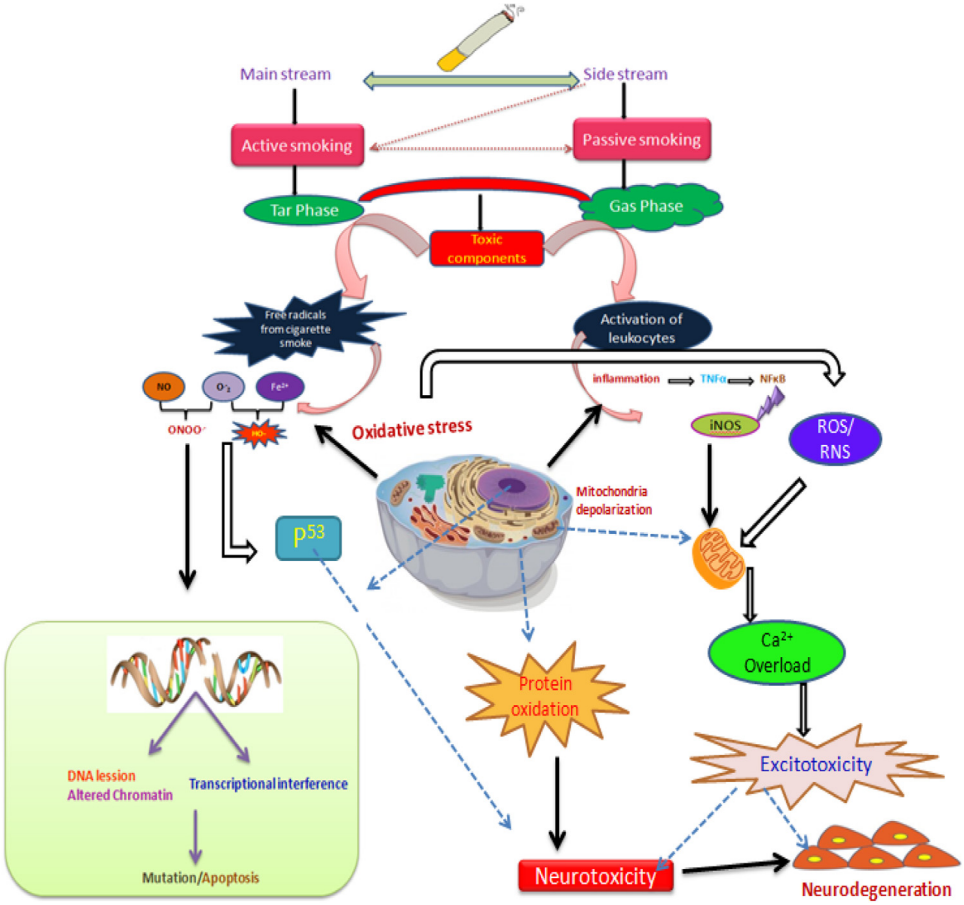

Fig. 3. Cigarette smoke-induced oxidative stress and cellular inflammatory response. Schematic illustration of exposure to reactive oxygen species derived from cigarette smoke through multiple pathways that lead to cellular damage and inflammation.

Fenton's chemistry in generating hydrogen peroxide radicals. Unregulated iron metabolism and Free radical production have been recognized as major player in pathogenesis of neurodegenerative disease. Generally, high lipid content generated by myelin and oligodendrocytes encourage considerable accumulation of iron and other metals while redox metals acts as catalytic center for this lipid factory. Deposition of iron plaque over myelin sheath appeal to an inflammatory response eliciting recruitment of inflammatory cell which enters the CNS to cause substantive damage and demyelination [79].

During metabolism or diseased condition, apart from reducing NO availability, superoxide oxide anion in combination with NO generates peroxynitrite that further boosts cellular oxidative stress. The vital role of NO is to control vascular tone, endothelial adhesion, and platelet aggregation. Earlier reports provided evidence that NO is involved in BBB modulation and pathological processes innate to inflammation [80]. In general, oxidative damage through ROS/RNS is well known to further trigger inflammation and apoptosis *via* cytokine-mediated immune response and caspase release. During this activation, anti-inflammatory, proinflammatory cytokines (TNFa, IL-1, and IL-6), anti-apoptotic agents were also triggered by peripheral and CNS cells (e.g., microglia and astrocytes) [81]. Release of excess free radical and inflammatory cytokines triggers the production of iNOS. This process activates the glutamate receptors resulting in the surplus production of glutamate. Overload of glutamate in the synapses will allow more calcium intake in to the mitochondria and other macromolecules leading to mitochondrial dysfunction and DNA lessions. As a result, cells undergo damage by ROS induced alterations of macromolecules. These alterations include lipoperoxidation of polyunsaturated fatty acids in membrane lipids, protein oxidation, DNA strand breakage, RNA oxidation, mitochondrial depolarization and apoptosis. Furthermore, mutations of the nuclear protein p53 which may lead to apoptosis are also associated to cigarette smoke toxicity [Fig 3]. Many reported scientific data show that elevated proinflammatory cytokine levels are associated with cerebral oxidative stress and apoptosis *via* production of ROS and other inflammatory mediators in the brain [82,83].

The human body has inherent antioxidant mechanisms. Generally, under normal conditions, these reactive free radicals/ROS are shattered by the body's defense agents such as superoxide dismutase, catalase, glutathione peroxidase, or (extracellular) antioxidant vitamins such as ascorbic acid (vitamin C), and α-tocopherol (vitamin E). Indeed, the existing scientific observation believes that ROS-mediated pathways contribute significantly to the pathogenesis of numerous NDs. This proposition is powerfully supported by *in vivo* and *in vitro* experiments in which oxidative damage/injury and inflammation induced by cigarette smoke were significantly attenuated by antioxidant supplementation [84,48]. In support of this hypothesis and scientific report, the Food and Nutrition Board of the National Academy of Sciences recommends greater intake of high dietary vitamin C for smokers than for nonsmokers. Nevertheless, many experimental studies have been conducted and revealed a number of contrasting results from *in vitro* and/or *in vivo* studies regarding the therapeutic effect of antioxidants in a number of neurodegenerative disorders [85–87]. In the studies of Hossain et al. [88] and Cherubini et al. [89], the authors proved that supplementation of antioxidant-rich compounds exhibited a beneficial effect on ischemic stroke, loss of BBB integrity, and inflammatory response in smoke-exposed BBB culture.

5. Neuropathological effect of cigarette smoke exposure

Cognitive and behavioral modifications in reaction to prenatal cigarette smoking were found to result from the chronic effect of nicotine, and high concentrations of carbon monoxide and other toxic components of cigarette smoke. Scientific data evidenced the neuropathological alterations in animal models of prenatal cigarette smoking [90,91]. In addition, Jacobsen and colleagues revealed an improved fractional anisotropy in diffusion tensor images of anterior cortical white matter and the anterior limb of the internal capsule in adolescents with prenatal cigarette smoking when compared with nonsmokers [92,93]. Furthermore, female adolescents exposed to cigarette smoke had smaller corpora callosa than those not exposed to cigarette smoke. For a long time, free radicals from the tar of cigarette smoke are believed to accumulate from hours to months when compared with the gas phase. They are involved in the elevation of Ca^{2+} and Na^{+} levels in cytosol and mitochondria. The excess influx of Ca^{2+} in mitochondria (excitoxicity) leads to neuronal injury. Overload of calcium in the mitochondria causes the membrane to swell and burst. The release of micro molecules and macromolecules in cytosol activates neurodegeneration [37]. The studies by Abreu-Villaca et al. [94] and Slotkin [95] explored that, administration of nicotine separately in rats did not exhibit much pathological effect in the brain, but taken together, these structural and functional alterations in the frontal and cerebellar sections explain the high risk of developing NDs in smokers and prenatally cigarette smoke-exposed children.

6. Conclusion

In the present review article, we summarize and present the effects of cigarette smoking in brain neurobiology and neurocognition. Many fundamental studies that dealt with the crucial issue showed that cigarette smoke exposure impacts neurological damage by promoting oxidative stress and inflammation. Even though scientific evidence and experimental studies have noticeably revealed that cigarette smoking is a key risk factor for the pathogenesis of a number of neuroinflammatory and neurovascular disorders, detailed toxicological and mechanistic studies that explain the commencement of these abnormalities have yet to be conducted *in vitro* or *in vivo*. We hope that this review encourages more investigations on how cigarette smoking affects the human brain.

Conflict of interest

The authors declare that there is no conflict of interest.

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