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Review Article
Involvement of Arachidonic Acid Metabolites Pathway and Nicotinic Acetylcholine Receptors (nAChRs) on Nicotine-induced Contractions (or Relaxations) in the Basilar Artery

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Abstract
Smoking is one of the most important risk factors for cerebral circulatory disorders and nicotine is considered to be the major pathogenic compound in cigarette smoke. Amelioration of nicotine-induced vasoconstrictions (or vasodilations) may provide a therapeutic target for the treatment of stroke. This study will review the involvement of arachidonic acid metabolites pathway and nicotinic acetylcholine receptors (nAChRs) on nicotine-induced contractions (or relaxations) in the basilar artery. Arachidonic acid metabolites pathway and nAChRs may be new drug targets and their selectivity antagonists (or agonists) may be new therapeutic drugs for the treatment of stroke.

Key words: Basilar artery, nicotine, vasoconstriction, vasorelaxation, arachidinic acid, nicotinic acetylcholine receptors (nAChRs), endothelium

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INTRODUCTION

Cigarette smoke is a significant risk factor of stroke[1-3]. Both active smoking and passive smoking pose a risk. The population-attributable risk for and stroke associated with smoking[4] is about 18.9%. Smoking is a chronic disease that tends to recur because of nicotine dependency, many patients continue smoking even after an attack of stroke. At one year after and stroke, 22% of patients are still smoking[5]. Therefore, support measures to enforce nonsmoking are required in this high-risk population. The risk after smoking cessation for 5-10 years is equal to that faced by a non-smoker.

There are two main types of stroke: Ischemic stroke due to lack of blood flow and hemorrhagic stroke due to bleeding. Cigarette smoking is also one of the most important risk factors of hemorrhagic stroke[6-10]. Cigarette smoking may be a risk factor for recurrent hemorrhagic stroke after aneurysm repair[9] and it has also been associated with symptomatic vasospasm after hemorrhagic stroke[11]. In recent studies, cigarette smoking has been shown to increase the risk of vasospasm following hemorrhagic stroke and smokers are 2.5 times more likely to experience a ruptured aneurysm than non-smokers[11-13]. However, it was reported that 37% of patients resume smoking after hemorrhagic stroke[6]. Cerebral vasospasm after subarachnoid hemorrhage (SAH) is the leading cause of delayed morbidity and mortality following aneurysmal SAH[14]. Cerebral vasospasm is a multi factorial disease process characterized by a combination of endothelial and smooth muscle cell dysfunction and inflammation[15-17].

Cigarette smoke is a highly complex mixture containing thousands of different compounds[18] and nicotine is considered to be the major pathogenic compound in cigarette smoke[19]. Nicotine is a chiral molecule and the S(-)-isomer is predominant in cigarette smoke, with the R(+)-isomer representing only 3-12% of total nicotine content[20,21]. This present studies have specifically studied effects of nicotine on the cerebral vascular after hemorrhagic stroke[22-24]. Therefore, amelioration of nicotine-induced vasoconstrictions (or vasodilations) may provide a therapeutic target for the treatment of stroke.

Nicotine is considered to most significantly affect cerebral arterial tone in the brain. Large arteries such as the basilar artery, make an important contribution to the total cerebral vascular resistance and are major determinants of local micro vascular pressure in the cerebral circulation[25].

Undoubtedly, understanding the mechanism of nicotine-induce contractions (or relaxations) in the basilar artery will be a crucial step for designing a more effective treatment plan. Although, the pharmacology of nicotine-induced vasocontractions (or vasodilations) was well studied, nicotine-induced vasoconstriction (or vasodilation) in the basilar artery was not well summarized in the basilar artery. In the present study, we will review the involvement of arachidonic acid metabolites pathway and nicotinic acetylcholine receptors (nAChRs) on nicotine-induced contractions (or relaxations) in the basilar artery. Arachidonic acid metabolites pathway and nAChRs may be new drug targets and their selectivity antagonists (or agonists) may be new therapeutic drugs for the treatment of stroke.

EFFECTS OF NICOTINE IN THE BASILAR ARTERY

Nicotine could induce contraction or relaxation of the basilar artery. Toda[26] reported that nicotine caused a transient relaxation in the canine basilar artery which pre-contracted with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). It has been reported that nicotine induced endothelium-dependent contraction in the basilar artery of rat[22-24,27] and canine[28]. It has been reported that nicotine induced endothelium-dependent rexalation in the basilar artery of porcine[29], guinea pig[30] and canine[26] (Table 1).

Recently, we have reported that the nicotine-induced contractions of the rat basilar artery are mostly endothelium-dependent at nicotine concentrations (3×10^{-5} to 3×10^{-3} mol L^{-1}). At higher nicotine concentrations (10^{-3} to 10^{-2} mol L^{-1}), nicotine-induced contraction is about 90% endothelium-dependent in the rat basilar artery[27].

In addition, nicotine not only induced contraction or rexalationin the basilar artery but also affect other pharmacological nature of the artery. For example, nicotine potentiated 5'-triphosphate (UTP)-induced contraction response through protein kinase C (PKC) activation in the canine basilar artery[31]. Nicotine-induced contraction appeared to be mediated by activation of nicotinic acetylcholine receptors (nAChRs), Rho-kinase and cyclooxygenase pathways in the rabbit corpus cavernosum[32]. Acute exposure to nicotine impaired NOS-dependent dilation of the rat basilar artery[33].

EFFICACY OF nAChRs IN THE BASILAR ARTERY

The effects of nicotine are mediated by the interaction of the alkaloid with a number of nAChRs. According to specific pattern of distribution, three different types of nAChRs exist: (1) Muscle-type nAChRs ($\alpha1\beta1\delta\epsilon$ and $\alpha1\beta1\delta\gamma$-nAChRs), (2) Ganglion-type nAChRs ($\alpha3\beta2$-nAChRs) and (3) Central nervous system (CNS)-type nAChRs ($\alpha4\beta2$, $\alpha3\beta2$ and $\alpha7$-nAChRs)[34,35] (Table 2).

Table 1: Effects of nicotine on the basilar artery

Year	Specimen of basilar artery	Dose of nicotine (μmol L^{-1})	Effects	Mechanism	References
1975	Canine	5-10000	Contraction and relaxation	nAChR, Na^+ pump	Toda[26]
1988	Canine	10000	Contraction	Endothelium-dependent, TXA_2	Shirahase *et al.*[28]
1997	Guinea-pig	100	Relaxation	Endothelium-dependent, NO	Jiang *et al.*[30]
1998	Porcine	100	Relaxation	NO, nAChR	Nguyen *et al.*[32]
1999	Guinea-pig	100	Relaxation	5-HT_1 receptor, NO	Mayhan *et al.*[33]
2000	Porcine	100	Relaxation	NO	Domino[34]
2001	Porcine	1-100	Relaxation	nAChR	Rang and Dale[35]
2002	Porcine	100		NO, nAChR	Li *et al.*[36]
2006	Porcine	100	Relaxation	α7-nAChR, NO	Moccia *et al.*[37] and Devillers-Thiery *et al.*[38]
2007	Rat	30-3000	Contraction	Endothelium-dependent, Arachidonic acid metabolites	Ji *et al.*[27]
2009	Porcine	100	Relaxation	PGE_2, EP_1 receptor	Lee *et al.*[39]
2011	Porcine	100	Relaxation	α7-nAChR, NO	Lee *et al.*[40]
2012	Monkey		Relaxation	NO	Si and Lee[41]
2012	Porcine	100	Relaxation	α3β2-nAChR	Si and Lee[42]
2013	Rat	3000	Contraction	Arachidonic acid metabolites, nAChR	Ji *et al.*[22-24]
2014	Porcine	100	Relaxation	L-type calcium channel, α3β2-nAChR	Wu *et al.*[29]

Table 2: Subtype of nAChRs

Receptor-type	Location	Effect and functions	Nicotinic agonists	Nicotinic antagonists
Muscle-type: $(\alpha_1)_2\beta_1\delta\varepsilon$ or $(\alpha_1)2\beta_1\delta\gamma$	Neuromuscular junction	EPSP, mainly by increased Na^+ and K^+ permeability	Acetylcholine Carbachol Suxamethonium	α-bungarotoxin α-conotoxin Tubocurarine Pancuronium Atracurium
Ganglion-type: $(\alpha_3)_2(\beta_4)_3$	Autonomic gangila	EPSP, mainly by increased Na^+ and K^+ permeability	Acetylcholine Carbachol Nicotine Epibatidine Dimethylphenylpiperazinium	Burropion 18-methoxycoronaridine Dextromethorphan Hexamethonium Ibogaine Mecamylamine Trimetaphan
Heteromeric CNS-type: $(\alpha_4)_2(\beta_2)_3$	Brain	Post and presynaptic excitation mainly by increase Na^+ and K^+ permeability. Major subtype involved in the rewarding effect of nicotine	Acetylcholine Cytisine Epibatidine Nicotine Nifene Varenicline	α-conotoxin Dextromethorphan Dihydro-β-erythroidine Mecamylamine
Further CNS-type: $(\alpha_3)_2(\beta_4)_3$	Brain	Post and presynaptic excitation	Acetylcholine Cytisine Epibatidine Nicotine	Dextromethopphan Hexamethonium Mecamylamine Tubocurarine
Homomeric CNS-type $(\alpha_7)_5$	Brain	Post and presynaptic excitation mainly by increase Ca^{2+} permeability. Major subtype involve in the pro-cognitive effects of nicotine. Also involved in the pro-angiogenic effects of nicotine and accelerate the progression of chronic kindly disease in smokers	Cytisine Epibatidine Dimethylphenylpiperazinium Varenicile	α-bungarotoxin Amantadine Dextromethorphan Mecamylamine Memantine Methylcaconitine

Ganglion-type and CNS-type nAChRs belong to the neuronal nAChR. These receptors were originally discovered in the nervous system but are also expressed in a variety of non-neuronal cells, for example, vascular smooth muscle cells from the basilar artery of the guinea pigs[36] and endothelial cells of the rat coronary microvascular[37]. The muscle-type nAChRs are present exclusively in the cell membranes of skeletal muscle[38].

Various nAChRs play different biological roles in the basilar artery. It has been reported that nicotine-induced relaxation in the canine basilar artery and nicotine-induced contraction in the canine mesenteric artery were the result of a specific action on nAChRs[26]. Wu *et al.*[29] have been reported that nicotine-induced relaxation in the porcine basilar artery were in relation to α3β2[39,40] and α7-nAChRs[36,41-48].

Mecamylamine was an antagonistof neuronal nAChRs[49-51]. Hexamethonium was an antagonist of ganglion-type nAChRs, which was one of the first compounds used to discriminate the ganglionic and muscle nAChRs[50]. Gallamine was an antagonist of the muscle-type nAChRs.

In this previous study[24], in the rat basilar artery, mecamylamine (CNS and ganglion-type nAChRs antagonist) and gallamine (muscle-type nAChR antagonist) attenuated the nicotine-induced contraction in a concentration-dependent manner but hexamethonium (ganglion-type nAChR antagonist) did not affect nicotine-induced contraction. These results suggested that nicotine-induced contraction involved the CNS nAChR subfamily and skeletal muscle nAChR subfamily pathways. The concentration of mecamylamine leading to attenuation was significantly lower (over 1/100th) than the concentration of gallamine, to obtain the same inhibitory effect on nicotine-induced contraction. In addition, it have been reported that nicotine is a very weak agonist of muscle nAChRs[52]. These results indicated that nicotine in the rat basilar artery showed a high affinity to the CNS-type nAChRs and low affinity to the muscle-type nAChRs.

Our group has also reported the nicotine-induced contractions of the rat basilar artery are mostly endothelium-dependent at nicotine concentrations (3×10^{-5} to 3×10^{-3} mol L^{-1}). At higher nicotine concentrations (10^{-3} to 10^{-2} moL L^{-1}), nicotine-induced contraction is about 90% endothelium-dependent in the rat basilar artery[27]. Neuronal nAChRs are expressed in vascular smooth muscle cells[38] and endothelial cells[37]. In contrast to this, skeletal muscle nAChRs are only present exclusively in skeletal muscle[38].

Taken together with our preview reports, nicotine-induced contraction in the rat basilar artery involved the CNS nAChR and skeletal muscle nAChR subfamily pathways. Nicotine has a lower agonistic potency for the muscle-type nAChRs and is a much more potent agonist for the neuronal nAChRs. Our group assumed that the CNS-type nAChRs in the endothelium play a key role to nicotine-induced contraction in the rat basilar artery.

The nAChRs played a significant role to nicotine-induced contraction (or rexalation) in the basilar artery. Furthermore, the nAChRs were also mediated nicotine-induced migration of vascular smooth muscle cells[36] and norepinephrine-induced contraction in the pial arteries of cat and rabbit[53,54].

The Ca^{2+} was one of the effectors of nAChR[34,55,56]. The nAChR activation could cause a significant elevation of the cytosolic concentrationsof Ca^{2+} in rat endothelium[57]. Nicotine does not induce a transient increase in the intracellular free Ca^{2+} concentration in rat microvascular endothelial cells[37]. It also have been reported that nicotine induced a significant Ca^{2+} influx in cultured superior cervical ganglionic cells but failed to affect calcium influx in cultured sphenopalatine ganglionic cells in the porcine basilar artery[41]. Stimulation of nAChR causes the depolarization and activation of L-type Ca^{2+} channel in rat pineal ocytes[58]. The nAChRs are inhibited by several drugs that are commonly thought to be specific for L-type Ca^{2+} channel[59,60]. It also have been reported that the sympathetic neuronal calcium influx through L-type Ca^{2+} channel was modulated by α3β2-nAChRs[29]. It have been considered that L-type Ca^{2+} channel played an important role in the regulation of functions, especially in the synthesis and release of vasoactiveendothelium-derived factors[61,62]. The global Ca^{2+} signals that activate smooth muscle cell contractionare largely due to the activation of L-type Ca^{2+} channels[61]. The L-type Ca^{2+} channels are present not only in vascular smooth muscle cells[63-66] but also in endothelium cells[62,67,68] in the arterial system. Nifedipine is an L-type Ca^{2+} channel blocker and selectively inhibited the nicotine-induced contractions of intracranial arteries but not of peripheral arteries[69]. This study also indicated that nicotine-induced contraction involved L-type Ca^{2+} channels and contraction of the rat basilar artery was inhibited by nifedipine (10^{-9} to 10^{-8} mol L^{-1})[24].

INVOLVEMENT OF ARACHIDONIC ACID METABOLITES PATHWAY ON NICOTINE-INDUCED CONTRACTIONS (OR RELAXATIONS) IN THE BASILAR ARTERY

Arachidonic acid is a key inflammatory intermediate factor and inflammation play a central role in tissue injury and many diseased states[70,71]. The levels of arachidonic acid metabolites are enhanced in the cerebrospinal fluid of SAH patients[22,23,72,73].

Phospholipase C (PLC) and phospholipase A_2 (PLA_2) catalyze the production of arachidonic acid from membrane phospholids during cellular stimulation. Arachidonic acid is metabolized mainly by 2 pathways: (1) The cyclooxygenase (COX) pathway generates the unstable intermediary endoperoxide prostaglandin (PG) H_2, which gives rise to prostaglandins, thromboxanes and prostacyclin, (2) The lipoxygenase (LOX) pathway generates 5(S)-hydroperoxy-6-trans-8,11,14-cis-eicosatetraenoic acid, which gives rise to 5(S)-hydroxy-6-trans-8, 11, 14-cis-eicosatetraenoic acid and leukotrienes.

It is also reported that nicotine-induced contraction of the rat basilar artery via the CNS-type nAChRs and muscle-type nAChRs pathways[24] and nAChRs signaling is involved in the PLC pathway[74,75].

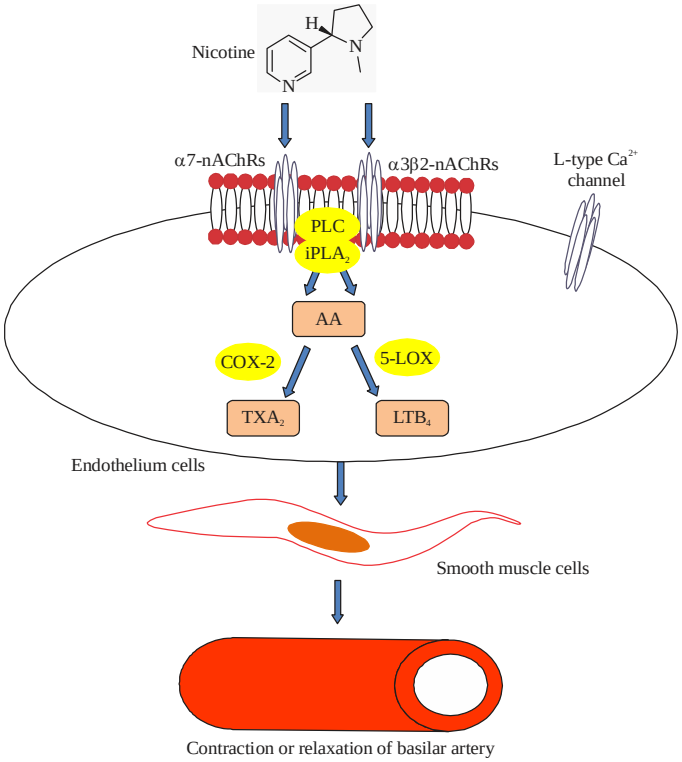

Fig. 1: Involvement of arachidonic acid metabolites nicotine-induced contractions (or relaxations) in the basilar artery

It has been reported that nicotine-induced contraction involves thromboxane A_2 (TXA_2) in the canine basilar artery[28]. In the rat coronary artery, nicotine-induced contraction involves endothelial COX-1 metabolites of arachidonic acid[76]. This present studies reported that the PLC (or calcium-independent PLA_2), COX-2, 5-LOX and BLT_2 pathways may be the main signaling pathways involved in nicotine-induced contraction in the rat basilar artery (Fig. 1)[21,30]. The $PGF_{2\alpha}$ could induce endothelium-dependent contraction in the porcine[77] and canine[78] basilar arteries. Nicotine could cause a transient relaxation in the canine basilar artery which pre-contracted[26,29] with $PGF_{2\alpha}$.

The PLA_2 is a family of enzymes that is ubiquitous in mammalian cells and plays an important role in the maintenance of membrane phospholipids, as well as the production of inflammatory lipid mediators that regulate cellular activity. In mammalian cells, PLA_2 is known to be present in several isoforms[79]. There are three broad classes of PLA_2 based on the cellular disposition and calcium dependence. A family of low molecular mass (14 kDa) enzymes, depending on high calcium concentrations (of the mmol L^{-1} order), have been termed $sPLA_2$. A second form, $cPLA_2$ is activated by low concentrations (μmoL L^{-1}) of calcium[80]. A third form, $iPLA_2$ is Ca^{2+}-independent and shares some characteristics with $sPLA_2$ and others[81] with $cPLA_2$. It has been reported that $iPLA_2$ represents about 80% of the total PLA_2 activity[82]. The $iPLA_2$ was present in the endothelial cells, but weak signals were also detected in the smooth muscle cells[83]. The $iPLA_2$ played a key role in the endothelium-dependent contractions to acetylcholine in the aorta of the spontaneously hypertensive rat[83]. Our group also reported that $iPLA_2$ was an important isoform among the three PLA_2 isoforms regarding contraction induced by nicotine. Nicotine-induced contraction in the rat basilar artery is partially due to PLC and $iPLA_2$ activation.

In the basilar artery, COX catalyses the production of prostanoids from arachidonic acid[84,85]. Two distinct COX isoforms have been identified and both perform the same catalytic reaction and inhibit the conversion of arachidonic acid to prostanoids. The COX-1 is expressed constitutively in most tissues throughout the body, including the gastrointestinal tract, kidneys and platelets. The COX-2 is normally expressed at low levels in normal tissue, but it is stimulated to express strongly by inflammatory mediators at sites of inflammation[86-88]. Our group indicates that COX-2 but not COX-1, is involved in nicotine-induced contraction in the rat basilar artery, suggesting that nicotine may play a role as a pro-inflammatory mediator.

The ZM-230487 (5-LOX inhibitor) attenuated the contraction of the rat basilar artery in a concentration-dependent manner. The 5-LOX is the key enzyme involved in leukotriene biosynthesis and catalyzes the initial steps in the conversion of arachidonic acid to these biologically active lipid mediators, which are known to exert proinflammatory effects *in vivo*[89]. In this present study concerning the effects of the 5-LOX inhibitor (ZM-230487) on vasopressin-induced contraction in the rat basilar artery, ZM-230487 attenuated the contraction[90]. As far as nicotine-induced contraction in the rat basilar artery is concerned, the activation of 5-LOX may play a role in promoting the formation of not only atherosclerotic lesions, but also aortic aneurysms[91]. These studies suggest that smoking and particularly nicotine, may activate the 5-LOX pathways in the cerebrovascular system.

Cigarette smoke is related to enhanced cysteinyl leukotriene (CysLT) synthesis[92]. The levels of leukotriene B_4 (LTB_4) and leukotriene E_4 (LTE_4) were 4 times higher in the blood of cigarette smokers than in that of the controls[93]. Moreover, the urinary excretion of thromboxane A_2 (TXA_2) metabolite was higher in cigarette smokers than in the controls[94]. The TXA_2 is a cyclooxygenase metabolite of arachidonic acid, whereas LTB_4 and CysLTs are the 5-lipoxygenase (5-LOX) metabolites of arachidonic acid.

The LTB_4, an endothelium-derived contracting factor, was found in the rat coronary artery[95] and the guinea pig aorta[96]. Neither LTC_4 nor LTD_4 lead to the contraction or relaxation of the isolated human cerebral artery strips[97]. Physiological concentrations of nicotine do not affect thromboxane production in the human umbilical vein[98].

In the previous study, we observed that the antagonists of the TXA_2 and CysLT receptors did not affect nicotine-induced contraction. In contrast, the antagonists of LTB_4 receptor (BLT_1 and BLT_2) significantly attenuated nicotine-induced contraction in the rat basilar artery. The concentration of LY255283 (a BLT_2 receptor antagonist) that produced attenuation was significantly lower than that of CP105696 (a BLT_1 receptor antagonist), in order to obtain the same inhibitory effect on nicotine-induced contraction. These results suggest that LTB_4 is involved in nicotine-induced contraction in the rat basilar artery, whereas, TXA_2 and CysLTs are not involved. Moreover, nicotine in the rat basilar artery exhibits a higher affinity for BLT_2 receptor than BLT_1 receptor. The study found that blockade LTB_4 receptors, BLT_1 and BLT_2, abrogate nicotine-induced cerebrovascular vasoconstriction in a dose-dependent manner whereas blockade of cysteinyl LT (CysLT, collectively LTC_4, LTD_4 and LTE_4) and TXA_2 receptors does not affect contractility.

PERSPECTIVES

Taken together with preview reports and this studies, nicotine-induced contractions (or relaxations) in the basilar artery is concentration-dependent and endothelium-dependent. This study provides novel pharmacological evidence for the first time that nicotine-induced vasoconstrictions (or vasorelaxations) is about 90% endothelium-dependent in the basilar artery and nicotine in the basilar artery showed a high affinity to the neuronal nAChR subfamily and low affinity to the skeletal muscle nAChR subfamily. The nAChRs signaling is involved in the arachidonic acid metabolites. Nicotine-induced contractions (or relaxations) might be due to the products of membrane phospholipids involving arachidonic acid metabolites pathway in the basilar artery (Fig. 1). This review elucidates the arachidonic acid metabolites pathways and nAChRs involved in nicotine-induced contractions (or relaxations). This study may represent a new cerebrovascular pathology and play critical roles in fatal cerebral circulatory disorders. Arachidonic acid metabolites pathway and nAChRs maybe new drug targets and their selectivity antagonists (or agonists) may be new therapeutic drugs for the treatment of stroke.

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