Cigarette smoking in human subjects produces diffuse vascular injury in many organ systems (8, 16, 27, 51). Although the morphological and functional effects of cigarette smoke and/or cigarette smoke extract on isolated blood vessels and endothelial cells in vitro have been examined, the pathogenesis of cigarette smoking-induced vascular damage in vivo is still uncertain. Morphological abnormalities, i.e., endothelial cell swelling, extensive subendothelial edema, and subendothelial blebs, and an increased number of subendothelial macrophages in the arterial wall have been observed in human subjects exposed to cigarette smoke for prolonged periods of time (2, 4, 32). Functionally, exposure of animals and endothelial cell monolayers to cigarette smoke has been shown to increase permeability to plasma proteins (3, 20, 23, 32) and to decrease nitric oxide synthase-mediated relaxation of blood vessels from human subjects (17, 18). In addition, recent studies from our laboratory suggest that cigarette smoke extract potentiates agonist-induced increases in microvascular permeability (36) and impairs nitric oxide synthase-mediated dilatation of resistance arterioles in vivo (48).

In addition to activation of guanylate cyclase via the synthesis and/or release of nitric oxide, relaxation of vascular smooth muscle can be influenced by activation of ATP-sensitive potassium channels and activation of adenylate cyclase. However, no studies have examined the effects of cigarette smoking on these important cellular dilator pathways. Thus the goal of this study was to examine the effects of cigarette smoke extract on dilatation of resistance arterioles in vivo in response to activation of ATP-sensitive potassium channels and in response to activation of adenylate cyclase.

**METHODS**

Preparation of animals. Adult male hamsters weighing between 120 and 140 g were anesthetized with pentobarbital sodium (6 mg/100 g body wt ip). A tracheotomy was performed to facilitate spontaneous breathing. A catheter was placed in a femoral vein for the purpose of infusing supplemental anesthesia (2–4 mg·100 g⁻¹·h⁻¹). A femoral artery was cannulated to measure arterial blood pressure, which remained constant during the experiment (data not shown). At the end of the experiment, all animals were killed with an intravenous infusion of anesthesia (60 mg/100 g body wt). All procedures were carried out after institutional approval and within institutional guidelines.

To visualize the microcirculation of the cheek pouch, we used a method described previously (35, 36, 48). Briefly, the left cheek pouch was spread gently over a small plastic baseplate, and an incision was made in the skin to expose the cheek pouch membrane. An upper chamber was positioned over the baseplate, and the cheek pouch membrane exposed between these two plates (35, 36, 48).

After these initial procedures, the hamster was transferred to a heated microscope stage. Body temperature was monitored and maintained constant via a feedback controller and heating pad. The cheek pouch chamber was connected to a reservoir that allowed continuous suffusion of the cheek pouch microcirculation with warm (36–38°C) bicarbonated buffer (pH 7.40) bubbled continuously with 95% N₂-5% CO₂. The chamber was also connected via a three-way valve to an infusion pump that allowed for the controlled administration of cigarette smoke extract and vasoactive agonists.

The cheek pouch microcirculation was epi-illuminated with a fiber-optic light source and viewed through an Olympus microscope. The image of the cheek pouch microcirculation was projected through the microscope and into a closed-circuit television system, which consists of television camera (Panasonic WV-1500), monitor (Panasonic TR-124 MA), and videocassette recorder (Panasonic AG-1230). The inner diameter of cheek pouch arterioles (2nd-order arterioles) was measured on-line by using a video image-shearing monitor (model 908, Instrumentation for Physiology and Medicine, San Diego, CA).

Agonists were mixed in the bicarbonate buffer and then superfused over the cheek pouch microcirculation. Applica-
tion of vehicle did not affect vessel diameter, and application of agonists was randomized. The diameter of cheek pouch arterioles was measured immediately before application of agonists and every 1 min during a 5-min application period. Steady-state responses to agonists were reached within 2 min after the application was started, and the diameter of arterioles returned to control within 3 min after application of agonist was stopped. This time course was similar in all groups of hamsters. We used steady-state responses of arterioles to the agonists to compare the effects of the various concentrations of cigarette smoke extract on vascular reactivity. We examined responses of second-order arterioles to consecutive application of different doses of the same agonist, and application of different agonists was separated by a period of 15 min. We chose to examine reactivity of second-order arterioles because they are important resistance vessels in the hamster cheek pouch (6, 7, 25), and thus changes in diameter of these vessels directly regulates tissue perfusion. We examined reactivity of one arteriole per hamster. In preliminary experiments, we determined that repeated applications of all agonists onto cheek pouch arterioles produced reproducible vasoconstriction (unpublished observations).

Preparation of cigarette smoke extract. A water-soluble extract of cigarette smoke (vapor phase) was prepared by using methods previously (19, 20, 36, 48) described. Briefly, smoke from eight reference cigarettes without filters (3A1, Tobacco and Health Research Institute, University of Kentucky, Lexington, KY) was collected with a modified 10-ml polypropylene syringe-driven apparatus. The smoke from each cigarette was bubbled slowly through 100 ml of phosphate-buffered saline (pH 7.4). The resulting suspension was filtered through a 0.20-µm filter (Acrodisc) to remove particulate material and bacteria and was stored in aliquots at −70°C until use. On the day of the experiment, one aliquot of the stock solution (considered 100% cigarette smoke extract) was thawed and diluted in buffer to the appropriate concentrations (0.1, 0.5, and 1.0%). In one study, we determined whether freshly made vs. frozen cigarette smoke extract affected responses of arterioles to the agonists. It is difficult to precisely determine the concentration of cigarette smoke products in blood and tissue in habitual smokers at rest and during cigarette smoking. The concentrations of all agonists onto cheek pouch arterioles produced reproducible vasoconstriction (unpublished observations). Thus, we initially examined responses of cheek pouch arterioles to activation of ATP-sensitive potassium channels by using aprikalim (0.1 and 1.0 µM) and cromakalim (0.1 and 1.0 µM) and to activation of adenylate cyclase by using isoproterenol (1.0 and 10 µM) and forskolin (0.1 and 1.0 µM). Then, we suffused cigarette smoke extract (0.5%) over the cheek pouch microcirculation. Thirty minutes after starting a continuous superfusion of cigarette smoke extract, we again examined responses of arterioles to aprikalim, cromakalim, isoproterenol, and forskolin. The concentrations of agonists used in these studies were based on previous studies (34) that indicated that these concentrations produced marked dilatation of cheek pouch resistance arterioles.

In a third group of hamsters (n = 8), a similar protocol was followed with the exception that we examined the effect of 1.0% cigarette smoke extract. Thus we initially examined responses of cheek pouch arterioles to activation of ATP-sensitive potassium channels by using aprikalim (0.1 and 1.0 µM) and cromakalim (0.1 and 1.0 µM) and to activation of adenylate cyclase by using isoproterenol (1.0 and 10 µM) and forskolin (0.1 and 1.0 µM). Then, we suffused cigarette smoke extract (1.0%) over the cheek pouch microcirculation. Thirty minutes after starting a continuous superfusion of cigarette smoke extract, we again examined responses of arterioles to aprikalim, cromakalim, isoproterenol, and forskolin.

In a fourth group of hamsters (n = 5), a similar protocol was followed with the exception that we examined the effect of freshly made cigarette smoke extract produced similar effects on reactivity of arterioles as did frozen cigarette smoke extract. Aprikalim (0.1 and 1.0 µM) diluted arterioles by 21 and 36%, respectively, and by 20 and 34%, respectively, after application of freshly made cigarette smoke extract. Cromakalim (0.1 and 1.0 µM) diluted arterioles by 23 and 44%, respectively, before and by 20 and 41%, respectively, after application of freshly made cigarette smoke extract. Isoproterenol (1.0 and 10 µM) diluted arterioles by 16 and 25%, respectively, before and by 12 and 21%, respectively, after application of freshly made cigarette smoke extract. Forskolin (0.1 and 1.0 µM) diluted arterioles by 13 and 28%, respectively, before and by 13 and 27%, respectively, after application of freshly made cigarette smoke extract. The conclusions drawn from these findings of studies using freshly made cigarette smoke extract are similar to those drawn from studies using frozen and thawed cigarette smoke extract (0.1%).

In a second group of hamsters (n = 5), a similar protocol was followed with the exception that we examined the effect of 0.5% cigarette smoke extract. Thus we initially examined responses of cheek pouch arterioles to activation of ATP-sensitive potassium channels by using aprikalim (0.1 and 1.0 µM) and cromakalim (0.1 and 1.0 µM) and to activation of adenylate cyclase by using isoproterenol (1.0 and 10 µM) and forskolin (0.1 and 1.0 µM). Then, we suffused cigarette smoke extract (0.5%) over the cheek pouch microcirculation. Thirty minutes after starting a continuous superfusion of cigarette smoke extract, we again examined responses of arterioles to aprikalim, cromakalim, isoproterenol, and forskolin.

Drugs. Aprikalim was a gift from Rhone-Poulenc Rorer. Aprikalim was dissolved in dimethylsulfoxide (DMSO) to make a stock solution of 1.0 mM. Dilutions from the stock were made in saline on the day of the experiment. Cromakalim was a gift from SmithKline Beecham Pharmaceutical. Cromakalim was dissolved in ethanol to make a stock solution of 1.0 mM. Dilutions from the stock were made in saline on the day of the experiment. Isoproterenol was purchased from Sanofi Winthrop Pharmaceuticals and mixed in saline on the day of the experiment. Forskolin was purchased from Calbiochem. Forskolin was dissolved in DMSO to make a stock solution of 0.1 mM. Dilutions from the stock were made in saline on the day of the experiment.

Statistical analysis. Repeated-measures analysis of variance with Student-Newman-Keuls test was used to compare responses of cheek pouch arterioles with the agonists before
RESULTS

Control conditions. Under control conditions (before superfusion with vehicle), activation of ATP-sensitive potassium channels by using aprikalim and cromakalim produced dose-related dilatation of cheek pouch arterioles. Aprikalim (0.1 and 1.0 µM) diluted arterioles by 13 ± 1 and 21 ± 2%, respectively. Cromakalim (0.1 and 1.0 µM) diluted arterioles by 13 ± 3 and 22 ± 3%, respectively. In addition, activation of adenylate cyclase by using isoproterenol and forskolin produced dose-related dilatation of cheek pouch arterioles before superfusion with vehicle. Isoproterenol (1.0 and 10 µM) diluted arterioles by 10 ± 1 and 18 ± 1%, respectively. Forskolin (0.1 and 1.0 µM) diluted arterioles by 11 ± 1 and 17 ± 1%, respectively.

Topical application of vehicle did not alter baseline diameter of cheek pouch arterioles. Diameter of cheek pouch arterioles was 55 ± 2 (SE) µm before application of vehicle and 54 ± 4 µm after application of vehicle (P > 0.05). Furthermore, application of vehicle did not alter dilatation of cheek pouch arterioles in response to activation of ATP-sensitive potassium channels and activation of adenylate cyclase (P > 0.05 vs. response before application of vehicle). Aprikalim (0.1 and 1.0 µM) diluted arterioles by 12 ± 2 and 18 ± 2%, respectively. Cromakalim (0.1 and 1.0 µM) diluted arterioles by 12 ± 2 and 20 ± 3%, respectively. Isoproterenol (1.0 and 10 µM) diluted arterioles by 9 ± 1 and 16 ± 2%, respectively. Forskolin (0.1 and 1.0 µM) diluted arterioles by 11 ± 1 and 17 ± 1%, respectively. Thus repeated application of agonists yields reproducible responses.

Effect of 0.1% cigarette smoke extract. Under control conditions, activation of ATP-sensitive potassium channels by using aprikalim and cromakalim produced dose-related dilatation of cheek pouch arterioles (Fig. 1). In addition, activation of adenylate cyclase by using isoproterenol and forskolin produced dose-related dilatation of cheek pouch arterioles under control conditions (Fig. 1; P < 0.05 vs. baseline diameter).

Topical application of 0.1% cigarette smoke extract did not alter baseline diameter of cheek pouch arterioles. Diameter of cheek pouch arterioles was 50 ± 2 (SE) µm before application of cigarette smoke extract and 48 ± 2 µm after application of cigarette smoke extract (P > 0.05). Furthermore, application of 0.1% cigarette smoke extract did not alter dilatation of cheek pouch arterioles in response to activation of ATP-sensitive potassium channels and activation of adenylate cyclase (P > 0.05; Fig. 1).

Effect of 0.5% cigarette smoke extract. Under control conditions, activation of ATP-sensitive potassium channels by using aprikalim and cromakalim and activation of adenylate cyclase by using isoproterenol and forskolin produced dose-related dilatation of cheek pouch arterioles (Fig. 2; P < 0.05 vs. baseline diameter).

Topical application of 0.5% cigarette smoke extract did not alter baseline diameter of cheek pouch arterioles. Diameter of cheek pouch arterioles was 51 ± 2 (SE) µm before application of cigarette smoke extract and 52 ± 2 µm after application of cigarette smoke extract (P > 0.05). In contrast to the effect observed with 0.1% cigarette smoke extract, application of 0.5% cigarette smoke impaired dilatation of cheek pouch arterioles in response to aprikalim, the high dose (1.0 µM) of cromakalim, the high dose (10 µM) of isoproterenol, and the high dose (1.0 µM) of forskolin (P < 0.05; Fig. 2).

Effect of 1.0% cigarette smoke extract. Under control conditions, activation of ATP-sensitive potassium channels by using aprikalim and cromakalim and activation

Fig. 1. Response of cheek pouch arterioles to aprikalim (A), cromakalim (B), isoproterenol (C), and forskolin (D) before (open bars) and after (solid bars) exposure to cigarette smoke extract (0.1%). Values are means ± SE; n = 7.
of adenylate cyclase by using isoproterenol and forskolin produced dose-related dilatation of cheek pouch arterioles (Fig. 3; *P < 0.05 vs. baseline diameter).

Topical application of 1.0% cigarette smoke extract did not alter baseline diameter of cheek pouch arterioles. Diameter of cheek pouch arterioles was 49 ± 2 (SE) μm before application of cigarette smoke extract and 50 ± 1 μm after application of cigarette smoke extract (*P > 0.05).

In addition, application of 1.0% cigarette smoke impaired dilatation of cheek pouch arterioles in response to activation of ATP-sensitive potassium channels and activation of adenylate cyclase (*P < 0.05; Fig. 3).

**DISCUSSION**

The present study is the first to examine the effects of cigarette smoke extract dilatation of resistance arterioles in vivo in response to activation of ATP-sensitive potassium channels and adenylate cyclase. There are two new findings of this study. First, a low concentration of cigarette smoke extract (0.1%) did not alter dilatation of cheek pouch arterioles in response to activation of ATP-sensitive potassium channels and adenylate cyclase. Second, higher concentrations of cigarette smoke extract (0.5 and 1.0%) impaired dilatation of cheek pouch in response to activation of ATP-
sensitive potassium channels and adenylate cyclase. The findings of the present study suggest that exposure of resistance arterioles to components of cigarette smoke alters important cellular vasodilator pathways.

Consideration of methods. Many previous studies have examined the effects of activation of ATP-sensitive potassium channels on large peripheral and cerebral blood vessels in vitro (26, 28, 33, 38–40, 43) and in vivo (9, 11, 52, 55). In addition, Mayhan (34) and other investigators (52) have examined the effects of activation of ATP-sensitive potassium channels on peripheral resistance arterioles. In general, activation of ATP-sensitive potassium channels with cromakalim, pinacidil, nicorandil, and aprikalim produces marked relaxation and/or dilatation of arteries and arterioles. Relaxation and/or dilatation of arteries and arterioles in response to activation of ATP-sensitive potassium channels in vitro and in vivo appears to be specific because glibenclamide inhibits responses to activation of ATP-sensitive potassium channels (9, 33, 34, 38, 44, 50). Furthermore, Mayhan has shown that dilatation of cheek pouch arterioles in response to activation of ATP-sensitive potassium channels with aprikalim and cromakalim is not related to the synthesis/release of nitric oxide or a nitric oxide-containing compound. The results of the present study support findings of previous studies (9, 11, 34, 55) that suggest an important role for activation of ATP-sensitive potassium channels in dilatation of blood vessels in vivo. In addition, the results of the present experiments extend findings of previous studies by examining responses of resistance arterioles in vivo to activation of ATP-sensitive potassium channels during exposure to cigarette smoke extract.

Relaxation of vascular smooth muscle also can occur via activation of adenylate cyclase via stimulation of β-adrenergic receptors and/or direct activation of adenylate cyclase by forskolin (15, 49). Although many previous studies have examined responses of arteries and arterioles to isoproterenol and forskolin, a recent study (21) has examined responses of hamster cheek pouch arterioles to isoproterenol and forskolin. This previous study (21) found that isoproterenol and forskolin produced pronounced dose-related dilatation of cheek pouch arterioles. Surprisingly, dilatation of cheek pouch arterioles in response to isoproterenol was partially inhibited by application of glibenclamide (21). This finding suggests a role for activation of ATP-sensitive potassium channels in isoproterenol-induced dilatation of cheek pouch arterioles. Dilatation of cheek pouch arterioles in response to forskolin, however, was not altered by treatment with glibenclamide. Although we did not examine a specific role for activation of ATP-sensitive potassium channels in dilatation of cheek pouch arterioles in response to isoproterenol in the present study, it is possible that inhibition of isoproterenol-induced vasodilatation by cigarette smoke is partially related to an effect on ATP-sensitive potassium channels. However, we also observed that cigarette smoke extract (0.5 and 1.0%) inhibited vasodilatation in response to forskolin, which presumably dilates cheek pouch arterioles independent of the activation of ATP-sensitive potassium channels (21). Thus it appears that cigarette smoke extract impairs reactivity of arterioles in response to activation of ATP-sensitive potassium channels and in response to activation of adenylate cyclase.

We examined the effects of various concentrations of cigarette smoke extract on baseline diameter of cheek pouch arterioles. We found that cigarette smoke extract did not alter baseline diameter of cheek pouch arterioles. Two other studies examined the effect of cigarette smoke extract on diameter of arteries in vitro. Holden et al. (19) found that cigarette smoke extract produced biphasic responses of intrapulmonary arteries. Relaxation of intrapulmonary arteries occurred at low concentrations of cigarette smoke extract (0.001–0.01%), and constriction of arteries occurred at higher concentrations (0.1–1.0%) of cigarette smoke extract. In other studies, investigators found that the gaseous phase of cigarette smoke produced relaxation of coronary arteries in vitro (12). The mechanism of relaxation appeared to be related to the activation of guanylate cyclase, presumably by production of nitric oxide. The results of the present study differ from previous studies (12, 19). We did not find a direct effect of cigarette smoke extract on baseline diameter of cheek pouch arterioles. There are, however, significant differences between the present study and previous studies (12, 19).

We examined responses of small arterioles contained within the hamster cheek pouch in vivo, and the previous studies examined responses of large bovine coronary and pulmonary arteries in vitro (12, 19). Thus the discrepancy between the present study and previous studies may be related to size of blood vessels studied, the tissue from which the blood vessels were derived, and/or a species difference in response to cigarette smoke extract. We examined the effects of topical application of cigarette smoke extract, made by bubbling cigarette smoke through a buffer solution, on arteriolar reactivity. There may be several limitations of this methodology. First, during cigarette smoking the products of inhaled smoke that interact with the endothelium and/or vascular smooth muscle are filtered by the lungs before entering the blood. In the present study, we were not able to examine the effects of inhaled smoke vs. smoke extract on reactivity of resistance arterioles, and thus we cannot exclude the possibility that reactivity of arterioles may be affected differentially by inhaled smoke. Second, there may be complex interactions between the components of blood and/or vascular wall and the products produced during cigarette smoking that may attenuate or exacerbate the effects of cigarette smoke. In the present study we were not able to examine these potential interactions and thus cannot draw conclusions with regard to the role of these potentially important interactions to impaired reactivity of arterioles. Although there may be limitations to the present study, we suggest that our findings provide new insights into the potential effects of cigarette smoking on important cellular vasodilator pathways.

Consideration of previous studies. No studies have examined the effect of cigarette smoke extract on
dilator responses of arterioles to activation of ATP-sensitive potassium channels and activation of adenylate cyclase. For the most part, previous studies have concentrated on an examination of the effects of cigarette smoking on endothelium-dependent, i.e., nitric oxide synthase-mediated, responses of peripheral blood vessels. Holden et al. (19) found that reactivity of intrapulmonary arteries in vitro in response to cigarette smoke extract (0.001–0.01%) could be inhibited by removal of the endothelium. Thus it appears that the endothelium may participate in the vascular response of intrapulmonary arteries during exposure to cigarette smoke. These investigators (19), however, did not examine whether cigarette smoke extract altered responses of intrapulmonary arteries to nitric oxide synthase-mediated agonists. Other studies using human subjects have shown that cigarette smoking impairs nitric oxide synthase-mediated relaxation of large peripheral blood vessels (17, 18). However, other studies using human subjects have shown either no alteration in nitric oxide synthase-mediated vasorelaxation (22) or increased sensitivity of vascular smooth to nitric oxide synthase-mediated vasodilators in smokers (47). Rubinstein et al. (48) have previously examined nitric oxide synthase-mediated dilatation of cheek pouch arterioles after exposure to cigarette smoke extract (1.0%). They found that dilatation of cheek pouch arterioles in vivo in response to acetylcholine was profoundly impaired after exposure to cigarette smoke extract (48). Dilatation of arterioles in response to nitroglycerin, however, was not altered by exposure to cigarette smoke extract, suggesting that the effects of cigarette smoke extract are specific for nitric oxide synthase-mediated responses. Although there appears to be some discrepancy in results concerning the effects of cigarette smoking on nitric oxide synthase-mediated vasoreactivity, the results from the previous study of Rubinstein et al. (48) and studies by other investigators (17, 18) suggest an important effect of cigarette smoking on nitric oxide synthase-mediated responses of blood vessels.

The present study is the first to examine the effects of cigarette smoke extract on other important cellular dilator pathways, i.e., activation of ATP-sensitive potassium channels and activation of adenylate cyclase. We found that low concentrations of cigarette smoke extract do not alter dilatation of arterioles in response to activation of ATP-sensitive potassium channels and activation of adenylate cyclase. Modest-to-moderate concentrations of cigarette smoke extract, however, produced profound impairment in dilatation of cheek pouch arterioles in response to activation of ATP-sensitive potassium channels and adenylate cyclase. Thus findings from the present series of experiments extend previous findings (17, 18, 48) by examining the effects of cigarette smoke extract on important cellular dilator pathways of resistance arterioles.

Mechanism of cigarette smoke extract-induced alterations in vascular reactivity. The chemical composition of cigarette smoke is complex, and it is difficult to determine which compound(s) may be involved in cigarette smoke extract-induced vascular injury. Nicotine, a major component of cigarette smoke, has been shown to increase the frequency of endothelial cell death and thus could be considered a mediator of vascular injury (29, 31). However, several studies failed to demonstrate consistent and significant functional and/or pathological alterations in vascular wall properties during exposure to nicotine (1, 24, 42), and no studies have examined the effects of nicotine on reactivity of resistance arterioles in response to activation of ATP-sensitive potassium channels and adenylate cyclase. Thus we cannot determine whether the impaired reactivity of arterioles observed in the present study during exposure to cigarette smoke extract is related to elevations in nicotine.

Cigarette smoke extract contains many toxic substances, in addition to nicotine, that may contribute to impaired vascular reactivity. Acrolein and acetaldehyde are highly soluble components of cigarette smoke extract and have been shown to cause irritation of airway and ocular mucosa in humans, impair mucociliary clearance in the upper airway, produce pulmonary edema in animals, and damage epithelial cells (13, 14, 30, 45). In addition, Holden et al. (20) have shown that cigarette smoke extract increases albumin flux across cultured porcine pulmonary endothelium, and this effect was predominantly due to the vapor phase of cigarette smoke. Furthermore, cigarette smoke extract contains considerable amounts of oxygen radicals such as superoxide anion and hydrogen peroxide that may contribute to vascular dysfunction observed in cigarette smokers (41). Thus, although the precise contribution of the various components of cigarette smoke extract to vascular reactivity cannot be determined from the present study, we speculate that it involves complex interactions between various components of cigarette smoke extract.

Summary and implications. We found that cigarette smoke extract produced a concentration-related impairment in dilatation of resistance arterioles in response to activation of ATP-sensitive potassium channels and activation of adenylate cyclase. We suggest that these findings may have important implications for chronic tobacco smokers. Studies have shown that cigarette smoking contributes to the development of many cardiovascular abnormalities, including tissue ischemia, atherosclerosis, stroke, and coronary artery disease (29, 37, 53, 54, 56). Several cellular mechanisms, including synthesis and/or release of nitric oxide, synthesis and/or release of endothelium-derived hyperpolarizing factor to activate ATP-sensitive potassium channels, and/or synthesis and/or release of prostaglandins to activate of adenylate cyclase (5, 10, 46), attempt to maintain adequate tissue blood flow during increases in demand. Although it is clear that cigarette smoking may alter the nitric oxide synthase-mediated pathway, the findings of the present study suggest that cigarette smoking also may contribute to vascular dysfunction, in part, by altering the ability of resistance arterioles to dilate in response to activation of ATP-sensitive potassium channels and activation of adenylate cyclase.
Thus our findings provide new insights into the effects of cigarette smoking on important cellular vasodilator pathways.

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