Chronic exposure to nicotine alters endothelium-dependent arteriolar dilatation: effect of superoxide dismutase

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Mayhan, William G., and Glenda M. Sharpe. Chronic exposure to nicotine alters endothelium-dependent arteriolar dilatation: effect of superoxide dismutase. J. Appl. Physiol. 86(4): 1126–1134, 1999.—The first goal of this study was to determine whether chronic injection of nicotine alters endothelium-dependent arteriolar dilatation. We measured the diameter of cheek pouch resistance arterioles (∼50 μm in diameter) in response to endothelium-dependent (acetylcholine and ADP) and -independent (nitroglycerin) agonists in control hamsters and hamsters treated with nicotine (2 μg·kg−1·day−1 for 2–3 wk). In control hamsters, acetylcholine (0.1 and 1.0 μM) dilated arterioles by 13 ± 2 and 31 ± 3%, respectively, and ADP (1.0 and 10 μM) dilated arterioles by 18 ± 1 and 30 ± 1%, respectively. In contrast, acetylcholine (0.1 and 1.0 μM) dilated arterioles by only 5 ± 2 and 12 ± 3%, respectively, and ADP (1.0 and 10 μM) dilated arterioles by only 7 ± 2 and 13 ± 3%, respectively, in animals treated with nicotine (P < 0.05 vs. response in control hamsters). Nitroglycerin produced similar dose-related dilatation of cheek pouch arterioles in control and nicotine-treated hamsters. Our second goal was to examine a possible mechanism for impaired endothelium-dependent arteriolar dilatation during chronic treatment with nicotine. We found that superfusion of the cheek pouch microcirculation with superoxide dismutase (150 U/ml) restored impaired endothelium-dependent, but did not alter endothelium-independent, arteriolar dilatation in hamsters treated with nicotine. Superfusion with superoxide dismutase did not alter endothelium-dependent or -independent arteriolar dilatation in control hamsters. We suggest that chronic exposure to nicotine produces selective impairment of endothelium-dependent arteriolar dilatation via a mechanism related to the synthesis/release of oxygen-derived free radicals. Acetylcholine; adenosine 5'-diphosphate; nitroglycerin; cheek pouch; hamsters; arterioles; endothelium-derived relaxing factor; oxygen radicals; N^6-monomethyl-L-arginine; nitric oxide

Although cigarette smoking and the use of smokeless tobacco products have been shown to impair nitric oxide synthase-dependent dilatation of large peripheral arteries (2, 7, 8, 10, 28) and resistance arterioles (32, 35), the precise component that accounts for vascular dysfunction remains unclear. Investigators have shown that nicotine has toxic effects on endothelium (11, 15, 17), and thus it has been suggested that nicotine may play an important role in impaired nitric oxide synthase-dependent vasoreactivity observed in users of tobacco products. In support of this concept, we have shown that acute intravenous infusion of nicotine impairs nitric oxide synthase-dependent dilatation of resistance arterioles (22).

Mechanisms by which nicotine and/or the use of tobacco products impair endothelium-dependent vasoreactivity have only recently been investigated. Murohara et al. (26) found that cigarette smoke extract-induced contraction of porcine coronary arteries was related to superoxide anion-mediated degradation of nitric oxide. In addition, treatment of isolated rabbit aortas with an oxygen radical scavenger attenuated cigarette smoke-induced impairment of arterial relaxation (28). Others (6, 25) have reported that acute treatment of smokers with vitamin C, an antioxidant, improved impaired endothelium-dependent reactivity of large peripheral arteries. Furthermore, we have recently reported that inhibition of oxygen radicals with superoxide dismutase could restore impaired endothelium-dependent reactivity of resistance arterioles during acute infusion of nicotine (23). Thus it appears that chronic smoking and acute exposure to cigarette smoke extract or nicotine may alter endothelium-dependent reactivity via the production of oxygen radicals.

Although our recent study (23) provides insight into mechanisms by which acute infusion of nicotine alters endothelium-dependent reactivity of resistance arterioles, it is important to examine the chronic effects of nicotine on endothelial function because this might more accurately reflect that found in chronic smokers. However, few studies have examined the effects of chronic nicotine exposure on vascular reactivity. One previous study found that chronic (2-wk) treatment of rats with nicotine did not alter acetylcholine-induced changes in perfusion pressure of the isolated mesenteric circulation (16). However, these investigators did not directly examine in vivo reactivity of resistance arterioles in animals treated with nicotine. Thus the effect of chronic treatment with nicotine on endothelium-dependent reactivity of vessels that directly regulate tissue perfusion remains unclear.

The first goal of the present study was to examine whether chronic treatment with nicotine alters endothelium-dependent reactivity of resistance arterioles in vivo. Our second goal was to examine a potential role for oxygen radicals in nicotine-induced impairment of endothelium-dependent reactivity of resistance arterioles.

METHODS

Preparation of animals. Adult male hamsters (n = 27) weighing between 110 and 150 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 artery for the measurement of arterial blood pressure, and a catheter was placed in a femoral vein for injection of supplemental anesthesia (2–4 mg·100 g⁻¹·h⁻¹). At the end of the experiment, all animals were killed with an intravenous infusion of the anesthetic (60 mg·100 g body wt). All procedures were carried out following institutional approval and within institutional guidelines.

To visualize the microcirculation of the cheek pouch, we used a method that we have described previously (21). 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 was used to maintain the suffusion fluid. This arrangement forms a triple-layered complex: the baseplate, the upper chamber, and the cheek pouch membrane exposed between these two plates.

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 bicarbonate buffer (temperature 37 ± 1°C; pH 7.40). The chamber was also connected via a threeway valve to an infusion pump that allowed for the controlled administration of vasoactive agonists.

Measurement of arteriolar diameter. 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 that consists of television camera (model WV-1500, Panasonic), monitor (model TR-124 MA, Panasonic), and videotape recorder (model AG-1240, Panasonic). The diameter of cheek pouch arterioles was measured online by using a video image shearing monitor (model 908, Instrumentation for Physiology and Medicine).

Agonists were mixed in the saline and then superfused over the cheek pouch microcirculation. Application of agonists was randomized. Diameter of cheek pouch arterioles (1 arteriole/hamster) was measured immediately before application of agonists, and every minute during a 5-min application period. Steady-state responses to agonists were reached within 2–3 min after the application was started, and the diameter of arterioles returned to baseline within 3 min after application of agonists was stopped. 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 10–20 min. We chose to examine reactivity of second-order arterioles because they are important resistance vessels in the hamster cheek pouch (3, 4, 14) and thus changes in diameter of these vessels directly regulate tissue perfusion.

Experimental protocol. Two to three weeks before the day of the experiment, hamsters were treated daily with an intraperitoneal injection of vehicle (saline; control hamsters) or nicotine (2 mg·kg⁻¹·day⁻¹). On the day of the experiment, hamsters were prepared as described in Preparation of animals. The cheek pouch microcirculation was superfused for 30 min before responses of arterioles to the agonists were tested.

In the first series of experiments (n = 7), we examined reactivity of cheek pouch arterioles in control hamsters. To demonstrate reproducible vasodilation, we examined repeated application of agonists in each hamster. Thus in this series of studies we initially examined responses of cheek pouch arterioles to endothelium-dependent agonists [acetylcholine (0.1 and 1.0 µM) and ADP (1.0 and 10 µM)] and an endothelium-independent agonist [nitroglycerin (0.1 and 1.0 µM)]. After examining the response of arterioles to the final concentration of the last agonist we waited 30 min and again examined responses of arterioles to acetylcholine, ADP, and nitroglycerin.

In a second series of experiments (n = 7), we examined reactivity of cheek pouch arterioles in hamsters treated with nicotine (2 mg·kg⁻¹·day⁻¹ ip). As described above for control hamsters, we initially examined responses of cheek pouch arterioles to endothelium-dependent and -independent agonists. Thirty minutes later, we again examined responses of arterioles to acetylcholine, ADP, and nitroglycerin as described above.

In a third series of experiments (n = 4), we examined the effect of superoxide dismutase on reactivity of arterioles in control hamsters. Thus, in these studies, we initially examined responses of cheek pouch arterioles to acetylcholine, ADP, and nitroglycerin in the presence of vehicle (saline). Then, we started a continuous topical application of superoxide dismutase (150 U/ml) to the cheek pouch microcirculation. Thirty minutes after starting superfusion with superoxide dismutase, we again examined responses of arterioles to the agonists.

In a fourth series of experiments (n = 5), we examined the effect of superoxide dismutase on reactivity of arterioles in hamsters treated with nicotine. Similar to that described above, we initially examined responses of cheek pouch arterioles to acetylcholine, ADP, and nitroglycerin in the presence of vehicle. Then, we started a continuous topical application of superoxide dismutase (150 U/ml) to the cheek pouch microcirculation. Thirty minutes after starting superfusion with superoxide dismutase, we again examined responses of arterioles to the agonists.

In a fifth series of experiments, we examined the effect of inhibition of nitric oxide synthase by using N°-monomethyl-L-arginine (L-NMMA; 1.0 µM) on reactivity of cheek pouch arterioles to the agonists in control hamsters. Thus, in these studies, we initially examined responses of arterioles to acetylcholine, ADP, and nitroglycerin in the presence of vehicle. Then, we started a continuous topical application of L-NMMA to the cheek pouch microcirculation. Thirty minutes after starting superfusion with L-NMMA, we again examined responses of arterioles to the agonists.

Drugs. Acetylcholine chloride, ADP, superoxide dismutase, and nicotine were purchased from Sigma Chemical (St. Louis, MO). L-NMMA was purchased from Calbiochem (La Jolla, CA). Nitroglycerin was purchased from Sololak Laboratories (Elk Grove Village, IL). All stock solutions of agonists were prepared with saline.

Statistical analysis. Analysis of variance with repeated measures and Newman-Keuls test were used to compare responses of arterioles in control hamsters and in hamsters treated with nicotine. A paired t-test was used to compare responses of arterioles before and during treatment with L-NMMA. Values are means ± SE. A P value of ≤0.05 was considered to be significant.

RESULTS

Response of cheek pouch arterioles in control and nicotine-treated hamsters. Baseline diameter of cheek pouch arterioles was 46 ± 2 µm in control hamsters and
53 ± 2 µm in hamsters treated with nicotine (P > 0.05). The initial application of acetylcholine (Fig. 1) and ADP (Fig. 2) produced dose-related dilatation of cheek pouch arterioles in control and nicotine-treated hamsters. However, the magnitude of vasodilation in response to acetylcholine and ADP was significantly less in hamsters treated with nicotine than in control hamsters (Figs. 1 and 2).

Repeated application of acetylcholine (Fig. 1) and ADP (Fig. 2) also produced dose-related dilatation of cheek pouch arterioles in control and nicotine-treated hamsters. Again, the magnitude of vasodilation in response to acetylcholine and ADP was less in nicotine-treated than in control hamsters (P > 0.05). Thus repeated application of agonists to cheek pouch arterioles elicits reproducible arteriolar dilatation. In addition, dilatation of cheek pouch arterioles in response to endothelium-dependent agonists is impaired in hamsters treated with chronic injection of nicotine.

To determine whether impaired responses of arterioles in nicotine-treated hamsters was related to a nonspecific effect, we examined responses of arterioles to nitroglycerin. Nitroglycerin elicited reproducible dose-related dilatation of cheek pouch arterioles that was similar in control hamsters and hamsters treated with nicotine (Fig. 3; P > 0.05). Thus it appears that the
Effects of nicotine on arteriolar dilatation are specific for endothelium-dependent agonists.

Response of cheek pouch arterioles in the presence of superoxide dismutase. Baseline diameter of cheek pouch arterioles in control hamsters was 46 ± 4 µm. Application of acetylcholine (Fig. 4), ADP (Fig. 5), and nitroglycerin (Fig. 6) produced dose-related dilatation of cheek pouch arterioles before superfusion with superoxide dismutase. Superfusion with superoxide dismutase did not alter baseline diameter of cheek pouch arterioles in control hamsters (46 ± 4 vs. 45 ± 4 µm; P > 0.05). In addition, responses of cheek pouch arterioles to the agonists were similar in the absence and presence of superoxide dismutase (Figs. 4–6). Thus it does not appear that superoxide dismutase alters reactivity of cheek pouch arterioles to acetylcholine, ADP, and nitroglycerin in control hamsters.

Baseline diameter of cheek pouch arterioles in nicotine-treated hamsters was 49 ± 3 µm. Topical application of acetylcholine (Fig. 4), ADP (Fig. 5), and nitroglycerin (Fig. 6) produced dose-related dilatation of cheek pouch arterioles before superfusion with superoxide dismutase. As shown above, the magnitude of vasodilatation in response to acetylcholine and ADP was significantly less in nicotine-treated compared with control hamsters (P < 0.05). Nitroglycerin, however, produced...
similar vasodilatation in control and nicotine-treated hamsters. Superfusion with superoxide dismutase did not alter baseline diameter of cheek pouch arterioles in hamsters treated with nicotine (49 ± 3 vs. 47 ± 2 µm; P > 0.05). In contrast to that observed in control hamsters, superfusion with superoxide dismutase potentiated responses of cheek pouch arterioles to acetylcholine (Fig. 4) and ADP (Fig. 5). In fact, responses of cheek pouch arterioles to acetylcholine and ADP during superfusion with superoxide dismutase in nicotine-treated hamsters were similar to that observed in control hamsters (P > 0.05). Vasodilatation in response to nitroglycerin, however, was not altered by superoxide dismutase (Fig. 6). Thus it appears that superoxide dismutase, although not affecting baseline diameter of cheek pouch arterioles, can prevent impairment of endothelium-dependent arteriolar reactivity in hamsters chronically treated with nicotine.

Response of cheek pouch arterioles in the presence of L-NMMA. Baseline diameter of cheek pouch arterioles before application of L-NMMA was 50 ± 2 µm. Topical application of acetylcholine, ADP, and nitroglycerin produced dose-related dilatation of cheek pouch arterioles before superfusion with L-NMMA (Fig. 7). Topical application of L-NMMA (1.0 µM) in control hamsters produced a modest constriction of cheek pouch arteri-

![Fig. 5. Response of cheek pouch arterioles to ADP in control hamsters (A) and nicotine-treated hamsters (B) before (open bars) and during (hatched bars) superfusion with superoxide dismutase (150 U/ml). Values are means ± SE. *P < 0.05 vs. response in control hamsters. †P < 0.05 vs. response before superfusion with superoxide dismutase.](image-url)

![Fig. 6. Response of cheek pouch arterioles to nitroglycerin in control hamsters (A) and nicotine-treated hamsters (B) before (open bars) and during (hatched bars) superfusion with superoxide dismutase (150 U/ml). Values are means ± SE.](image-url)
In addition, L-NMMA (1.0 µM) significantly inhibited responses of cheek pouch arterioles to acetylcholine and ADP but not to nitroglycerin (Fig. 7). Thus it appears that acetylcholine and ADP dilate cheek pouch arterioles via a nitric oxide synthase-dependent mechanism. This finding is similar to that which we have reported previously (18).

DISCUSSION

The present study is the first to examine the chronic effect of nicotine on endothelium-dependent and -independent reactivity of resistance arterioles in vivo. We found that chronic injection of nicotine for 2–3 wk, at a concentration that produces a plasma concentration of nicotine similar to that observed in smokers (1, 13, 16, 27, 29, 31, 33), impaired endothelium-dependent, but not -independent, dilatation of resistance arterioles. In addition, we examined the potential role of oxygen radicals in nicotine-induced impairment of endothelium-dependent reactivity of resistance arterioles in vivo. We found that treatment of the cheek pouch microcirculation with superoxide dismutase reversed nicotine-induced impairment of endothelium-dependent vasodilatation. We suggest that impairment in endothelium-dependent responses of blood vessels observed in smokers and users of tobacco products may be related to the synthesis/release of oxygen-derived free radicals to presumably inactive nitric oxide.

Consideration of methods. We examined the "chronic" (2 wk of exposure) effects of treatment with nicotine on endothelium-dependent and -independent responses of cheek pouch arterioles. We chose this time period for treatment with nicotine on the basis of previous studies (16, 29) that have examined the effects of nicotine on the cardiovascular system. It is important to note that treatment with nicotine for a period of 2 wk may not truly represent chronic exposure. It is possible that longer periods of exposure to nicotine may produce dramatically different responses of blood vessels to the agonist and may affect the ability of superoxide dismutase to restore impaired endothelial dependent function of cheek pouch arterioles.

To determine the role of nicotine treatment on endothelium-dependent (nitric oxide synthase-dependent) reactivity of cheek pouch arterioles, we examined responses to acetylcholine and ADP. We have shown previously that dilatation of cheek pouch arterioles in response to acetylcholine, but not nitroglycerin, can be attenuated by application of enzymatic inhibitors of nitric oxide synthase (18). Findings of the present study support our previous finding (18). In addition, in the present study we found that L-NMMA inhibited dilatation of cheek pouch arterioles in response to ADP. Thus it appears that arterioles of the hamster cheek pouch exhibit typical endothelium-dependent responses, and we suggest that the synthesis/release of nitric oxide accounts for dilatation of cheek pouch arterioles in response to acetylcholine and ADP.

To determine whether the production of oxygen radicals accounted for impaired endothelium-dependent reactivity of arterioles during chronic treatment with nicotine, we applied superoxide dismutase to the cheek pouch microcirculation. We found that acute treatment of the cheek pouch microcirculation with superoxide dismutase restored impaired endothelium-dependent vasodilatation in hamsters chronically treated with nicotine. Superoxide dismutase, however, did not alter endothelium-dependent responses of arterioles in control hamsters and did not alter vasodilatation in response to nitroglycerin in control or nicotine-treated hamsters. Thus it appears that the effects of superoxide dismutase are specific for endothelium-dependent ago-
and are specific for hamsters treated with nicotine.

Our finding that acute superfusion with superoxide dismutase restores impaired endothelium-dependent vascular reactivity in hamsters chronically treated with nicotine may be somewhat surprising. One might have predicted that, if oxygen radicals are produced during chronic treatment with nicotine, then this might damage the endothelium and thus irreversibly impair endothelium-dependent reactivity. Thus one might not have expected that acute superfusion with superoxide dismutase would produce the dramatic effects on endothelium-dependent vascular reactivity observed in the present study. However, it is interesting to note that previous studies have examined the effects of chronic disease states (hypertension, diabetes mellitus and heart failure) on endothelial function have shown that acute inhibition of oxygen radical formation can potentiate impaired endothelium-dependent vasoreactivity (5, 12, 19, 20, 30). Thus results of the present study appear to mimic those observed in other disease states.

In addition, we thought that, if oxygen radicals were produced chronically by nicotine treatment, then we might see a change in baseline diameter of cheek pouch arterioles in hamsters treated with nicotine. Furthermore, we reasoned that, if oxygen radicals were elevated by nicotine exposure, then superfusion with superoxide dismutase might alter diameter of cheek pouch arterioles in nicotine-treated hamsters. However, we found that baseline diameter of cheek pouch arterioles was similar in control and nicotine-treated hamsters and that superoxide dismutase did not alter baseline diameter of arterioles in nicotine-treated hamsters. Thus, we suggest that although oxygen radicals appear to contribute to impaired dilatation of cheek pouch arterioles during treatment with nicotine, these substances do not appear to be synthesized/released chronically to an extent that affects baseline diameter. It is possible that the chronic production of low levels of oxygen radicals may influence reactivity of arterioles in response to agonists that stimulate an increase in nitric oxide production. In addition, it is possible that oxygen radicals may be released in response to the various endothelium-dependent agonists and thus impair vascular reactivity by inactivating nitric oxide.

In the present study we did not examine plasma levels of nicotine or its metabolite cotinine during chronic treatment with nicotine. However, previous studies have used a similar protocol to examine the chronic effects of nicotine in experimental animals (16, 29). In addition, a previous study (16) has shown that chronic treatment with nicotine at a concentration similar to that used in the present study produces plasma levels of nicotine and cotinine similar to those observed in chronic smokers (1, 13, 27, 31, 33). Thus we suggest that the protocol used in the present study is appropriate and mimics levels of nicotine observed in chronic smokers.

Consideration of previous studies. Many previous studies have examined the effects of cigarette smoking and/or cigarette smoke extract on endothelium-dependent responses of large and small blood vessels.

Studies using animal models have shown that smoking and the components of cigarette smoke impair endothelium-dependent responses of blood vessels (26, 28, 32, 35). Mechanisms that contribute to impaired endothelium-dependent reactivity of blood vessels after exposure to cigarette smoke have also been examined. We found that cigarette smoke extract-induced impairment in endothelium-dependent dilatation of cheek pouch arterioles could be restored by treatment with indomethacin, suggesting an important role for oxygen radicals and/or vasconstrictor prostanoids (32). This finding was confirmed by Suzuki et al. (35) using aqueous smokeless tobacco. These investigators found that smokeless tobacco impaired endothelium-dependent dilatation of cheek pouch arterioles and that this impairment could be reversed by treatment with indomethacin (35). Other studies using porcine coronary arteries (26) and the rabbit aorta (28) have shown that cigarette smoke extract-induced impairment of endothelium-dependent reactivity could be restored by treatment with superoxide dismutase. The findings of the present study suggest that chronic treatment with nicotine, a major component of cigarette smoke, impairs endothelium-dependent responses of resistance arterioles via the synthesis/release of oxygen radicals. Thus our present study supports and extends the findings of previous reports (26, 28, 32, 35).

Smoking adversely affects the cardiovascular system in human subjects. Smoking is associated with an increased risk of atherosclerotic vascular disease, hypertension, myocardial infarction, unstable angina, sudden cardiac death, and stroke (15, 24, 36). The adverse effects of smoking on vascular function have also been examined in human subjects. These studies have shown that cigarette smoking (acute and chronic) impairs nitric oxide synthase-mediated relaxation of large blood vessels (2, 6, 8–10, 34, 37). In addition, it appears that cessation of smoking is associated with improvement of endothelial function in human subjects (2). Mechanisms that contribute to impaired endothelium-dependent relaxation of large blood vessels during cigarette smoking have been investigated. Studies by Motoyama et al. (25) and Heltzer et al. (6) found that impaired endothelium-dependent vasodilation observed in chronic smokers could be restored by acute treatment with vitamin C, an antioxidant. Thus it appears that oxygen radical formation plays an important role in impaired reactivity of large conduit vessels in chronic smokers. The findings of the present study extend that of previous reports (6, 25) by examining one component of cigarette smoke that accounts for impaired endothelium-dependent vasoreactivity and by examining responses of resistance arterioles, vessels that directly regulate tissue perfusion. Furthermore, it is interesting to note that, similar to the findings reported in the present study, these previous studies (6, 25) suggest that the chronic adverse effects of smoking on endothelial function could be restored by acute treatment with an antioxidant. Thus on the basis of findings using
vitamin C in chronic smokers (6, 25) and of a study that examined endothelium-dependent responses in former smokers (2) it does not appear that long-term exposure to cigarette smoke produces irreversible endothelial dysfunction.

Although many studies have examined the effects of cigarette smoking, cigarette smoke extract, and/or smokeless tobacco products on endothelium-dependent responses of blood vessels, few studies have examined the precise role of nicotine on endothelial function. One previous study has examined the effect of chronic treatment with nicotine on endothelium-dependent reactivity (16). These investigators found that chronic (2-wk) treatment with nicotine, at a dose similar to that used in the present study, did not alter acetylcholine-induced changes in perfusion pressure of the rat mesenteric circulation (16). The discrepancy between this previous study (16) and the present study is not clear, but may relate to the methodology used to examine vascular reactivity and/or the vascular bed examined. In the previous study (16), the investigators examined the pressure drop across the isolated perfused mesentery in rats in response to acetylcholine. Thus these investigators did not directly examine vascular reactivity of a resistance arteriole in an in vivo setting. In addition, because these investigators (16) did not examine the role of nitric oxide in acetylcholine-induced changes in perfusion pressure of the mesenteric circulation, the precise role of nitric oxide in this response is not clear. Furthermore, these investigators did not examine the possibility that the experimental procedures did not damage the endothelium and thus affected the degree of vasodilation observed in response to acetylcholine.

In summary, we examined the effect of chronic treatment with nicotine on endothelium-dependent reactivity of resistance arterioles in vivo. We found that chronic treatment with nicotine impaired reactivity of arterioles to endothelium-dependent, but not -independent, agonists. Furthermore, we examined the potential role of oxygen radicals in impaired endothelium-dependent reactivity of resistance arterioles during chronic treatment with nicotine. We found that superfusion with superoxide dismutase restored impaired endothelium-dependent responses of cheek pouch arterioles in hamsters treated with nicotine. On the basis of these findings, we suggest that the chronic use of tobacco products, which contain nicotine as a major component, may contribute to the pathogenesis of cardiovascular-related disease via an impairment of endothelium-dependent vascular reactivity by an oxygen radical-mediated mechanism.

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