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REGULAR ARTICLE

Cigarette smoking impairs bradykinin-stimulated tissue plasminogen activator release in human coronary circulation

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KEYWORDS
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Abstract

Background: Cigarette smoking is a major risk factor for acute coronary thrombosis. Bradykinin (BK) can induce the release of tissue plasminogen activator (tPA) from the coronary vasculature. The purpose of this study was to investigate whether smoking reduces BK-stimulated tPA release in human coronary circulation.
Materials and methods: We examined two groups: 20 current smokers and 19 nonsmokers. By cardiac catheterization, graded doses of BK (0.2, 0.6 and 2.0 μg/min) and papaverine (PA) (12 mg) were administered into the coronary artery. Coronary blood flow (CBF) was measured using a Doppler flow wire. Blood samples from the aorta (Ao) and coronary sinus (CS) were assayed.
Results: BK increased both coronary artery diameter (CD) and CBF to a similar extent in the two groups. The net coronary tPA release was dose-dependently increased by BK in the two groups, but the degree of this increase in current smokers was significantly lower than that in nonsmokers. BK did not change plasminogen activator inhibitor type 1 (PAI 1) levels in either group. PA did not alter either tPA or PAI-1 levels in either group.
Conclusions: These results suggest that cigarette smoking deteriorates coronary fibrolytic activity, independent of changes in CBF. These findings can at least partly explain the higher risk of coronary thrombosis in smokers.

Abbreviations: NO, nitric oxide; tPA, tissue-type plasminogen activator; PAI-1, plasminogen activator inhibitor-1; BK, bradykinin; LAD, left anterior descending; CS, coronary sinus; Ao, aorta; CBF, coronary blood flow; CD, coronary artery diameter; PA, papaverine; MAP, mean arterial pressure; HR, heart rate; ACE, Angiotensin converting enzyme.

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Introduction

Cigarette smoking is not only closely related to atherosclerosis in the systemic and coronary vascular systems [1], but also is a major risk factor for acute coronary thrombosis [2], which may cause acute myocardial infarction [3] and sudden cardiac death [4]. Although the mechanisms underlying these associations have not yet been fully elucidated, several studies have shown that cigarette smoking induces vascular endothelial dysfunction [5–7]. Under physiological conditions, endothelial cells release nitric oxide (NO), prostacyclin, tissue-type plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1). Through the relative balance between the acute release of tPA and its subsequent inhibition via complex formation with PAI-1, endothelium can regulate thrombosis and fibrinolysis [8,9]. The plasminogen activator system is one of the major defenses against coronary thrombosis. Reduced fibrinolytic activity may therefore increase the risk of cardiovascular events. Indeed, in the human forearm vasculature, tPA release induced by bradykinin (BK) was lower in smokers than in nonsmokers [10]. However, the effect of BK on tPA release in the coronary vasculature of smokers has not yet been examined.

BK is a vasoactive polypeptide that has cardioprotective effects [11]. BK has been shown to cause endothelium-dependent vasodilation through the production of NO, prostacyclin and endothelium-derived hyperpolarizing factor through the B2 receptor in human coronary arteries [12,13]. BK also caused tPA release in cultured endothelial cells [8]. An intra-arterial administration of BK stimulated tPA release in human brachial vasculature [14]. Furthermore, BK infusion induced tPA secretion in human coronary circulation [15].

The major aim of this study was to investigate whether cigarette smoking reduces the BK-induced release of tPA in human coronary circulation.

Methods

Subjects

The study protocol was approved by the Ethical Committee of Shiga University of Medical Science, and written informed consent was obtained from all patients. All of the study patients were hospitalized for the evaluation of atypical chest pain or abnormality on electrocardiogram. We examined two groups: 20 current smokers and 19 nonsmokers (Table 1). Control subjects consisted of lifelong nonsmokers. Current smokers had smoked at least 10 cigarettes per day (average 23 ± 12) for more than 10 years (average 37 ± 9 years), and maintained their smoking habits when admitted to the hospital. The two groups were matched in age, gender, lipid levels, hypertension and diabetes mellitus. All of the study patients underwent diagnostic cardiac catheterization for the evaluation of atypical chest pain or abnormality on electrocardiogram and had angiographically normal coronary arteries. Patients with myocardial infarction, congestive heart failure, cardiomyopathy or valvular heart disease were excluded from the study. Subjects treated with ACE inhibitors or angiotensin-1 receptor antagonists were excluded in the present study. All cardiac medication was withdrawn at least 72 h before the study.

Table 1 Patient characteristics

	Nonsmoker (n = 20)	Current smoker (n = 19)	P
Age (yr)	61.5 ± 1.8	61.1 ± 2.0	N.S.
Sex (male)	16	17	N.S.
Body mass index (kg/m^2)	25.1 ± 0.7	24.7 ± 0.5	N.S.
Total cholesterol (mg/dL)	190 ± 6	196 ± 10	N.S.
Triglycerides (mg/dL)	129 ± 17	136 ± 18	N.S.
HDL cholesterol (mg/dL)	49 ± 4	47 ± 3	N.S.
PARC, pg/ml	6.2 ± 1.4	7.6 ± 0.9	N.S.
ACE (IU/L)	10.8 ± 1.1	10.8 ± 0.8	N.S.
Aldosterone (pg/mL)	69.5 ± 8.0	59.8 ± 8.1	N.S.
tPA antigen (ng/mL)	7.1 ± 0.8	5.3 ± 0.5	N.S.
PAI-1 antigen (ng/mL)	6.9 ± 1.8	6.1 ± 1.4	N.S.
Hypertension (%)	40	37	N.S.
Diabetes Mellitus (%)	30	32	N.S.
Medications			
β-blocker (%)	35	37	N.S.
Calcium blocker (%)	40	53	N.S.
Nitrates (%)	50	63	N.S.

Data are presented as the mean value ± SE or number (%) of subjects.
HDL = high density lipoprotein, PARC = plasma-active renin concentration, ACE = angiotensin-converting enzyme, tPA = tissue plasminogen activator, PAI-1 = plasminogen activator inhibitor type 1.

Protocol

Cardiac catheterization was performed between 9 a.m. and 11 a.m. in the fasting state. A 0.014-inch Doppler-tipped guidewire (Jometrics FloWire, JoMed Inc., Rancho Cordova, CA) was advanced to the proximal segment of the left anterior descending (LAD) coronary artery to measure blood flow velocity, as previously reported [15]. All drugs were infused directly into the left main coronary artery via the guide catheter at infusion rates ranging between 0.5 and 1 ml/min. A 6F multipurpose catheter (GCS6, Goodtec, Gifu,