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Survey review

Cigarette smoking impairs nitric oxide-mediated cerebral blood flow increase: Implications for Alzheimer's disease

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ABSTRACT

Cerebral blood flow is mainly regulated by nitrergic (parasympathetic, postganglionic) nerves and nitric oxide (NO) liberated from endothelial cells in response to shear stress and stretch of vasculature, whereas sympathetic vasoconstrictor control is quite weak. On the other hand, peripheral vascular resistance and blood flow are mainly controlled by adrenergic vasoconstrictor nerves; endothelium-derived NO and nitrergic nerves play some roles as vasodilator factors. Cigarette smoking impairs NO synthesis in cerebral vascular endothelial cells and nitrergic nerves leading to interference with cerebral blood flow and glucose metabolism in the brain. Smoking-induced cerebral hypoperfusion is induced by impairment of synthesis and actions of NO via endothelial nitric oxide synthase (eNOS)/neuronal NOS (nNOS) inhibition and by increased production of oxygen radicals, resulting in decreased actions of NO on vascular smooth muscle. Nicotine acutely and chronically impairs the action of endothelial NO and also inhibits nitrergic nerve function in chronic use. Impaired cerebral blood supply promotes the synthesis of amyloid β that accelerates blood flow decrease. This vicious cycle is thought to be one of the important factors involving in Alzheimer's disease (AD). Quitting smoking is undoubtedly one of the important ways to prevent and delay the genesis or slow the progress of impaired cognitive function and AD.

1. Introduction

The epoch-making discovery of endothelium-derived relaxing factor by Furchgott and Zawadzki (1) led to the seminal finding that this factor is the gaseous molecule nitric oxide (NO) liberated from endothelial cells via stimulation by chemical substances such as acetylcholine (ACh), ATP, bradykinin and substance P or application of physical stimuli like shear stress and stretch to endothelial cells (2). Cerebral blood flow increase is mainly mediated via endothelium-derived NO and NO liberated from nitrergic nerves innervating vasculatures (3). Parasympathetic postganglionic (nitrergic) nerves play quite important roles in dilating the cerebral vasculature, but the counteracting vasoconstrictor actions of adrenergic nerves is only minimal in the brain. In contrast, in extracerebral vasculatures, adrenergically-induced vasoconstriction is more evident than nitrergic nerve-derived vasodilatation (4). Therefore, cerebral arterial tone and blood flow are mainly regulated by endothelium- and nitrergic nerve-derived NO.

Impaired blood supply to the brain owing to cerebral vascular dysfunction is a major clinical feature of Alzheimer's disease (AD) (5). One of the important factors inducing cerebral hypoperfusion is impairment of actions of NO derived from endothelia and nitrergic nerves on vascular smooth muscle (6). Therefore, reduced synthesis and actions of constitutively synthesized NO result in decreased blood flow and reduced glucose supply to the brain, possibly leading to impaired cognitive function and AD. Decreased blood supply to the brain induces both increased amyloid β (Aβ) production (7) and decreased clearance of intraneuronal Aβ (8) and Aβ inhibits endothelial function; this vicious cycle is expected to play a role in deteriorating brain function (9). Vasodilator actions of NO are impaired by the production of oxygen radicals and the synthesis of NO is blocked by an endogenously liberated NOS inhibitor, asymmetric dimethyl-arginine (ADMA), which is formed from

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arginine residues by protein arginine methyltransferase type I (10). Therefore, these factors are expected to reduce the actions of NO from the endothelia and neurons, thus decreasing blood flow to the brain. Cigarette smoking is known to reduce cerebral blood flow due to interfering with endothelial function and to degradation of NO by producing oxygen radicals (11) (Fig. 1).

This review summarizes the possible mechanisms of action of active and passive smoking or nicotine on cerebral vascular endothelial function, nitrergic nerve function and blood flow in reference to cognitive failure and AD. Recent advances in the prophylaxis and drug therapies against AD are summarized with special emphasis. Smoking is internationally accepted to be one of the important factors promoting impairment of cerebral blood perfusion and generation of cognitive failure and AD.

2. Smoking and cerebral vascular tone and blood flow

In the brain, blood flow is regulated not only by pial arterioles but also by the main trunk of the basal cerebral arteries; therefore, arterial and arteriolar diameter changes are important factors influencing cerebral blood flow (12). The oxidative stress induced by cigarette smoke exposure is a potential mechanism for initiating cardiovascular dysfunction, including impairment of endothelial function and NO-mediated vasodilatation (13). Infusion of aqueous cigarette smoke extract into the alveolar air space of an isolated lung mounted in tyrosine solution increased sodium peroxynitrite and 3-nitrotyrosine, suggesting that relatively stable oxidants in the smoke extract appear to pass through the pulmonary alveolar wall into the blood and induce systemic oxidative stress, which likely facilitates oxidative modification of low-density lipoprotein and endothelial dysfunction (14). Rat cerebral arterioles (closed cranial preparations) were dilated by topical application of ACh. One hour after a one-minute exposure to cigarette smoke, ACh constricted the cerebral arterioles, but preparations treated with either fasudil (Rho-kinase inhibitor) or apocynin (reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase inhibitor) instead dilated in response to ACh (15). Inhibition of Rho-kinase and NADPH oxidase activities appear to prevent the cigarette smoke-mediated impairment of endothelium-dependent vasodilatation. Recently, cigarette smoke extract (CSE) without nicotine and tar is also known to cause endothelial dysfunction via increased vascular oxidative stress (16), and stable carbonyl compounds (acrolein and methyl vinyl ketone) in the CSE induce protein kinase C-dependent activation of NADPH oxidase and subsequent generation of reactive oxygen species via NADPH oxidase (17,18). A functional transcranial Doppler study demonstrated impaired visually evoked flow velocity response caused by cigarette smoking in otherwise healthy young subjects (19). The number of cigarettes smoked per day was negatively correlated with frontal gray matter perfusion measured at 5 weeks of abstinence from alcohol in alcohol dependent individuals; improvement of cerebral perfusion by alcohol abstinence was hindered by cigarette smoking (20). Kochanowicz et al. (21) obtained evidence suggesting that the direct effect of smoking one cigarette on the circulation includes peripheral vasodilatation with possible constriction of the anterior, middle and posterior cerebral arteries in healthy male volunteers. Flow velocity responses evoked by visual stimulation in the posterior cerebral arteries were worse in smokers and former smokers than in non-smokers; however, no significant difference was found between former and current smokers (22).

Continued smoking was associated with increased resistance in uterine, umbilical, and middle cerebral arteries and also led to low fetal weight at birth (23). Maternal smoking appears to interfere with placental and fetal circulation via factors eliminating NO production and augmenting the production of oxygen radicals or vasoconstrictor substances and results in harmful effects in newborns (11).

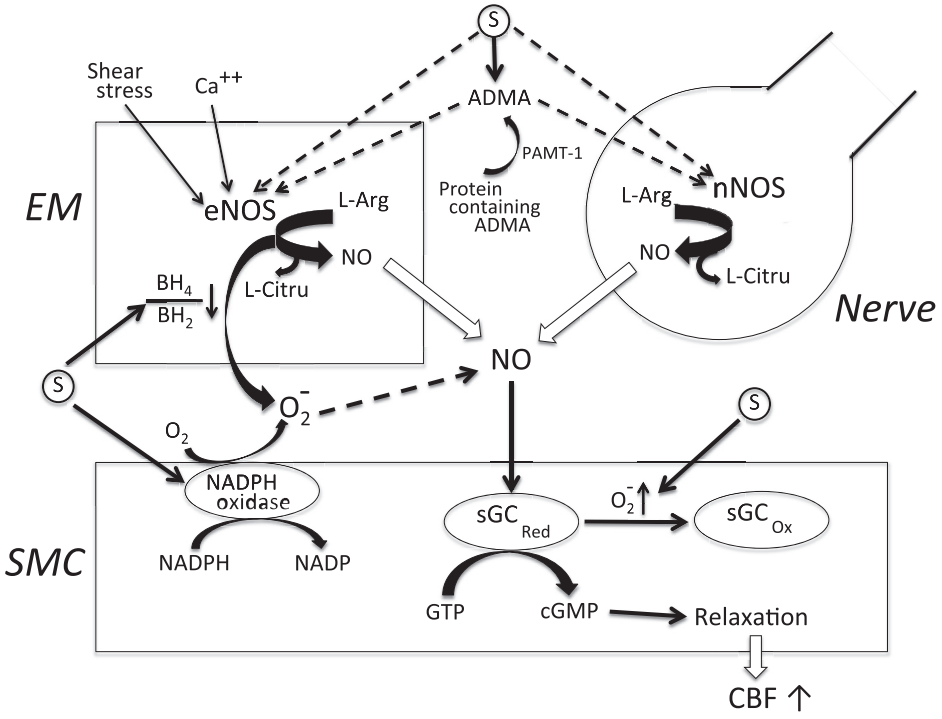

Fig. 1. Schematic presentation of NO synthesis and its degradation and also sites of action of smoking (S). EM, endothelium; SMC, vascular smooth muscle cell; Nerve, nitrergic nerve; eNOS, endothelial NOS; nNOS, neuronal NOS; L-Arg, L-arginine; L-Citru, L-citrulline; ADMA, asymmetric dimethylarginine; BH_4, tetrahydrobiopterin; BH_2, dihydrobiopterin, O_2^-, superoxide anion; sGCred, reduced soluble guanylyl cyclase; sGCox, oxidized soluble guanylyl cyclase; GTP, guanosine triphosphate; cGMP, cyclic guanosine monophosphate; CBF, cerebral blood flow. Solid line, stimulation; broken line inhibition.

2.1. Passive smoking

Effects of passive maternal smoking on the fetal-placental-maternal unit were comparable to those with active maternal smoking as determined by increased resistance in maternal vasculature and adaptive changes of cerebroplacental circulation for maintaining fetal cerebral circulation (24). Passive smoking impaired microvascular function and increased plasma ADMA in healthy male non-smokers (25). Although the authors did not determine the influence on cerebral circulation, increases in circulating ADMA are expected to impair cerebral circulation via increased degradation of NO from endothelial cells and nitrergic nerves.

2.2. Nicotine

Nicotine acts on autonomic ganglia and nerve terminals to liberate neurotransmitters such as norepinephrine, ACh, NO, and polypeptides. Nicotine acutely dilates cerebral vasculatures in humans and experimental animals via the release of NO from perivascular nitrergic nerves (26). Chronic exposure to nicotine elicits blunted NO-induced vasodilatation in pial arteries and increase in cortical blood flow (27). Chronic nicotine appears to induce cerebral hypoperfusion via degradation of NO by increased oxidative stress, whereas acute and chronic exposure to nicotine impairs endothelial function through decreased eNOS-derived NO and decreased NO bioavailability possibly as a result of oxidative stress (11).

Treatment for 60 min of isolated canine basilar arteries with nicotine (10^{-6} M), which is equivalent to the serum level of habitual smokers, attenuated endothelium-dependent dilatation and NO synthesis; nicotine also inhibited NO synthesis in cultured vascular endothelial cells (28). NO synthase-dependent, but not independent, pial arteriolar vasodilatation in vivo was impaired and superoxide anion was increased in rats chronically (2 weeks) treated with nicotine; apocynin alleviated impaired NOS-dependent cerebral vasodilatation; chronic exposure to nicotine increased p47phox protein in the parietal cortex (29). It was suggested that chronic exposure to nicotine impairs NOS-dependent cerebroarterial dilatation by a mechanism related to the formation of superoxide anions.

3. Cigarette smoking and Alzheimer's disease (AD)

Cardiovascular risk factors, including smoking, hypercholesterolemia, hypertension, alcohol consumption and diabetes mellitus, aggravate risk for vascular dysfunction that contributes to dementia (30). Vascular risk factors participate in impairments of endothelial function and increase the risk of incident AD dementia (31). Midlife hypertension is associated with cognitive decline (32). Smoking is associated with an increased risk of AD (33,34). History of smoking, alcohol consumption and increased homocysteic acid are also involved in cognitive decline or AD (35). The progression of cognitive deterioration appears to be related to regional cerebral blood flow affected by the neuropathologic changes of AD (36).

The increased risk for AD and dementia was associated with exposure to environmental tobacco smoke at home and exposure duration (37). Exposure to cigarette smoke appears to increase AD onset and exacerbates its features in transgenic mouse models of AD (38). Banning smoking in public areas may help to reduce a worldwide dementia epidemic. A history of cigarette smoking in the healthy elderly cohort was associated with decreased structural integrity of multiple brain regions, specifically affected by incipient AD (39). Smoking-induced cerebral oxidative stress is suggested to be a potential mechanism promoting AD pathology (40). Midlife vascular risk factors, including smoking, increase the risk for AD (34). Patients with AD have sparser and more tortuous retinal vessels and narrower retinal venules compared with matched individuals without dementia (41). These authors suggested that changes in retinal microvasculature may reflect similar pathophysiological processes in cerebral microvasculature in the brain of AD patients. In Chinese elderly men, the incidence of AD and vascular dementia was higher in individuals who are currently smoking compared with those who never smoked; smoking together with alcohol consumption was related to a higher risk of AD and vascular dementia, whereas it was not in individuals that did not smoke and drink alcohol (42).

3.1. Amyloid-β

Nicotine stimulates mRNA expression of amyloid precursor protein (APP) in the amygdale and hippocampus in mice; treatment of neuroblastoma cells with nicotine increased the expression of APP, whereas co-treatment with mecamylamine, a nicotinic receptor antagonist, attenuates the stimulating effect of nicotine on APP, suggesting that nicotine facilitates the increase in APP expression (43). In transgenic mouse models of AD, exposure to smoking increases the severity of some abnormalities typical of AD, including amyloidogenesis, neuroinflammation, and tau phosphorylation (38).

Hypoxia increases Aβ deposition and neuritic plaque formation and potentiates the memory deficit in APP transgenic mice (44). There is a link between cerebral ischemia/hypoxia and APP processing (45). Brain hypoperfusion appears to result in the classic neurodegenerative regions involving the formation of Aβ plaques and neurofibrillary tangles (5). Cerebral hypoperfusion triggers early vascular disposition of peripherally applied human $A\beta_{1-42}$, later forming stable Aβ deposits in mice (46). Hypoxia rapidly increases hypoxia-inducible factor -1α expression which in turn enhances β-site APP cleaving enzyme 1 (BACE1) promoter activity that causes an increase in Aβ generation due to higher APP cleavage (47). Cerebral hypoperfusion associated with impaired endothelial function by smoking also participates in the increased production of Aβ. Levels of oxidative stress were increased in the hippocampus of the group of rats exposed to cigarette smoke; smoking affects APP processing by increasing the production of secreted APPβ and accumulation of β-amyloid peptide in the hypocampus CA3 and dentate gyrus region (48). There is evidence suggesting that the loss of NO in cultured human cerebrovascular endothelium causes increased expression of APP and BACE1, thereby resulting in increased secretion of Aβ; increased expression of APP and BACE1 as well as increased production of Aβ is detected in the cerebral microvasculature and brain tissue of eNOS-deficient mice (49).

In pressurized segments of rat posterior cerebral arteries and ring segments of the rat aorta, treatment with Aβ decreased ACh-induced, endothelium-dependent vasodilatation (50). In isolated rat basilar arteries exposed for 6 h or longer to $A\beta_{1-40}$ or $A\beta_{25-35}$, ACh-induced endothelium-dependent dilatation was reduced and basal phosphorylation of eNOS (at Ser^{1177}) appeared reduced, suggesting that eNOS activity is inhibited by Aβ (51). There is evidence that vasoactive Aβ disturbs endothelium-dependent factors, disrupting cerebrovascular regulation (52). Circulating $A\beta_{1-40}$ impairs cerebrovascular function in transgenic mice over-expressing mutated forms of APP (53).

Cerebral hypoperfusion due to endothelial as well as nitrergic nerve dysfunction promotes Aβ production and Aβ inhibits cerebral vasodilatation and decreases cerebral blood flow mediated via eNOS and nNOS-derived NO, leading to the vicious cycle of decreased cerebral blood flow, increased production of Aβ and impaired NO production and action (Fig. 2) (9). It is also suggested

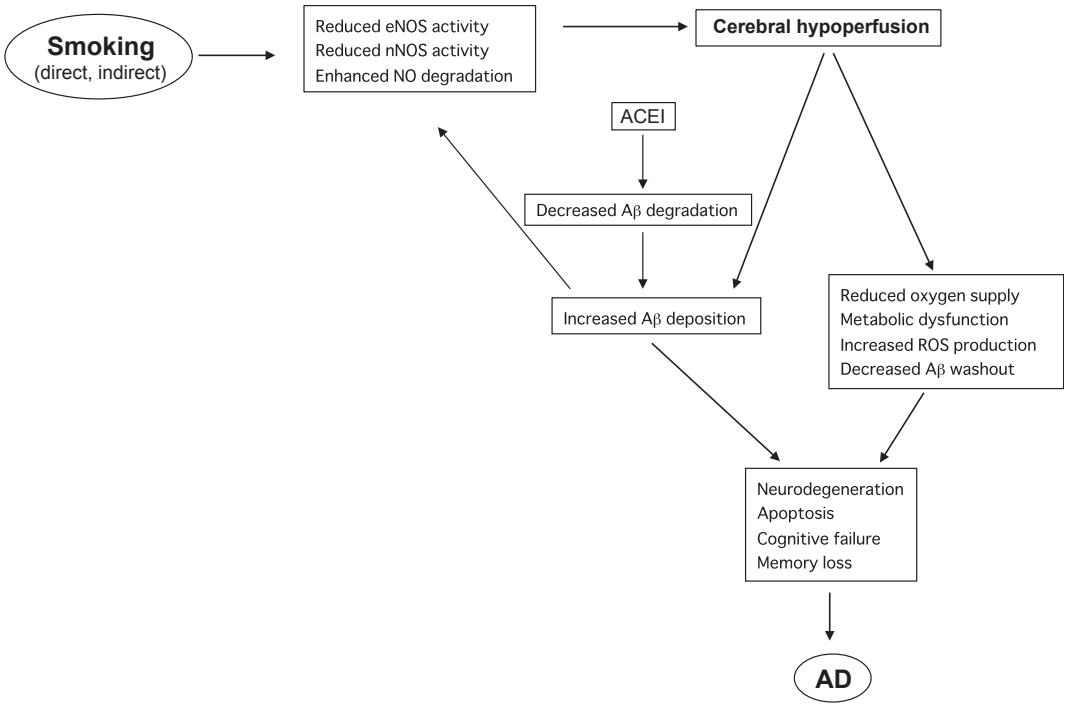

Fig. 2. Summarized scheme of direct and indirect actions of smoking on NO synthesis, action and degradation, cerebral blood flow, and Aβ synthesis/degradation in the pathogenesis of AD. ACEI: angiotensin converting enzyme inhibitor.

that decreased blood flow and glucose metabolism in the brain precede Aβ disposition associated with AD, and Aβ accumulation leads to further decreases in cerebral blood flow (54).

4. AD prophylaxis and drug therapy

4.1. Prophylaxis—the way to increase cerebral blood flow via NO production

The most important way of preventing AD is to reduce or eliminate the burden of AD pathology (55) by eliminating or controlling life style factors, such as smoking (56), alcohol intake (57), sedentary habit (58), obesity (59), and mental stress in daily life (60) and also pathological conditions of hypertension (61,62), diabetes mellitus (63), hyperlipidemia (64) and hyperhomocysteinaemia (65,66). Cognitive failures and AD once established owing to non-recommendable life-habits, especially smoking that impairs cerebral circulation not only to the smokers themselves but also to the non-smokers in their vicinity are not reversed by correcting the habits; however, some cardiovascular drug therapy is expected to slow the progress of AD.

4.1.1. Diet

There is evidence suggesting that higher adherence to the Mediterranean diet is associated with reduced risk of developing mild cognitive impairment and with reduced risk of mild cognitive impairment to AD (67). In a prospective cohort study on older black and white adults, stronger adherence to the Mediterranean diet may reduce the rate of cognitive decline among black, but not white, older adults (68). Higher adherence to a Mediterranean diet was associated with slower Mini-Mental State Examination cognitive decline in elderly French individuals (69). The Mediterranean-type dietary pattern appears to reduce the rate of cognitive decline in black and white older adults (70). In an elderly Australian cohort, there was a significant difference in adherence to the Mediterranean diet between healthy controls and AD subjects and in adherence between healthy subjects and those with mild cognitive impairment (71). There is evidence supporting the hypothesis that the Mediterranean diet and Dietary Approach to Stop Hypertension are associated with slower rates of cognitive decline in older persons (72).

There is a significant increase in verbal memory scores after caloric restriction, but no significant memory changes are observed in the control group and the group of increased uptake of unsaturated fatty acid (73). High intake of fish by Japanese living in fishing villages (74), Alaskan native American (75), and Greenland Eskimos (76) contributes to low incidence of cardiovascular disease in these populations. Increased daily intake of fish improves endothelial function via increased release of NO in human and animal studies (77). In participants aged 65–94 years, dietary intake of n-3 polyunsaturated fatty acids and weekly consumption of fish may reduce the risk of incident AD (78). Fish consumption, but not vegetable, alcoholic beverage, or dairy product consumption, is associated with decreased endothelial dysfunction (79). Total energy and animal fat correlated highly with AD prevalence data; diet, obesity, and smoking are suggested to be major risk factors for AD (80).

After virgin olive oil, rich in the Mediterranean diet, was administered over two periods of 3 weeks to males with stable coronary heart disease, plasma oxidized LDL and lipid peroxide levels were decreased and activities of glutathione peroxidase were increased (81). In older adults, consumption of 1–6 alcoholic beverages weekly is associated with a lower risk of incident dementia (82).

4.1.2. Physical exercise

Regular exercise may improve endothelial function via increased blood flow and laminar shear stress that induce eNOS activation via serine/threonine protein kinase Akt and result in enhancement of NO release from endothelial cells. However, its benefit depends on the type and intensity of training performed;

only regular moderate physical activity promotes an antioxidant state and preserves endothelial function (58). Light physical exercise at midlife, such as gardening, walking, regular exercise involving sports, were associated with reduced odds of dementia compared to hardly any exercise; findings were similar for AD alone (83). Higher midlife fitness levels seem to be associated with lower hazards of developing dementia later in life (84). Both higher physical activity and higher Mediterranean-type diet adherence are independently associated with reduced risk of AD (85).

4.2. Drug therapy

4.2.1. Renin-angiotensin system blockers

Midlife hypertension is associated with cognitive decline (32). Hypertension accelerates the development of AD-related functional alterations through cerebral vasculature impairment and reduced NO production (62).

Angiotensin (ANG)-induced, endothelium-derived NO-mediated vasodilatation and blood flow increase have been summarized in our previous review article (86). Dysfunction of ACh-induced, endothelium-dependent pial vessel dilatation caused by acute, single smoking in rats was prevented by ANG-II type 1 (AT_1)-receptor blockade by valsartan (87). In patients with a diagnosis of probable AD, treatment with renin-ANG-system blockers appears to modulate serum adipocytokines and glucose homeostasis, potentially allowing cognitive decline in AD patients (88). In elderly hypertensive patients with AD, treatment with telmisartan increased cerebral blood flow in the right supra-marginal gyrus, superior parietal lobule, cuneus, and lingual gyrus and showed beneficial effects on cognitive deficits, compared with amlodipine (89). Candesartan and donepezil prevented ANG II-induced memory impairment, cerebral blood flow reduction, and ACh level decrease in the cortex and hippocampus, suggesting that ANG II, via the AT_1 receptor, improves special memory function, cerebral blood flow and brain ACh levels (90). Streptozotocin-induced diabetic mice exhibited a decline of spatial learning and memory; treatment with telmisartan improved memory deficit and reduced $A\beta_{42}$ and anti-β-amyloid precursor protein of the hippocampus and cortex without affecting hyperglycaemia and hypoinsulinaemia, suggesting that this AT_1 receptor-blocker ameliorates memory deficits in diabetic mice (91). Treatment of stroke-prone spontaneously hypertensive rats with imidapril, an angiotensin converting enzyme (ACE) inhibitor, increased the plasma concentrations of NO_2/NO_3 and augmented cerebral arterial diameter and mean blood flow, both of which are diminished by treatment with L-NAME, suggesting that imidapril protects cerebral vasculatures in these hypertensive rats by elevating the release of NO (92).

In newborn pigs, the AT2 receptor agonist CGP42112A induced pial arterial dilatation that was blocked by treatment with L-NA, suggesting that NO release contributes to AT2 receptor-mediated vasodilatation (93). Treatment of type 2 diabetes mellitus with a newly developed AT2 receptor agonist (C21) increased cerebral blood flow, but an anti-dementia drug memantine did not influence the flow; treatment with C21 alone or a combination of C21 and memantine increased hippocampal field-excitatory postsynaptic potential; treatment with C21 or memantine increased ACh level, suggesting a new therapeutic approach against cognitive decline using C21 and memantine (94). Ca^{2+} channel blockers, ACE inhibitors, and AT_1 receptor blockers may be beneficial in diminishing the risk of dementia associated with hypertension (95). However, there is evidence suggesting that ACE degrades Aβ (96–98). Therefore, lowering ACE levels by ACE inhibitors may have adverse consequences for patients with AD (Fig. 2). Hypertension accelerates the development of AD-related functional alterations through cerebral vasculature impairment and reduced NO production in a mouse model of the disease (62). Accumulation of cellular Aβ and tau were decreased with telmisartan (0.3 mg/kg/day, given orally for 6–18 months) in SHR-stroke-resistant rats (99).

4.2.2. Peroxisome proliferator-activated receptor γ (PPARγ) agonists

PPARγ serves as potential therapeutic targets for treating the metabolic syndrome and its related risk factors (100,101), mainly participating in elimination of the synthesis and actions of constitutively induced NO (102). PPARγ agonists, such as pioglitazone, rosiglitazone, and the synthetic agonist GW1929, are used as a therapeutic agent in neurological disorders, including improvement of memory recognition (103).

The use of rosiglitazone was associated with improved cognition and memory in patients with mild to modulate AD disease (104). Clinical trials reported that PPARγ agonists improved cognition and memory in AD patients with data derived from their effects on peripheral tissues, including cerebral vasculatures, rather than on the central nervous system (105). In patients with AD accompanied by type II diabetes mellitus that were treated daily with pioglitazone, cognition and regional blood flow in the parietal lobe were improved, while the control group showed no improvement; plasma $A\beta_{40}/A\beta_{42}$ ratio increased in the control group but showed no change in the pioglitazone group (106). One-month oral administration of pioglitazone ameliorated the production of reactive oxygen species, promoted eNOS phosphorylation, and increased available NO, resulting in improvement of cerebral arterial relaxation in rats (107). Treatment with pioglitazone restored in vivo muscle oxidative capacity in diabetic rats (108). Metformin restored endothelial function through inhibiting oxidative stress and increasing NO availability on activation of the adenosine monophosphate-activated protein/PPARγ pathway in obese diabetic mice (109).

There is evidence suggesting that total area and staining intensity of $A\beta_{1-42}$-positive amyloid deposits in the hippocampus and cortex of APPV7171 transgenic mice are reduced when animals are given a 7 day oral treatment with pioglitazone (110). Whether the decreased Aβ deposit is related to NO-mediated increase in cerebral blood flow is not determined. However, increased amounts of Aβ impair endothelial function (51); therefore, the pioglitazone-induced decrease in Aβ is expected to improve endothelium-dependent cerebral vasodilatation. In a murine model of AD, pioglitazone reduced brain levels of soluble and insoluble Aβ levels and the reduction of amyloid levels was associated with a reversal of contextual memory deficits (111). In the triple transgenic mouse model of AD, treatment with pioglitazone improved learning on the active avoidance task, reduced serum cholesterol, and decreased hippocampal Aβ and tau deposits, suggesting that thiazolidines can ameliorate cognitive deficits associated with AD-related pathology (112).

In type 2 diabetic mice, PPARγ activation by telmisartan appears to protect against cognitive decline by preserving the integrity of the blood brain barrier (113). In transgenic mice expressing a dominant negative mutation in human PPARγ (P467L), dilator responses to exogenously applied and endogenously produced NO were impaired in large cerebral arteries in vitro and small cerebral arterioles in vivo; mechanisms underlying these inhibitory effects after interference with PPARγ involved Rho kinase but not oxidative stress-related mechanisms (114). These authors suggest that therapeutic approaches to target PPARγ in cerebral vasculature may be beneficial in preventing or slowing the progression of vascular diseases in the brain.

As compared with pioglitazone, GFT1803, a PPAR agonist that activates PPAR isoforms (α, β and γ), in the APP/PS1 mouse model produced quantitatively superior and qualitatively different

therapeutic effects with respect to amyloid plaque burden and insoluble Aβ content (115).

4.2.3. 5-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins)

In anesthetized Zucker obese rats, rosuvastatin improved cerebrovascular function independently from its lipid-lowering effect by the inhibition of NAD(P)H oxidase (116). Simvastatin improved reactivity of cerebral arteries, rescued the blood flow response to neuronal activation, attenuated oxidative stress and inflammation, and reduced cortical soluble Aβ levels and the amount of Aβ plaque-related dystrophic neuritis in APP transgenic mice (117). Simvastatin fully restored short- and long-term memory in adult, but not in aged mice; these beneficial effects occurred without any decreasing effect of this statin on brain Aβ levels or plaque load, suggesting that brain-penetrant statins bear therapeutic promise in early AD (118).

Treatment with a statin was associated with a significantly lower risk of dementia in a cohort of elderly patients in Taiwan (119). Statin use was associated with 61% lower AD mortality, whereas the use of other cholesterol-lowering medications was not (120). On the other hand, analyses from studies on established dementia from two large randomized controlled trials indicate that statins have no benefit on the primary outcome measures (121).

4.2.4. Acetylcholinesterase (AChE) inhibitors

AChE inhibitors, widely known as effective AD therapeutics, increase cerebral blood flow in AD patients (122–126). Increasing cerebral blood flow is an efficient means to supply oxygen and glucose to brain tissues in AD patients. ACh liberated from cholinergic neurons innervating cerebral arteries, even if any, does not seem to participate in liberating NO from the endothelium (9), since ACh applied to monkey and dog cerebral arteries does not induce relaxations but instead elicits contraction (26).

Electrical stimulation of the basal forebrain increased cortical cerebral blood flow in anesthetized rats and treatment with heptylphysostigmine potentiated the stimulation-induced blood flow increase, suggesting that this effect may participate in the efficacy of the AChE inhibitor for treatment of AD (127). Electrical stimulation of the parasympathetic ganglion resulted in cerebral vasodilatation in dogs (128) (Fig. 3) and monkeys (129) and increased

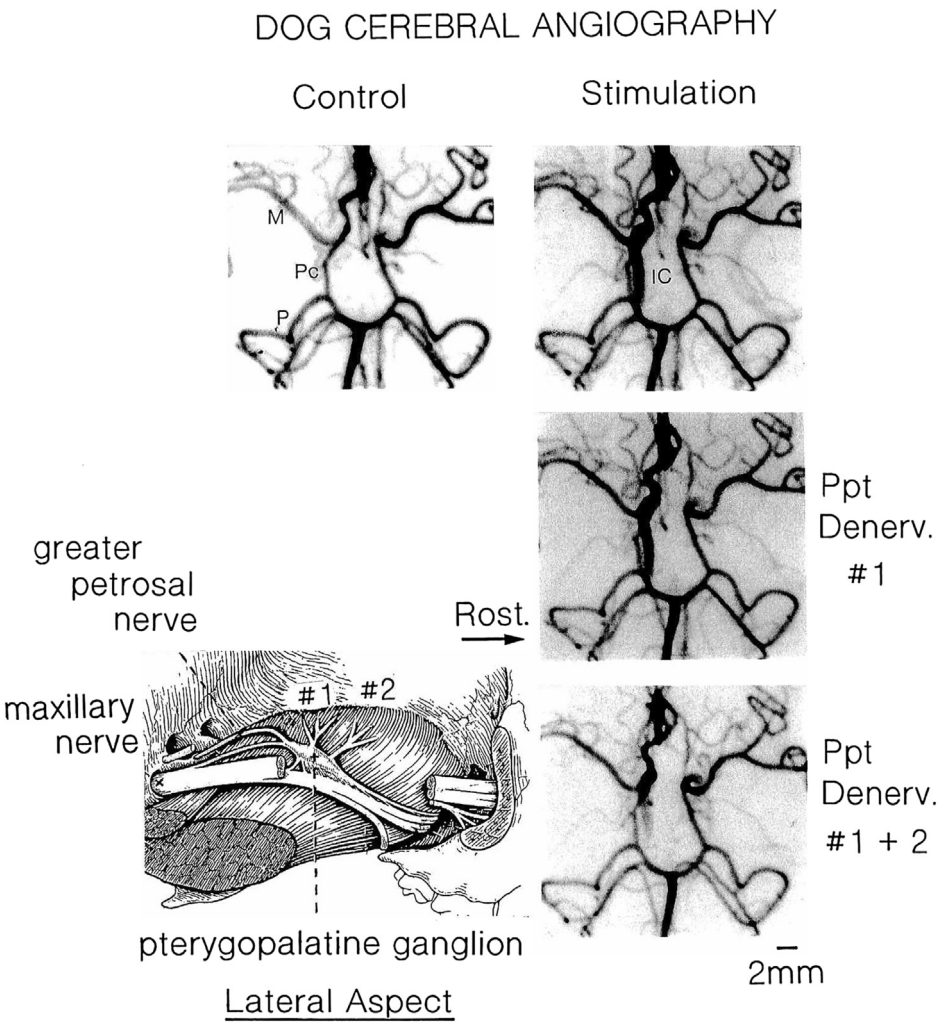

Fig. 3. Modification by sectioning (Denerv) of postganglionic neurons from the pterygopalatine ganglion of vasodilator responses to stimulation of the proximal petrosal nerve (10 Hz) of middle (M) and posterior (P) cerebral, posterior communicating (Pc), and intracranial internal carotid (IC) arteries of an anesthetized dog. The inset indicates the lateral aspect (rostral side, right) of the pterygopalatine ganglion and neurons to the ganglion (greater superficial petrosal nerve) and those out of the ganglion (1 and 2). Recordings: top left, before nerve stimulation; top right, during nerve stimulation without nerve sectioning; middle right, during nerve stimulation after denervation of position #1; during nerve stimulation after denervation of positions #1 and #2.
Reproduced with permission from J Cereb Blood Flow Metab 20: 700–708, 2000.

cortical blood flow in rats (130,131). However, mechanisms underlying muscarinic receptor activation in cerebral vasculatures are not involved in the vasodilator response (128,129,131). The pre- and postganglionic nerve stimulation activates parasympathetic, nitrergic neurons innervating cerebral arteries and arterioles, both of which liberate NO generated via nNOS activation for cerebral vasodilatation (128,129). AChE inhibitors appear to potentiate ACh actions at the site of pterygopalatine ganglia by inhibiting the degradation of ACh liberated from the pre-synaptic sites. Enhanced ACh actions result in increasing postganglionic nitrergic nerve impulses and enhancing the release of NO from nerve terminals (9). Another site of action of AChE inhibitors would be presynaptic cholinergic nerve terminals innervating the inferior salivatory nucleus; the increased release of ACh activates the nuclear cells sending down more impulses through the pterygopalatine ganglion to nitrergic neurons.

The cerebral blood flow in the middle and posterior cingulate cortex increased in mild AD patients after donepezil treatment, which was the neural substrate of the medial cholinergic pathway; the baseline cerebral blood flow and its changes after drug treatment were correlated with the behavioral changes in AD Assessment Scale-Cognitive subscale scores (126). Increase in the dosage of donepezil from 5 to 10 mg/day was significantly more effective in improving the AD Assessment Scale score and cerebral blood flow (132).

4.2.5. Sildenafil

Erectile dysfunction is widely known to result mainly from dysfunctional nitrergic nerves and also impaired actions of endothelium-derived NO (133). The phosphodiesterase-5 inhibitor sildenafil is regarded as an efficient therapeutic against erectile dysfunction (134,135). Increased incidence of erectile failure is seen in patients with AD (136). Sildenafil enhances neurogenesis and it has also a memory enhancing action; therefore, it is suggested that targeting phosphodiesterase-5 with sildenafil offers novel strategies in the treatment of memory impairment (137). L-Citrulline, an effective precursor of L-arginine and NO, is a potent hydroxyradical scavenger; therefore, its supplementation appears to be useful for treatment of erectile dysfunction and AD (138). Data concerning the efficacy of sildenafil on cognitive dysfunction and AD are still insufficient.

4.2.6. Others

Topical application of ACh produced dilatation in rat cerebral arterioles; however, 1 h after a 1 min smoking, the effect of ACh was reversed to vasoconstriction: pre-treatment with fasudil or apocynin reversed the vasoconstriction by smoking to vasodilatation, suggesting that inhibitions of Rho-kinase and NADPH oxidase activities appear to prevent the smoking-induced impairment of endothelium-dependent, NO-mediated vasodilatation (15). In anesthetized rats, cerebral pial arterioles were dilated by ACh; after smoking, ACh constricted the arterioles but induced vasodilatation following pretreatment with varenicline, a selective nicotinic ACh receptor agonist, suggesting that varenicline appears to prevent the smoking-induced impairment of endothelium-dependent vasodilatation (139).

5. Summary

This review article summarizes clinical and experimental observations supporting that cigarette smoking-induced impairment of cerebral vasodilatation and blood flow is one of the risk factors for spatial memory disturbance and AD in humans and experimental animals. Cerebral vascular dysfunction and hypoperfusion in the brain are quite important clinical features in AD patients. Acute and chronic smoking as well as passive smoking impairs cerebral blood flow due to decreased syntheses and actions of NO liberated from endothelial cells and nitrergic nerves and to augmented oxidative stress. This is also true when nicotine is administered, except for acute application of nicotine, which stimulates nitrergic nerves and liberates NO. Cerebral hypoperfusion due to decreased actions of NO by smoking would participate in impaired cognitive function and AD. Cerebral blood flow decrease promotes the production of Aβ and Aβ impairs the NO production; removal of the smoking habit is expected to be effective in interfering with this vicious cycle. There are many ways to prevent AD by maintaining good quality health habits in daily life from young age (moderate exercise, adequate food intake, no smoking, limited alcohol drinking and reduced stress) and also by early extensive treatment of hypertension, diabetes mellitus, hypercholesterolemia. Recent advances in research on cardiovascular disease and diabetes therapeutics, such as AT1 receptor antagonists and PPARγ agonists, have been proven to be effective in treating cognitive failure and AD. Further development of research on potent and safe therapeutics should be encouraged. In addition, prophylaxis from a young age by controlling daily life-habits, especially quit smoking, would also be important. Social and governmental efforts as well as doctor's advice to patients are required to increase success in preventing onset and progress of AD.

Conflict of interest

The authors declare no competing financial interests in relation to the work described in this report.

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