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REVIEW

Neuropathology of cigarette smoking

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Abstract It is well established that cigarette smoking is hazardous to health and is a risk factor for many chronic diseases. However, its impact on the brain, whether it be from prenatal exposure to maternal cigarette smoking, cerebrovascular disease, Alzheimer's disease (AD) or Parkinson's disease, is still not very clear. Neuroimaging and neuropathological investigations suggest that there are heterogeneous effects of cigarette smoking on the brain. On the one hand, it is quite clear that cigarette smoking causes damage to endothelial cells, resulting in increased risk of cerebrovascular disease. On the other hand, it seems to be associated with different Alzheimer's pathologies in post-mortem brains and experimental models, despite the fact that epidemiological studies clearly indicate a positive correlation between cigarette smoking and increased risk for AD. Interestingly, cigarette smoking appears to be associated with reduced Parkinson's pathology in post-mortem brains. However, although nicotine in cigarettes may have some neuroprotective actions, the effects of all the other toxic compounds in cigarettes cannot be ignored. It is, therefore, our aim to summarize what is known about the neuropathology of cigarette smoking and, in particular, its implications for neurodegenerative diseases.

Keywords Cigarette smoking · Atherosclerosis · Neurodegeneration · Alzheimer's disease · Parkinson's disease · Prenatal exposure to maternal cigarette smoking

Introduction

Cigarette smoking is known to be a major risk factor for many chronic diseases. According to a report by the World

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Health Organization (WHO), tobacco use is the second most significant risk factor for the development of non-transmissible diseases. About 9 % of global deaths are attributed to tobacco use, including direct consumption of tobacco and exposure to second-hand smoke [135]. However, despite extensive public education programmes, many people are still not fully aware of the impact of smoking. In the UK, it has been found that, when asked, half of smokers underestimated the number of people who die annually from smoking-related diseases. Furthermore, and perhaps more worryingly, 8 % of smokers did not believe that smoking could have a profound impact on health and lead to premature death [126]. The leading causes of death from smoking are cardiovascular diseases, chronic obstructive pulmonary disease and lung cancer [40]. However, the association of smoking with many other diseases, including those affecting the nervous system, is not well understood. Cigarette smoking is an important contributor to cerebrovascular disease and Alzheimer's disease (AD), and it also affects brain development in infants. On the other hand, some epidemiological findings suggest that smoking is negatively correlated to Parkinson disease (PD), and potentially has a neuroprotective role. In this review, we summarize the current literature regarding the effects of cigarette smoking on brain development and the neuropathology of cerebrovascular disease, AD and PD.

Effects of prenatal exposure to maternal cigarette smoking

Prenatal exposure to maternal cigarette smoking (PEMCS) is a key environmental factor that can affect brain development. PEMCS may elicit prolonged effects on cognition and behavior in children. Cognitive deficits such as poor performance on reading, mathematical skills, language development and memory have been reported in children with maternal smoking history [25, 43, 45, 46]. However, the question of whether PEMCS actually causes the cognitive changes is still controversial because some reports have shown little association between the two after adjustment for covariates such as maternal education level and intelligence quotient (IQ) [17, 48, 73]. Social, environmental and genetic factors can have significant effects on cognitive performance in children so it remains difficult to determine the independent role of tobacco smoke exposure during pregnancy. On the other hand, behavioral changes had been reported in children with PEMCS. The Norwegian Mother and Child Cohort Study reported that smoking during pregnancy increased subsequent risk for offspring toward externalizing problems (oppositional behavior, aggressive behavior, overall active behavior) in both sexes after adjustment for relevant confounders [120]. In another large scale population-based study, PEMCS was found to be associated with increased psychiatric morbidity in early adulthood [35].

PEMCS-induced global brain volume reduction in children

Alterations of brain structure in offspring with PEMCS have been reported in several studies. They confirm that the effects of PEMCS are long-lasting, with changes in brain structure and function being observed from infancy to adolescence [108, 112]. A prospective study of 7,042 pregnant women showed that fetuses of mothers who smoked during pregnancy had reduced head circumference and head growth compared to those of mothers who did not smoke during pregnancy [112]. Reduced head circumference, an indicator of brain volume, is associated with poor cognitive function [101, 102]. Similarly, differences in total cerebral volume have been found in children with attention deficit-hyperactivity disorder (ADHD), schizophrenia and autism [37]. Another magnetic resonance imaging (MRI) study revealed that children (mean age 12.3 years) with PEMCS had significant reduction in cortical gray matter and total parenchymal volumes, as well as smaller head circumferences than those of non-exposed counterparts [108]. Hence, the effects of PEMCS on brain development are likely to be long-lasting.

PEMCS induced regional structural changes in the brain

Several studies have reported changes in brain regions related to auditory processing, which in turn may lead to the observed learning difficulties. Jacobsen and colleagues reported increased fractional anisotropy (FA) in diffusion tensor imaging (DTI) of anterior cortical white matter and the anterior limb of the internal capsule in adolescents with PEMCS compared to non-exposed controls. The anterior limb of the internal capsule contains auditory thalamocortical and corticofugal fibers. Increased FA reflects maturational increases in cell packing density, fiber diameter, directional coherence and myelination. The observed FA changes may indicate disruption of the development of auditory corticofugal fibers which subsequently results in deficits in auditory processing [65]. Disturbed auditory functioning in the offspring of smokers has also been reported in other studies [29, 79]. Peck and colleagues [100] found that infants with PEMCS had higher auditory brainstem-evoked responses compared to unexposed controls. Kable and colleagues [67] reported that PEMCS was negatively related to latency of auditory brainstem

responses in 6-month infants. Auditory processing deficit has been hypothesized as one of the mechanisms leading to subtle speech perception problems in children, which will further affect language and reading development [20]. This may partly explain why children who experienced PEMCS showed cognitive impairment or poorer academic performance in some reports [25, 89].

Abnormalities in brain regions related to attention control and response inhibition have also been reported. In a prospective study on preterm infants, those with PEMCS showed significant reduction in frontal and cerebellar volumes compared to unexposed infants [36], suggesting a reduced maturation in these brain regions. ADHD is associated with activation deficit and reduced volume in the frontal lobes and cerebellum. The cerebellum may influence the frontal cortex via the thalamus. They work together to control attention, motor preparation and emotion [42, 80, 119]. In a functional MRI (fMRI) study, children with PEMCS showed greater activation in several brain regions including the frontal cortex. However, activation in the cerebellum upon stimulation was reduced. Therefore, it was suggested that there was inefficient recruitment of regions required for response inhibition [18]. The corpus callosum is another region that has been implicated in the pathology of ADHD. Smoke-exposed female adolescents had smaller corpora callosa compared to the non-exposed female control subjects [99]. Taken together, these structural and functional changes in frontal and cerebellar regions may explain an increased risk for developing ADHD and some aggressive behavior in children with PEMCS.

Cognitive and behavioral changes in response to prenatal cigarette smoking are thought to be a result of long-lasting effects of nicotine, low concentration of carbon monoxide and other cigarette components. Neuropathological changes in animal models of PEMCS provide evidence to explain some of the abnormalities. For instance, Roy and colleagues conducted several studies to investigate the histopathological changes in animals with prenatal nicotine exposure. They found that the offspring had reduced numbers of cells in the somatosensory cortex and in the hippocampus. Smaller cell size, decreased dendritic branching and increased dendritic spine density were also found in these regions, suggesting that the neuronal maturation processes were affected [109–111]. Electron microscopy studies revealed abnormal arrangement of cisternae of the rough endoplasmic reticulum, accumulation of cytoplasmic vacuoles and increased free ribosomes that might impair normal protein synthesis. Abdel-Rahman and colleagues reported that the offspring of pregnant rats that received daily subcutaneous nicotine infusion showed increased acetylcholinesterase (AChE) activity in the brains. Histological analysis showed increased neuronal cell death in the cerebellar granular cell layer as well as increased immunoreactivity of glial fibrillary acidic protein (GFAP) in the CA1 region of hippocampus and in the cerebellum [2, 3]. Increased GFAP immunoreactivity in the brain and cerebrospinal fluid (CSF) is linked with neuronal abnormality and neuropsychiatric disorders such as autism [4]. The expression and the function of receptors are also altered in prenatal nicotine-exposed animals. In two studies reported by Eppolito and colleagues, the nicotine-exposed animals had impaired cognitive function and increased anxiety-like behaviors, as well as abnormal expression of nicotinic acetylcholine receptors (nAChR). The mRNA expression of the nAChR was deregulated temporarily in adolescence but ultimately reduced in the hippocampus and medial prefrontal cortex when they reach adulthood [38, 39]. All those long-lasting changes in the brain may partly explain the increase risk for developing ADHD and some aggressive behavior in children with PEMCS. The effects of cigarette smoking on the brain, based on human and experimental animal studies, are summarized in Table 1. It is clear that further experimental investigation of the neuropathology of the brain at different developmental states after PEMCS is needed.

Cigarette smoking and cerebrovascular diseases

Cigarette smoking is an important modifiable risk factor for cerebrovascular accidents (CVA). The recent INTERSTROKE study showed that current smokers have a two-fold increased risk of stroke of all type, and smoking contributed to about 18 % of strokes worldwide [90]. Current smoking has a 2.2- to 3.1-fold increased risk of subarachnoid hemorrhage when compared with never and former smoking combined [41]. Furthermore, cigarette smoking is a risk factor for lacunar infarction [64, 69] and is associated with progression of small vessel disease (SVD) [128]. There is evidence supporting a pathogenic link between smoking and the three main categories of cerebrovascular pathology, i.e., atherosclerotic large vessel disease, saccular (Berry) aneurysm (SA), and SVD (Table 2).

Role of cigarette smoking: promoting atherosclerosis and arterial wall remodeling

The atherothrombotic properties of cigarette smoking have been covered extensively in a recent review [31]. Cigarette smoking produces systemic pro-inflammatory and oxidative stress, contributing to all major steps of atherothrombosis [30, 32]. The serum levels of inflammatory cytokines interleukin-1β (IL-1β) and tumor necrosis factor alpha (TNF-α) were found to be 1.7- and 2.4-fold higher in active smokers than in non-smokers [15]. In essence, cigarette smoking causes endothelial dysfunction and injury,

Table 1 Effects of PEMCS on brain structure related to cognition

References	Methodology, sample, and location	Age, the Outcome was collected	Parameter for assessing brain development	Confounders measured	Outcome
Human studies					
Miyao et al. [83]	Matched-pair longitudinal, participants selected from 11 hospitals, Japan	Newborn	Head circumference	Birth weight, child's gender, maternal age and gestation period	Newborns from the smoking mothers had smaller head circumferences
Kallen [68] Lindley et al. [76]	Retrospective, Swedish Medical Birth Registry, Sweden	Newborn	Head circumference <32 cm, head circumference <two standard deviations (−2 SD)	Infant's birth weight	Cigarette exposure was associated with increase risk of small head circumference in infants Stop smoking between the first prenatal care visit and week 32 of pregnancy prevented smoking-associated deficits in infant head circumference
Roza et al. [112]	Prospective, Generation R study, Netherland	Early, mid- and late pregnancy	Brain ultrasound: head circumference, biparietal diameter, transcerebellar diameter, atrial width of the lateral ventricle	Maternal age, fetal gender, maternal height, maternal body mass index, maternal educational level, maternal ethnicity, parity, maternal, alcohol consumption, maternal prenatal anxiety and maternal prenatal depression	Maternal smoking is associated with growth reduction in fetal head circumference and biparietal diameter. It is also associated with smaller fetal atrial width of lateral ventricle and transcerebellar diameter
Jacobsen et al. [65]	Retrospective, participants recruited from community, Spain	Age 13–18 years	DTI: white matter fractional anisotropy	Offspring's age, gender, birth weight, symptoms of inattention, years of education, smoking history, maternal education, maternal alcohol consumption, lifetime episodes of cannabis use	PEMCS was associated with increased FA in right and left frontal regions and in the genu of the corpus callosum
Rivkin et al. [108]	Retrospective, participants selected from a hospital in Boston, USA	Age 10–14 years	MRI: head circumference, cortical gray matter volume, white matter, subcortical gray matter, cerebrospinal fluid, total parenchymal volume	Maternal exposure to cocaine, alcohol, marijuana, child's gender and age at scan	Cigarette exposure was associated with significant reductions in cortical gray matter and total parenchymal volumes and head circumference after adjustment with demographic characteristics
Toro et al. [123]	Retrospective, the Saguenay Youth Study, Canada	Age 12–18 years	MRI: thickness of Orbitofrontal, middle frontal, and parahippocampal cortices	Maternal education, family income, subject's age, breast-feeding history	Orbitofrontal, middle frontal, and parahippocampal cortices were thinner in smoke-exposed, as compared with non-exposed, individuals

Table 1 continued

References	Methodology, sample, and location	Age, the Outcome was collected	Parameter for assessing brain development	Confounders measured	Outcome
Paus et al. [65, 99]			Size of corpus callosum		Reduction of the overall size of the corpus callosum in PEMCS subjects
Ekblad et al. [36]	Retrospective, PIPARI study, Finland	Newborn Infants selected for low birth weight, low gestational age	Brain ultrasound/MRI: head circumference, total brain volume, regional brain volume (cerebral cerebellar, frontal lobe medulla oblongata and the pons, basal ganglia and thalami)	Infant's gestational age at birth, birth weight, sex, patent ductus arteriosus, intraventricular hemorrhage, combined chronic lung disease, necrotizing enterocolitis, and septicemia as neonatal inflammatory disease, MRI equipment, maternal alcohol consumption during pregnancy	PEMCS was associated with smaller frontal lobe and cerebellar volumes in preterm infants
Derauf et al. [34]	Prospective, participants recruited from the Hawaii-site of the IDEAL study, USA	Age 3–5 years	MRI: cortical and subcortical volumes, total intracranial volume, cortical thickness	Age at time of MRI, child's gender, handedness and pulse sequence; prenatal marijuana exposure, handedness,	Children with PMECS showed cortical thinning in perisylvian and lateral occipital cortices and volumetric increases in frontal regions and decreases in anterior cingulate
Anblagan et al. [8]	Case–control, participants recruited from a hospital, UK	Gestational age = 22–27 weeks; 33–38 weeks	MRI: volumes of fetal brain	Maternal age, BMI, parity, education; birth weight, gestational age at birth, fetal sex	Maternal smoking is associated with reduced brain volume
Liu et al. [77]	Prospective, Maternal Lifestyle Study, USA	Age = 13–15 years	MRI: volume of the thalamus, caudate, putamen, pallidum, hippocampus, amygdala, accumbens. Thickness of cortical regions	Head circumference at birth, gestational age, maternal alcohol use, age, sex, race/ethnicity, IQ, family poverty, and socioeconomic status	Adolescents with PEMCS had smaller pallidum volume

Reference	Methodology	Age the Outcome was collected	Parameter for assessing brain development	Outcome
Animal studies (maternal exposure to nicotine)				
Roy and Sabherwal [109]	Pregnant Wister rats, daily i.p. injection of nicotine from gestation day 6 to term	Postnatal days 10, 20 and 40	Toluidine blue staining, thionine staining, electron microscopy	Reduction of body and brain weight. Reduction of cortical thickness, decreased cell size in the somatosensory cortex. Increased neuronal density, decreased dendritic branching and increased dendritic spine density of Layer 5 of somatosensory cortex. Irregular arrangement of cisternae of rough endoplasmic reticulum, paucity of free ribosomes, and frequent cytoplasmic vacuoles

Table 1 continued

Reference	Methodology	Age the Outcome was collected	Parameter for assessing brain development	Outcome
Roy and Sabherwal [110]	Pregnant Wistar rats, daily nicotine injection from gestational day 6 to term	Postnatal day 40	Toluidine blue staining, Golgi staining, electron microscopy	Reduction of areas of dentate gyrus, CA3, CA1 of hippocampus. Distal dentritic arbor was reduced. Increased spine density in the granule cells, terminal and basal dendrites of the pyramidal neurons of CA3, CA1 of the hippocampus. Less apical dendritic thorny excrescence in CA3 pyramidal neurons. Increase in free ribosomes and dilatation of rough endoplasmic reticulum and Golgi apparatus cisternae in pyramidal neurons of the CA3 and CA1 regions
Roy et al. [111]	Pregnant SD rats, daily nicotine sc infusion from gestational day 4 to 21	Postnatal days 21 and 30	Cresyl violet staining	Substantial decrease in cell size, with corresponding decrements in cell layer thickness, and increments in cell packing density in the hippocampal CA3 and dentate gyrus Reduction in the proportion of medium-sized pyramidal neurons, and an increase in the proportion of smaller, non-pyramidal cells in layer 5 of the somatosensory cortex. Elevated numbers of glia in the hippocampus and somatosensory cortex
Abdel-Rahman et al. [2, 3]	Pregnant SD rats, daily nicotine sc infusion from gestation day 4 to 20	Postnatal days 7, 30, 60	Brain AChE activity, IHC of GFAP	Increase in brain AChE activity in brainstem and cerebellum. Decrease in surviving Purkinje neurons in the cerebellum. Increase in GFAP immunostaining in cerebellar white matter
Eppolito et al. [38]	Pregnant Long-Evans rats, daily infusion of nicotine from gestation day 4 to postnatal day 10	Postnatal days 30 and 75	In situ hybridization	Increased expression of α4, β2 and α7 nAChR subunit mRNA in the hippocampus of adolescent rats compared to adult rats. Persistent decreases in nAChR mRNA expression in the hippocampus of adulthood that was not apparent in adolescence

Table 2 Overview of the effects of cigarette smoking on cerebral vessels

Main site of action	Small vessels	Large vessels	
	BBB	Endothelial cells	Vascular smooth muscle cells
Major mechanisms	Alpha7 nicotinic acetylcholine receptor as main mediator Pro-inflammatory state with increase interleukin, tumor necrosis factor, and metalloproteinase Decrease tight junction protein ZO-1 Impair ion-transporter Na^+-K^+-$2Cl^-$ cotransporter (NKCC)	Activate p38 mitogen-activated protein kinase-mediated inflammatory signaling pathway Pro-inflammatory state with increase metalloproteinase	Activate nuclear factor-κB Pro-inflammatory state with increase interleukin, tumor necrosis factor, and metalloproteinase Increase smooth muscle cell apoptosis Decrease collagen synthesis
Effect	Increase BBB permeability and development of small vessel disease	Endothelial dysfunction and promote unstable plaque formation	Promote arterial wall remodeling and formation of aneurysm

promotes generation of unstable plaque, increases plaque thrombogenesis, enhances platelet aggregation, and produces a hypercoagulable state with concomitant impaired fibrinolysis.

The atherothrombotic effects of cigarette smoking on large cerebral vessels have been investigated in different experimental models. Direct visualization of autopsy-obtained human middle cerebral vessels with the electron microscope showed swollen and disrupted endothelium after dimethyl sulfoxide (DMSO)-soluble (lipid-soluble) cigarette smoke particles (DSP) treatment [137]. The p38 mitogen-activated protein kinase (MAPK)-mediated inflammatory signaling pathway was activated after DSP treatment in rat middle cerebral and basilar arteries. There was concomitant upregulation of metalloproteinase 13 (MMP13) at both transcriptional and protein expression levels [129]. Current evidence suggests that increased activities of MMP contribute to extracellular matrix destruction and formation of unstable plaque [87]. Apart from the inflammatory factors, upregulation of endothelin receptors type A and B has been demonstrated in rat cerebral vessels after DSP treatment [61, 114]. Endothelin-1 stimulates proliferation of vascular smooth muscle cells (SMC) and neointimal formation in atherosclerosis, which is mediated by endothelin receptor type A [72].

The aforementioned effects of cigarette smoking contribute similarly to the pathogenesis of cerebral aneurysm rupture. The hypercoagulable state exerts hemodynamic stress to the vessel wall. Damage of endothelial cells sustains inflammation. In particular, cigarette smoking causes functional transformation of the vascular smooth muscle cells from a contractile phenotype to a pro-inflammatory phenotype. Ali and co-workers [6] demonstrated that cigarette smoking decreased the expression of vascular SMC marker genes and myocardin, and increased the expression of genes encoding for inflammation and matrix remodeling, including MMP, monocyte chemo-attractant protein-1, IL-1, and TNF-α. Furthermore, cigarette smoking activates nuclear factor-κB (NF-κB) in vascular SMC, with increased release of IL-1β, TNF-α, and MMP-2/9 [136]. IL-1β decreases biosynthesis of collagen in SMC [9]. TNF-α has been shown to induce apoptosis of vascular SMC [66]. Aoki and co-workers [10] showed that NF-κB was highly activated in human SA and inflammatory pathways were crucial in initiating cerebral aneurysm development. Taken together, cigarette smoking facilitates matrix degradation and arterial wall remodeling in the formation of aneurysms.

Smoking and cerebral small vessel disease

Cerebral small vessel disease (SVD) has been increasingly recognized as an important cause of cerebrovascular and

neurodegenerative diseases. The definition of SVD is not uniform but encompasses all pathologies affecting perforating small arteries, arterioles, capillaries and veins [96]. The clinical spectrum ranges from lacunar stroke to more diffuse neurological deficit with cognitive decline, gait disturbance, and dementia. The established risk factors include increasing age, diabetes mellitus, hypertension and smoking [69]. The pathological changes include small vessel atherosclerosis, fibrinoid necrosis, lipohyalinosis, microaneurysms, arteriolosclerosis, and segmental arterial disorganization [92] (Fig. 1). The pathological changes depend on the type of vessel involved, with atherosclerosis more commonly seen in larger perforators, and other changes seen more in small arterioles.

The underlying pathogenesis of SVD is not fully elucidated. The long held view is that of a microatheroma-ischemic mechanism, in which the small vessels are blocked by microatheroma with consequent downstream ischemic events [131]. However, this hypothesis fails to address the diffuse and heterogeneous clinical manifestations of SVD. A recent systematic review of the literature examining 39 studies involving 2,300 subjects showed that many lacunar lesions have no arteriolar occlusion and are associated with luminal dilation of vessels [12]. Failure of blood–brain barrier (BBB) has been postulated to be the initiating mechanism of SVD [133]. Post-mortem neuropathological examination of the caudate putamen region of the SVD patients showed an increased expression of endothelial thrombomodulin, an antithrombotic anti-inflammatory glycoprotein, in the arteriolosclerotic vessels [49]. The study confirms endothelial abnormality in SVD. Endothelial dysfunction has been demonstrated in lacunar stroke [121]. MRI studies showed increased BBB permeability in lacunar disease [122, 132]. An animal study with spontaneously hypertensive stroke prone (SHRSP) rats supported breakdown of BBB as an initial event causing endothelial leakage at multiple sites, and thrombotic occlusion of small vessels as a late event in cerebral SVD [115].

Role of cigarette smoking in the dysfunction of the blood–brain barrier

The deleterious effects of cigarette smoking on the BBB have been demonstrated by different experimental models.

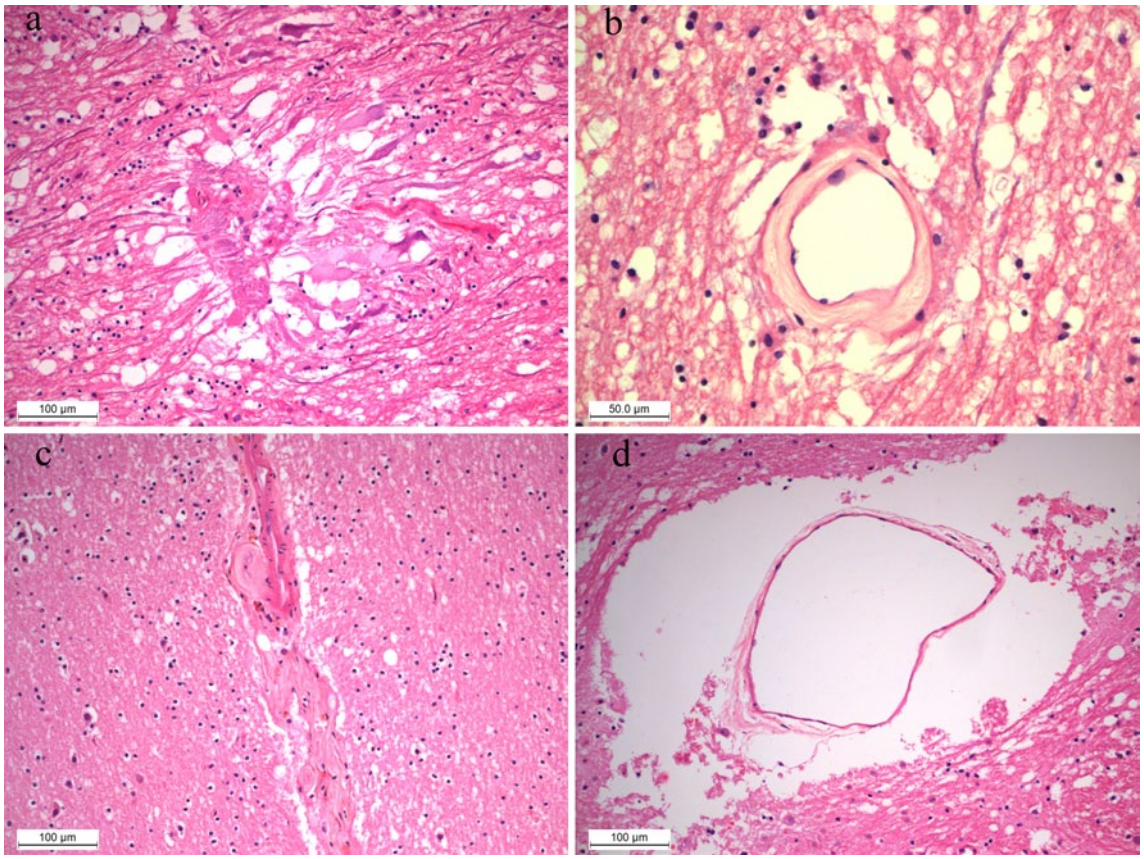

Fig. 1 Pathological changes in cerebral small vessel disease: 46-year-old male with 2 years history of gait disturbance; heavy smoker with no history of hypertension or diabetes; died of pneumonia. **a** Fibrinoid necrosis of deep white matter vessels [Hematoxylin and eosin (H&E) stain, ×200]. **b** Arteriolosclerotic vessel (H&E, ×400). **c** Perforating arterioles with segmental hyalinization and disorganization (H&E, ×200). **d** Dilated perivascular space (H&E, ×200)

Huang and co-workers [62] have shown nicotine-induced BBB damage in a mice model. Circulating endothelial cells have been used as an indicator of vascular damage after various stresses or insults. The study showed that the blood circulating brain microvascular endothelial cell (BMEC), a specific BBB constituent cell, was increased in mice after nicotine treatment. In addition to BMEC, increased CSF albumin indicates increased BBB permeability. The effects were not observed in alpha7 nicotinic acetylcholine receptor (α7nAChR) knockout mice. The results suggest a significant role of α7nAChR in mediating the effect of nicotine in BBB dysfunction.

Hossain and co-workers [60] found significant pro-inflammatory properties of cigarette smoking on human BMEC. By studying the effect of tobacco smoke whole soluble extract on an in vitro flow-based BBB model, they found marked expression of pro-inflammatory adhesion molecules P-selectin, vascular cell adhesion molecule-1 and E-selectin; significant increase in the serum levels of pro-inflammatory mediators IL-1β, TNF-α, MMP-2 and MMP-9; and transcriptional upregulation of various pro-inflammatory genes. Furthermore, the loss in BBB integrity was significantly increased when coupled with flow-cessation/reperfusion.

Cigarette smoking has been shown to modulate tight junction proteins in the BBB. Hawkins and co-workers demonstrated that nicotine decreased expression of ZO-1 tight junction protein in the BBB, resulting in increased permeability [52]. The effect is mediated by α7nAChR [1]. In addition to tight junction changes, Paulson and co-workers showed in both in vitro and in vivo models that nicotine, mediated by α7nAChR, altered the function of the BBB Na^+–K^+–$2Cl^-$ co-transporter (NKCC) [97, 98]. This resulted in raised extracellular potassium levels and cerebral edema.

Cigarette smoking and neurodegeneration of Alzheimer's disease

Cigarette smoking has been considered to be an important risk factor leading to Alzheimer's disease. AD is the major cause of dementia. In 2011, 33.9 million AD patients were estimated worldwide and the prevalence is expected to triple over the next 40 years [16]. The harmful effects of cigarette smoking have been the subject of speculation for decades, and smoking has been considered to be "an aging accelerator" [19]. Starting from the early 1980s, researchers began to study the association between cigarette smoking and AD. In fact, a slow evolution can be observed from these studies. In the beginning, the major focus for AD research was on the role of genetic factors and head trauma. The influence of environmental factors on AD has been under-estimated. There are some epidemiological studies showing no significant association between AD and smoking [44, 57]. However, this view has been challenged in the late 1980s and early 1990s by new findings supporting the idea that cigarette smoking can have an impact on AD, but these findings are inconsistent. Some of them showed little association, while others show possible positive association, or even negative association [24, 27, 51, 53]. Most of the findings were generated from epidemiological studies and not much evidence was obtained from autopsy brains. However, as more epidemiological studies and brain imaging studies have been conducted, it has now been generally accepted that smoking is a risk factor for the development of AD [16]. Data from animal studies have shown that smoking induces pathological changes, and accelerated progression of AD [58, 84]. We review here the effects of smoking on AD in the following sections with particular focus on the neuropathology. The acute effects of smoking/nicotine administration are not the focus of this article.

Smoking-induced pathological changes in the brain: data from human and animal studies

Senile plaques (SPs), beta-amyloid peptide (Aβ), neurofibrillary tangles (NFTs) and tau protein

The proposed association between cigarette smoking and AD is largely based on epidemiological research that focuses on assessment of cognitive function. Only a few studies have been based on the study of post-mortem brains. In these studies, staining and quantification of senile plaques (SP) and neurofibrillary tangles (NFT) have yielded mixed results. Many of them do not show an increase in the number of SPs or NFTs. In most human studies, the number of SPs (or the amount of Aβ) was lower in smokers and the number of NFTs (or the amount of tau) was reduced or unchanged [28, 56, 127]. Only one study reported an increase of SPs in smokers [125].

The earliest findings from human brain were published in 1997 when Ulrich and colleagues compared the changes of NFTs and SPs in unselected brains from patients with smoking history [127]. In this study, 301 subjects were included and their history of smoking was analyzed retrospectively, regardless of their cognitive function or history of dementia. Among 72 sex-and age-matched smoker/non-smoker pairs, they found that the smokers had fewer NFTs and SPs. The difference was more pronounced when considering the female smokers only [127]. However, one should note that the histological stains used (Methenamine-silver for SPs and Gallyas for NFTs) would only detect aggregated forms of Aβ and tau, respectively. The oligomeric or fibrillar Aβ would not have been detected. In

addition, the study did not include screening of any inherited risk factors such as the allele of apoE. Conflicting results were published later by Tyas and colleagues who found that former smokers displayed more SPs than non-smokers in their hippocampal and neocortical regions. The number of NFTs seen in smokers and non-smokers was similar [125]. One year later, another research study that targeted the levels of soluble and insoluble Aβ40 and Aβ42 in brain homogenates analyzed by enzyme-linked immunosorbent assay (ELISA) kits was reported [56]. It was found that the Braak stage was significantly lower in smoking controls compared to non-smoking controls (without AD), consistent with the results of Ulrich and colleagues [127]. Furthermore, the levels of soluble and insoluble Aβ40 and Aβ42 in brains of AD smokers were significantly lower than those in AD non-smokers, and the level was also lower in smoking controls compared to non-smoking controls. The authors speculated that nicotine in the cigarette smoke might bind to nicotinic acetylcholine receptors to stimulate the production of non-amyloidogenic processing of APP. Similar findings were reported by Court and colleagues who showed a reduction of insoluble Aβ deposition in the entorhinal cortex of psychiatrically and neurologically normal smoking subjects, but no significant changes in the levels of hyperphosphorylated tau and soluble Aβ [28]. Given that SPs and NFTs are the pathological hallmarks of AD, if judgment is made solely based on these findings, it might mislead us to conclude that smoking might be protective against AD! It is difficult to explain the findings. The authors of these studies pointed out that the structural changes in smokers (SPs, Aβ levels and NFTs) might not necessarily be due to a direct functional effect. They also speculated that the changes in the level of SP and Aβ might have resulted from the action of the nicotine in tobacco because of the beneficial effects of nicotine [28, 56, 127]. While it is still unclear of these pathological findings in postmortem human brain, new findings about tau, which could be transmissible when they are still soluble, may implicate that toxic effects of cigarette smoking may not be necessary in a form of SPs or NFTs.

Regardless of the conflicting findings in post-mortem brains, data from animal studies seem to be in line with expectations. Effects of smoking in peripheral systems, especially in the respiratory system have been extensively studied in animals. However, there are relatively few publications on the in vivo effects of tobacco smoke on SPs and NFTs. A recent study has been conducted on the APP/PS1 transgenic mice that slowly develop senile plaques around 5- to 6-month-old. These mice were exposed to cigarette smoke in smoking chambers 30–60 min/day, 5 days a week for 4 months. Compared to the unexposed control mice, those exposed to high dose of smoke had a significant increase of Aβ burden (stained with 4G8, a specific antibody against Aβ) in the hippocampus and cortex by 7 month-old. These mice also had more thioflavin-S positive stained structures in both cortex and hippocampus, indicating that they had more fibrillar amyloid deposits [84]. Since most AD cases are sporadic, it would also be important to study the effects of smoking on wild-type animals. Our laboratory had compared the effects of chronic smoking on normal Sprague–Dawley rats. After daily exposure to cigarette smoke for 56 days, the rats had more Aβ (stained with a specific antibody against rodent Aβ) and more sAPPβ (a precursor form of Aβ) in their hippocampus. The levels of phospho-tau were also markedly increased. No SPs or NFTs were identified in either the control or smoking groups within this short time-frame [58]. Based on the results from these two animal studies, it is possible that smoking promotes the development of AD-related neuropathology by modulating the production of Aβ.

In many reports, the effects of nicotine were frequently used to support some of the findings, especially those related to Aβ and SPs. Nicotine was shown to modulate the APP-signaling cascade in multiple ways. It could reduce the expression of BACE1 and increase the secretion of sAPPα [85, 88, 103]. Nicotine treatment also reduces the levels of Aβ in APP-transgenic mice [54, 78]. Apart from modulating the production of Aβ, nicotine also reduces the fibrillization of Aβ [113] and promotes the breakdown of fibrillar Aβ in vitro [93]. These data seem to support the changes of SPs and Aβ observed in smoking human subjects. On the other hand, nicotine may exert negative effect on tau and its related pathology. Early studies showed that nicotine increased phosphorylation of tau in SH-SY5Y and SK-N-MC neuroblastoma cells [55, 130]. Similar results were obtained in 3xTg-AD transgenic mice which received 5 months nicotine treatment [91]. Rats with intra-hippocampal injection of Aβ also showed exacerbated tau phosphorylation and cognitive impairment if nicotine was administrated daily for 14 days [33]. These findings seem to support the animal data from our group [58]. However, it remains difficult to explain why human and animal studies showed marked differences. As mentioned above, the effects of oligomeric Aβ and small aggregated tau may be more toxic to synapses and axons/dendrites. This may explain why we could not observe SPs or NFTs, but synaptic degeneration occurs. Also, since nicotine is just one of ~5,000 compounds inside tobacco, it is unreasonable to expect all the effects of tobacco to be attributable to nicotine.

Brain atrophy, loss of neurons, changes in gray and white matter

Studies with MRI and voxel-based morphometry have shown that normal subjects with a history of smoking have

decreased gray matter density or volume in brain regions associated with early AD [7, 23, 47, 138]. Meta-analysis also confirms a decrease of regional gray matter volume in smokers [95]. Reduction in gray matter density is known to occur in AD patients and patients with mild cognitive impairment (MCI) are more likely to develop AD later if they have great reduction of gray matter density. For white matter, studies using DTI have shown a reduction in FA which reflects density of fibers and myelin, associated with other imaging abnormalities, in the corpus callosum in smokers [75]. The findings positively correlate with the duration of regular smoking [75]. These studies not only demonstrate the harmful effects of smoking on the brain, but also provide a better correlation between tobacco and its functional outcome. To date, neuronal cell loss has not been found in animal models of chronic smoking, suggesting that large scale global brain atrophy is unlikely to be found in these animals [58, 84]. Reduced expression of synaptic proteins (synapsin-1, synaptophysin) and alteration in cytoskeleton-related protein (tubulin, drebrin) have been reported in cigarette smoke-exposed rats [58], indicating possible synaptic degeneration and axonal deficits.

Possible mechanisms that links the neuropathology of AD and cigarette smoking

Oxidative stress

Many compounds in cigarette smoke are toxic and are oxidative stress inducers. For instance, tar in cigarette smoke contains $>10^{17}$ long-lived radicals per gram, and the gas phrase of cigarette contains $>10^{15}$ more reactive radicals per gram [26]. These free radicals are believed to play crucial roles in promoting AD and cognitive dysfunction in smokers. Increased free radical damage to cerebral cortex has been reported in AD patients and current smokers [118]. Cigarette smoking is also associated with decreased free radical scavengers. Smokers have been reported to have lower serum levels of antioxidants and anti-oxidative enzymes [5, 71]. In animal studies, exposure to cigarette smoke induces oxidative stress and related damage in their brains. Khanna and colleagues reported increased expressions of genes encoding for pro-oxidant iNOS, NOX4, dual oxidase 1 and $p22^{phox}$ in the brains of cigarette smoke-exposed rats. The levels of Nrf2 were also increased, suggesting an induction of oxidative stress [70]. Our laboratory has also found increased levels of 8-hydroxyguanosine, a marker for oxidative DNA damage, in the hippocampus of cigarette smoke-exposed rats [58].

The oxidative stress induced by cigarette smoking can be an upstream event to trigger cellular damage and histological changes in AD brains. In vitro data show that oxidative stress modulates APP processing through altering the activities of β- and γ-secretases, and it promotes production of Aβ through the JNK and PKR-eIF2α-signaling pathways [86, 106, 117]. Oxidative stress can also activate JNK directly to induce a number of cellular events. The levels of phospho-JNK are increased in cigarette smoke-exposed rats [58]. JNK is one of the kinases to phosphorylate tau. In SAMP8 mice (an age-associated AD animal model), inhibition of JNK attenuates cognitive decline and reduces tau hyperphosphorylation, suggesting the importance of JNK in mediating the histological and memory changes in AD pathogenesis [94]. JNK is an apoptosis mediator in different tissues including neurons [21]. Activation of JNK can induce apoptosis that may result in neuronal cell loss and atrophy. Oxidative stress is also linked to synaptic loss. Nitric oxide (NO) can affect mitochondrial respiration and fission/fusion dynamics. Increasing lines of evidence suggest that dysfunction of synaptic mitochondria causes synaptic failure and loss [63]. Electron micrographs of autopsy specimens of AD reveal alterations of mitochondria (elongation, disruption of the cristae, accumulation of osmophilic material) in neurons with depletion of dendritic spines and loss of dendritic branches [14]. Moreover, it has been reported that white matter injury in aged adult is associated with free radical injury to myelin [11]. All these data suggest that cigarette smoke might accelerate AD pathology through an oxidative mechanism.

Neuroinflammation

Neuroinflammation is believed to play a key role in the pathogenesis of AD and the aging process. This is partly supported by histological findings that abundant activated microglia and astrocytes are found near SPs and NFTs; the levels of inflammatory markers are elevated in the AD brains compared to healthy controls [107]. Cigarette smoking can induce inflammatory responses in the peripheral circulation. Data from the NHANES III study reveal that smokers have elevated levels of inflammatory markers (C-reactive protein, white blood cell count, fibrinogen) in the serum and the levels are positively associated with smoking status [13]. Although it is uncertain how these peripheral inflammatory changes could affect our brain, it has been shown that some inflammatory mediators such as cytokines can pass through regions where there is an absence of BBB; or they could act on endothelial cells or perivascular cells to produce mediators signaling to the brain. Some activated neutrophils could also infiltrate into the brain to produce cytokines. Therefore, it is possible for peripheral inflammation to modulate cerebral immune responses [81]. Nicotine, for example, had been shown to regulate brain endothelial cells, enhance infiltration of leukocytes into the brain and induce the expression of

inflammatory mediators, cytokines, chemokines and adhesion molecules during ischemia/reperfusion injury [22]. Therefore, cigarette smoking may induce direct neuroinflammation through the brain endothelial cells or through inducing inflammation in the peripheral circulation. Animal studies suggest that smoking can induce neuroinflammation. In Lewis rats, chronic exposure to cigarette smoke for 6 weeks increased protein expression levels of class II MHC, IFN-γ and TNF-α; the gene expression of cytokines such as IL-1α, IL-1β and IL-6 was also increased [70]. Another group also reported increased levels of IL-6 in the cerebrum of cigarette smoke-exposed rats, and the changes in IL-6 were not mediated through oxidative stress [74]. Similar effects were also found in the APP/PS1 mice, which showed increased numbers of activated microglia after 4-month exposure to cigarette smoke [84].

Smoking and neuropathology of Parkinson's disease

There have been a large number of epidemiological studies looking at possible associations between smoking and the risk of developing PD. Such studies have a number of confounds, not least the fact that PD is under-reported on death certificates, particularly in smokers in whom other systemic conditions may predominate. Related to this, smokers may die earlier from these smoking-related conditions so there can be an inherent age-related selection bias. However, meta-analyses of the data suggest that there may be a 50 % reduction of risk of PD in smokers [134]. There are multiple possible mechanisms underlying this protective effect of smoking, the most basic perhaps being the stimulation of dopamine release from nigro-striatal dopaminergic neurons via nicotinic acetylcholine receptors [104]. Based on this premise and some encouraging data from animal model studies, suggesting a neuroprotective effect of nicotine, the use of specific nicotinic receptor agonists as an adjunct to conventional L-dopa therapy has been suggested [105]. Another potential protective mechanism is via a direct interaction with the key protein component of the Lewy bodies found in PD, alpha-synuclein (αSN). Fibrillization and aggregation of αSN are thought to be a key part of the pathological process and biochemical studies have shown that nicotine can slow or inhibit αSN fibril formation [59].

To date, there have been very few studies directly addressing the effect of smoking on the PD pathology at post-mortem. The largest is a recent study by Tsuang and colleagues [124] who reported an association between heavy lifetime cigarette smoking and reduced Lewy-related pathology (LRP) accumulation. The study was carried out in a large community-based prospective cohort and was based on observations in 238 autopsies. There was not only a global decrease in LRP in the heavy smokers but also a significantly reduced frequency of LRP in the substantia nigra. As the effect was only evident in heavy smokers, the authors suggest that there may be some sort of exposure–response relationship. Interestingly, there appeared to be no effect on the extent of Alzheimer-type pathological changes in post-mortem human brain in this study. In another recent Japanese study, it has been suggested that an association between smoking and certain single nucleotide polymorphisms in the SNCA gene (encoding αSN) can also modify the disease risk, thereby reinforcing the possibility of a biologically relevant interaction between nicotine and αSN [82].

In some cases, parkinsonism is related to vascular rather than αSN-related pathologies, particularly in the event of lacunar infarcts in the basal ganglia. Even in idiopathic PD, with full-blown αSN pathology, there is often associated vascular pathology in the basal ganglia. It is, therefore, somewhat surprising that there is an inverse relationship between smoking and PD risk bearing in mind that smoking is one of the major risk factors for vascular pathology, particularly atherosclerosis. However, the association between the incidence of vascular disease and PD risk is still unclear and requires further investigation [116].

Conclusions

Cigarette smoking has multiple effects on our brains and it induces structural changes that are related to cognitive development, behavioral changes and neurodegenerative diseases as summarized in Fig. 2. There are two major concerns when we review the neuropathological changes associated with cigarette smoking. Firstly, there are too many chemicals in the tobacco smoke. The complexity of the composition makes it quite difficult to have a complete picture of chemical-specific toxicity. A number of studies focus on nicotine partly because of the important role of α7nAChR in the central nervous system. Although it is possible to explain some of the experimental findings or clinical observations with the nicotine specific pathways, the precise mechanisms or molecular pathways mediated by tobacco smoke remain unclear. To date, many chemical components in tobacco have been identified, but there are few studies investigating their BBB permeability and distribution inside the brain. This uncertainty makes it more difficult to conduct chemical-specific toxicity test in cell culture and animal models. The second concern is the deviation observed occasionally between neuropathology and epidemiological findings; an example is AD. Although sufficient evidence at the epidemiologic level supports the conclusion that a history of smoking is associated with increased risks of AD and dementia, the findings on SPs and NTFs do not always support this notion. The

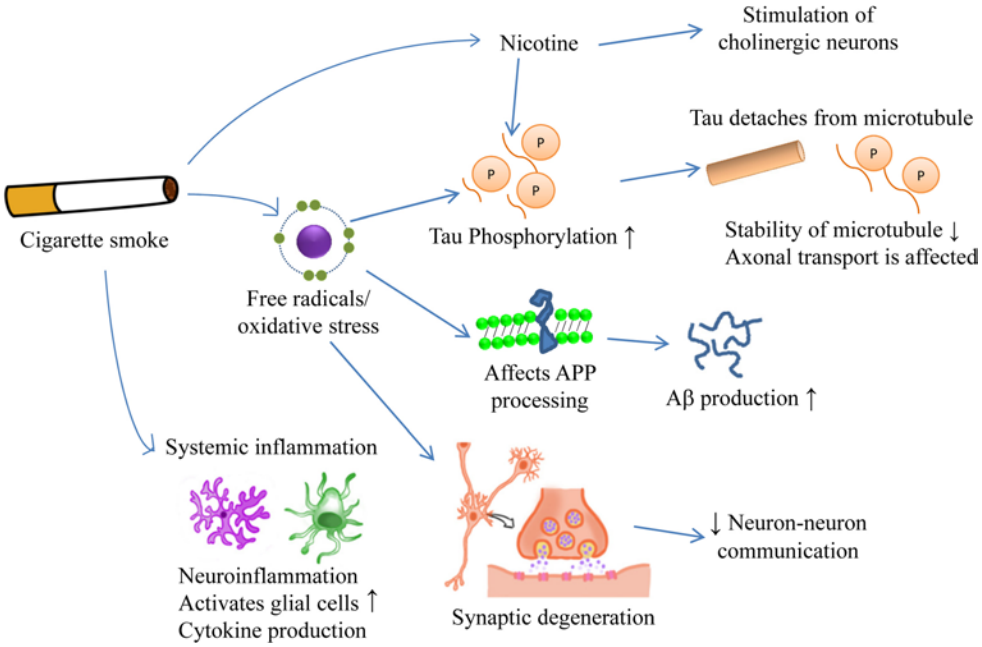

Fig. 2 Summary of the effects of cigarette smoking in human and rodent. Cigarette smoking can induce oxidative stress and inflammation, which may lead to neuropathological changes in the brain. There exist differential structure changes between human and rodents after smoking or exposure to cigarette smoke

traditional neuropathological examinations on postmortem brains rely mainly on the identification and quantification of specific lesions (e.g., SPs, NTFs, αSN). These specific markers are useful for the diagnosis of diseases but they may not always correlate to the clinical symptoms or severity. Therefore, they should not be used alone for studying the correlation between risk factors and diseases. On the other hand, longitudinal monitoring of smoking habits and disease severity is ideal for studying their temporal relationship, but this requires the examination of structural changes in living human subjects, which may be difficult. Some preclinical changes in the brains, e.g., atrophy, white and gray matter abnormalities, silent infarcts can be examined with advanced brain imaging, yet these changes are often regarded as non-specific. Also, it will be difficult and expensive to implement regular brain imaging for any individual adult who appears to be healthy.

Although cigarette smoking can be a risk factor leading to AD, it appears be a protective factor for PD because of the reduction of LRP. Similar to AD, neuropathology appears to be reduced in patients who smoke. However, as pointed out above, the vascular effects of cigarette smoking and the free radicals as well as inflammatory factors triggered by cigarette smoking cannot be neglected. Further post-mortem brain or animal experiments are needed to determine the effects of smoking in terms of progression of deterioration or beneficial effects.

Finally, we take the case of cerebrovascular diseases and smoking as an example to illustrate future research directions. The pathogenesis of cigarette smoking-induced atherosclerosis and aneurysm formation in large vessels has been extensively studied. In contrast, the investigation into the role of cigarette smoking in cerebral SVD is in its infancy. The clinical course and the temporal effects of cigarette smoking have not been established. This is difficult to accomplish in human studies as the disease is slowly progressive and requires extended periods of patient follow-up. Many insights regarding the mechanisms of SVD have been gained by neuroimaging studies [133]. However, MRI-postmortem pathological correlation studies on SVD have shown that there are "MRI invisible" lesions, including white matter tissue changes and cortical microinfarcts [50]. Animal studies can circumvent many of the difficulties and complement human studies. In particular, examination of cigarette smoking-induced changes on cerebral small vessels may help to establish the temporal sequence and topographic distribution of the different SVD pathological lesions. This may also shed light into the initiating events of SVD in general.

We have summarized and discussed the effects of cigarette smoking in PEMCS, cerebrovascular disease, AD and PD. It is clear that each disease requires further investigation, whether in postmortem brain or animal experiments, because we currently have a lot of conflicting evidence. In addition, we should initiate more experimental studies of PEMCS, because it is impossible to investigate neuropathology to trace any developmental defect of the brain. We hope that this review can stimulate more research in how cigarette smoking or even other means of smoking affect our brains.

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