Short-term effects of transdermal nicotine on acute tissue plasminogen activator release in vivo in man

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Abstract

Objective: Cigarette smoking impairs peripheral endothelium-dependent vasodilatation and acute tissue plasminogen activator (t-PA) release in man. The aim of the study was to determine if this endothelial dysfunction is, in part, mediated by the effects of nicotine.

Methods: Blood flow and plasma fibrinolytic factors were measured in both forearms of eight healthy male non-smokers during unilateral brachial artery infusion of the endothelium-dependent vasodilator, substance P (2 to 8 pmol/min). Endothelium-independent vasodilatation was assessed using intra-arterial infusion of sodium nitroprusside (2 to 8 μg/min). Subjects attended after 7 days treatment with transdermal nicotine or placebo in a double blind randomised crossover design.

Results: Plasma cotinine concentrations rose from 0.4±0.1 (placebo) to 125±25 ng/ml during nicotine administration (P<0.001). On both treatment days, substance P caused dose-dependent increases in blood flow and plasma t-PA antigen and activity concentrations (P<0.001 for all) but had no effect on plasma plasminogen activator inhibitor type 1 (PAI-1) concentrations. Compared with placebo, nicotine administration increased the substance-P-induced release of t-PA antigen and activity (P<0.05 for both) without an effect on endothelium-dependent or -independent vasodilatation.

Conclusions: Short-term transdermal nicotine treatment does not affect endothelium-dependent vasomotion but does increase substance-P-induced t-PA release in vivo in man. This suggests that nicotine administration alters specific aspects of endothelial function and enhances the acute endogenous fibrinolytic capacity in vivo. The long-term effects of nicotine exposure, including the potential to cause depletion of endothelial t-PA stores, now needs to be assessed.

Keywords: Blood flow; Endothelial function; Thrombolysis

1. Introduction

Cigarette smoking is a major risk factor for cardiovascular disease [1] and is associated with acute coronary thrombosis and sudden cardiac death [2]. The mechanisms underlying these associations are unknown although previous studies have demonstrated that regular smokers have impaired endothelium-dependent vasodilatation in both the peripheral [3] and coronary circulations [4]. Endothelial dysfunction may, therefore, contribute to the thrombotic consequences and complications of cigarette smoking. However, whilst endothelium-dependent regulation of vascular tone is important, this may not reflect other crucial aspects of endothelial function such as haemostasis and fibrinolysis.

Focal areas of endothelial denudation and thrombus deposition are a common finding on the surface of atheromatous plaques and usually remain subclinical. However, in the presence of an imbalance in the haemostatic or fibrinolytic system such microthrombi may propagate ultimately leading to arterial occlusion [5]. The degradation and clearance of intravascular thrombus is regulated by tissue-type plasminogen activator (t-PA), a serine protease that is released from the endothelial cells through the translocation of a dynamic intracellular storage pool. The efficacy of plasminogen activation and fibrin degradation is determined by the relative balance between...
the acute release of t-PA and its subsequent inhibition through formation of complexes with its inhibitor, plasminogen activator inhibitor type 1 (PAI-1). Thus, through the acute release of t-PA, endothelial function may have a central role in the regulation of intravascular thrombus formation and, if impaired, may contribute to the pathogenesis of acute myocardial infarction and sudden cardiac death. We have previously described an in vivo model to assess the acute release of t-PA from the endothelium in the forearm vascular bed of man [6]. Using this approach, we have been able to demonstrate that cigarette smoking markedly impairs the acute peripheral release of t-PA [7]. However, the mechanism of this attenuated endothelial response was not established.

Nicotine is a major component of cigarette smoke that is rapidly absorbed following inhalation. Nicotine replacement therapy (NRT), either as a gum or patch preparations, has become freely available for over-the-counter sale as a medication to assist in smoking cessation. A number of reports of thrombotic cardiovascular events have been reported amongst individuals regularly using NRT [8]. Cell culture and in vivo animal studies [9–12] have indicated that nicotine is directly toxic to endothelial cells and may have an effect on the fibrinolytic balance. There is currently little information about its impact on endothelium-dependent vasodilatation or acute t-PA release in vivo in man. Therefore, the aims of this study were to determine whether nicotine impairs endothelium-dependent vasodilatation and whether it affects the endogenous fibrinolytic capacity in the peripheral circulation of man.

2. Methods

2.1. Subjects

Eight healthy male non-smokers participated in the study which was undertaken with the approval of the local research ethics committee and in accordance with the Declaration of Helsinki. The written informed consent of each subject was obtained before entry into the study. None of the subjects received vasoactive or nonsteroidal anti-inflammatory drugs in the week before the study, and all abstained from alcohol for 24 h before, and from food and caffeine-containing drinks on the day of, the study. All studies were performed in a quiet, temperature-controlled room maintained at 22–25°C.

2.2. Intra-arterial drug administration

The brachial artery of the nondominant arm was cannulated with a 27-standard wire gauge steel needle (Cooper’s Needle Works Ltd., Sheffield, UK) under local anaesthesia. The cannula was attached to a 16-gauge epidural catheter (Portex Ltd., Kent, UK) and patency was maintained by infusion of saline (0.9% Baxter Healthcare Ltd., Norfolk, UK) via an IVAC P1000 syringe pump (IVAC Ltd., Basingstoke, UK). The total rate of intra-arterial infusions was maintained constant throughout all studies at 1 ml/min. Pharmaceutical grade substance P (Clinalfa AG, Läufelfingen, Switzerland) and sodium nitroprusside (Faulding DBL Pharmaceutical, Leamington, UK) were administered following dissolution in saline.

2.3. Measurements

Blood flow was measured in both forearms by venous occlusion plethysmography using mercury-in-silastic strain gauges applied to the widest part of the forearm [13]. During measurement periods, the hands were excluded from the circulation by rapid inflation of the wrist cuffs to a pressure of 220 mmHg using E20 Rapid Cuff Inflators (D.E. Hokanson, Washington, USA). Upper arm cuffs were inflated intermittently to 40 mmHg for 10 s in every 15 s to achieve venous occlusion and obtain plethysmographic recordings. Analogue voltage output from an EC-4 Strain Gauge Plethysmograph (D.E. Hokanson) was processed by a MacLab analogue-to-digital converter and Chart™ v3.3.8 software (AD Instruments, Castle Hill, Australia) and recorded onto a Macintosh Classic II computer (Apple Computers, Cupertino, USA). Calibration was achieved using the internal standard of the plethysmograph.

Blood pressure was monitored in the non-infused arm at intervals throughout each study with a semi-automated non-invasive oscillometric sphygmomanometer (Takeda UA 751, Takeda Medical, Tokyo, Japan).

Venous cannulae (17-gauge) were inserted into the deep large subcutaneous veins of the antecubital fossae of both arms. Blood (10 ml) was withdrawn simultaneously from each arm and collected into acidified buffered citrate (Biopool Stabilyte, Umeå, Sweden for t-PA assays) and citrate (Monovette, Sarstedt, Nümbrecht, Germany for PAI-1 assays) tubes, and kept on ice before being centrifuged at 2000×g for 30 min at 4°C. Platelet-free plasma was decanted and stored at −80°C before assay. Plasma PAI-1 antigen and t-PA antigen were determined as previously described [6,7] using ELISA (Coazla PAI-1 and t-PA, Chromogenix AB) and t-PA activity was measured using a photometric method (Coaset t-PA, Chromogenix AB). Haematocrit was determined by an Ac T Counter (Coulter Corporation, Miami, USA) at baseline and during infusion of 8 pmol/min of substance P. Plasma lipid fractions were measured by an enzymatic colorimetric method (Boehringer Mannheim GmbH Diagnostica, Germany). LDL cholesterol was derived according to the method of Friedewald et al. [14]. Plasma cotinine was determined by gas–liquid chromatography as previously described [15].
2.4. Study design

Subjects attended on two occasions separated by at least 1 week. Topical nicotine or placebo patches were applied for 7 days prior to the study day in a double blind randomised crossover design. The dose of nicotine administered was 17.5 mg (Nicotinell TTS® 10) but was increased to 35 mg (Nicotinell TTS® 20) for the final 4 days if well tolerated. ‘High dose’ placebo patches were administered in a similar manner such that double blinding was maintained. On the study day, subjects attended fasted and rested recumbent throughout. Strain gauges and cuffs were applied, and the brachial artery of the non-dominant arm was cannulated as described above. Forearm blood flow was measured every 10 min. Saline was infused for the first 30 min to allow time for equilibration with the final measurement taken as the baseline blood flow, time 0. Thereafter, the subjects received intra-arterial substance P at 2, 4 and 8 pmol/min for 10 min at each dose. After a 30-min washout of saline infusion, the subjects received also an intra-arterial infusion of sodium nitroprusside (SNP) at 2, 4 and 8 μg/min for 10 min at each dose to assess endothelium-independent vasodilatation. Tissue-plasminogen activator was measured at baseline and with each dose of substance P. Plasminogen activator inhibitor was measured at baseline and at substance P 8 pmol/min. In this model, SNP infusion does not affect fibrinolytic variables [6,16] and was, therefore, not measured. The order of the substance P and SNP infusions was randomised between subjects in each study but remained constant for each subject. Plasma cotinine concentrations were measured at baseline on each study day.

2.5. Data analysis and statistics

Plethysmographic data were extracted from the Chart™ data files and forearm blood flow (FBF) was calculated for individual venous occlusion cuff inflations by use of a template spreadsheet (Excel v5.0; Microsoft Corporation, Cambridge, USA). Recordings from the first 60 s after wrist cuff inflation were not used because of the variability in blood flow this causes [13]. The average of the last five recordings from a 3-min interval of FBF measurement were used for analysis. The percentage change from baseline blood flow in the infused arm was calculated, as previously described [13], from the ratio of the infused and non-infused arm blood flow:

\[
\text{% change in blood flow} = 100 \times \frac{(I_b/NI_b - I_n/NI_n)}{I_b/NI_b}
\]

where \(I_b\) and \(NI_b\) are the infused and non-infused forearm blood flows at baseline (time 0) respectively, and \(I_n\) and \(NI_n\) are the infused and non-infused forearm blood flows at a given time point, respectively.

Estimated net release of t-PA activity and antigen was previously defined [6,7] as the product of the infused forearm plasma flow (based on the mean haematocrit, Hct, and the infused forearm blood flow, FBF) and the concentration difference between the infused ([t-PA]_Inf) and non-infused arms ([t-PA]_Non-inf)

\[
\text{estimated net t-PA release} = \text{FBF} \times (1 - \text{Hct}) \times ([t-PA]_\text{Inf} - [t-PA]_\text{Non-inf}).
\]

Data were examined, where appropriate, by two-way analysis of variance (ANOVA) with repeated measures and two-tailed paired Student’s t-test using Excel v5.0 (Microsoft). All results are expressed as mean±standard error of the mean (S.E.M.). Statistical significance was taken at the 5% level.

3. Results

All subjects were normotensive with a normal serum lipid profile and plasma glucose concentration (Table 1). Nicotine administration significantly increased plasma cotinine levels from 0.4±0.1 to 125±25 ng/ml \((P<0.001,\ \text{paired } t\text{-test})\). There were no significant changes in blood pressure, heart rate, haematocrit or blood flow in the non-infused forearm during each of the study days (Table 2). During nicotine administration, the heart rate and the non-infused and infused forearm blood flows were consistently higher than during placebo (Table 2). Two subjects were unable to tolerate the higher dose of nicotine and returned to the 17.5 mg nicotine patch for the remainder of the 7 days.

Substance P and SNP caused dose-dependent increases in FBF during placebo and nicotine administration \((P<0.001\ \text{for all, ANOVA})\). Because of baseline differences, absolute FBF during substance P and SNP infusion were greater with nicotine administration \((P<0.05,\ \text{two-way ANOVA})\). However taking account of these baseline differences, there were no significant differences in the percentage increase in FBF with substance P or SNP infusion during nicotine administration (Table 2).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline subject characteristics (mean±S.E.M.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>29±3 years</td>
</tr>
<tr>
<td>Heart rate</td>
<td>68±3 /min</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>91±3 mmHg</td>
</tr>
<tr>
<td>Fasting plasma glucose concentration</td>
<td>87±2 mg/dl</td>
</tr>
<tr>
<td>Serum lipid profile</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol concentration</td>
<td>154±8 mg/dl</td>
</tr>
<tr>
<td>HDL cholesterol concentration</td>
<td>46±4 mg/dl</td>
</tr>
<tr>
<td>LDL cholesterol concentration</td>
<td>77±8 mg/dl</td>
</tr>
<tr>
<td>Triglyceride concentration</td>
<td>114±26 mg/dl</td>
</tr>
</tbody>
</table>
Plasma tissue plasminogen activator (t-PA) and plasminogen activator inhibitor type 1 (PAI-1) concentrations during nicotine and placebo administration

### Table 2
Forearm blood flow and systemic haemodynamics during nicotine and placebo administration

<table>
<thead>
<tr>
<th>Substance P (pmol/min)</th>
<th>Sodium nitroprusside (µg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Nicotine administration</th>
<th>Heart rate (/min)</th>
<th>Mean arterial pressure (mmHg)</th>
<th>Absolute forearm blood flow (ml/100 ml/min)</th>
<th>Non-infused arm</th>
<th>Infused arm</th>
<th>Percentage change in forearm blood flow</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>69±3</td>
<td>92±4</td>
<td>4.8±0.7</td>
<td>5±0.6</td>
<td>0</td>
<td>159±25/217±34 281±46 164±40 227±55</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Placebo administration</th>
<th>Heart rate (/min)</th>
<th>Mean arterial pressure (mmHg)</th>
<th>Absolute forearm blood flow (ml/100 ml/min)</th>
<th>Non-infused arm</th>
<th>Infused arm</th>
<th>Percentage change in forearm blood flow</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>68±3</td>
<td>90±3</td>
<td>3.5±0.5</td>
<td>3.9±0.8</td>
<td>0</td>
<td>211±44/300±66 309±52* 178±23 242±30</td>
</tr>
</tbody>
</table>

*P<0.001 one-way ANOVA; ¹P<0.05 two-way ANOVA (nicotine vs. placebo administration).

Compared with the non-infused arm, substance P caused dose-dependent increases in plasma concentration of t-PA antigen and activity in the infused arm during nicotine and placebo administration (Table 3). The infused arm plasma concentrations and estimated net release of t-PA antigen and activity were greater with nicotine administration in comparison to placebo (Fig. 1 and Table 3). There were no significant changes in plasma PAI-1 concentrations either between treatment groups or before and after substance P infusion (Table 3).

### 4. Discussion

In healthy male volunteers, short-term nicotine administration, sufficient to increase plasma cotinine concentrations to those observed in cigarette smokers [3,17], was associated with an increase in substance-P-induced t-PA release, but had no effect on endothelium-dependent vasodilatation. This suggests that short-term nicotine administration alters specific aspects of endothelial function and enhances the acute endogenous fibrinolytic capacity in

### Table 3
Plasma tissue plasminogen activator (t-PA) and plasminogen activator inhibitor type 1 (PAI-1) concentrations during nicotine and placebo administration

<table>
<thead>
<tr>
<th>Substance P dose (pmol/min)</th>
<th>Nicotine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Plasma t-PA antigen (ng/ml)</th>
<th>Nicotine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-infused arm</td>
<td>4.5±0.3</td>
<td>4.4±0.2</td>
</tr>
<tr>
<td>Infused arm</td>
<td>3.9±0.3</td>
<td>4.3±0.3</td>
</tr>
<tr>
<td>Forearm difference</td>
<td>-0.6±0.2</td>
<td>-0.1±0.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Plasma t-PA activity (IU/ml)</th>
<th>Nicotine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-infused arm</td>
<td>1.9±0.1</td>
<td>2.2±0.2</td>
</tr>
<tr>
<td>Infused arm</td>
<td>1.9±0.1</td>
<td>2.4±0.2</td>
</tr>
<tr>
<td>Forearm difference</td>
<td>0.0±0.1</td>
<td>0.2±0.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Plasma PAI-1 antigen (ng/ml)</th>
<th>Nicotine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-infused arm</td>
<td>32±6</td>
<td>30±6</td>
</tr>
<tr>
<td>Infused arm</td>
<td>30±6</td>
<td>31±5</td>
</tr>
</tbody>
</table>

*P<0.05 two-way ANOVA (infused vs. non-infused arm); ¹P<0.05 two-way ANOVA (nicotine vs. placebo); ¹P<0.001 one-way ANOVA.
suggest chronic nicotine exposure depletes the free pool of brain capillary t-PA antigen [12]. The act of smoking acutely releases t-PA causing an elevation in plasma t-PA concentrations [18] that appears to be blunted in chronic cigarette smokers [19]. Indeed, chronic smoking causes a reduction in the subsequent ability to release t-PA when challenged with desmopressin [20] or venous occlusion [21]. These findings are consistent with our observations of enhanced acute t-PA release with short-term nicotine exposure and our previous findings [7] of increased basal plasma t-PA concentrations in chronic cigarette smokers but a reduced acute release of t-PA. However, further studies are now required to assess how rapidly the impairment of t-PA release reverses on cessation of cigarette smoking, and what effect nicotine supplementation has in recent ex-smokers.

The mechanisms of action of nicotine on t-PA release are unknown, but may be mediated by induction of gene expression [11] or processing of t-PA antigen at the post-transcriptional level [12]. As with cigarette smoking, there does appear to be an important difference between the effects of nicotine during acute and chronic administration [11,12], and whilst short-term nicotine administration appears to potentiate acute t-PA release, chronic administration may cause a reduction. This may be a consequence of the depletion of intracellular t-PA stores, desensitisation of the endothelium to further stimulation, or paradoxically a reduction in the acute storage pool due to preferential up-regulation of constitutive t-PA release. In the present investigation, short-term nicotine exposure significantly increased the capacity of the endothelium to release t-PA when challenged by substance P infusion. However, we did not observe a rise in basal plasma concentration of t-PA antigen to accompany this associated increase in acute stimulated t-PA release. This suggests that nicotine may require a more protracted period of administration or necessitate synergy with a stimulus for t-PA release, such as other gas-phase components of cigarette smoke.

Epidemiological studies of long-term nicotine treatment have not been conducted but relevant information can be inferred from studies of chewing tobacco or snuff users where there is systemic absorption of nicotine but not of other combustion products. These studies have found no evidence of an increased risk of myocardial infarction or sudden cardiac death [22,23]. Two prospective studies involving treatment of smokers with known cardiovascular disease using transdermal nicotine have also failed to find an association between nicotine use and the risk of acute cardiovascular events [24,25]. Indeed, one study of smokers [25] reported more adverse events with placebo than nicotine patches suggesting a protective role of nicotine. Moreover, an experimental study of smokers with known coronary artery disease demonstrated that nicotine supplementation caused a substantial reduction in exercise-induced reversible myocardial perfusion defects as assessed.

Fig. 1. Net release of tissue plasminogen activator (t-PA) antigen (solid lines) and activity (dashed lines) during placebo (open circles) and nicotine (closed circles) administration. One-way ANOVA: \( P < 0.001 \) for all responses. Two-way ANOVA: \( *P < 0.05; \quad P < 0.001 \) (nicotine vs. placebo).
by quantitative SPECT scanning [26]. Although there are differences between epidemiological and experimental studies, these results suggest that nicotine in itself is not a direct cause of tobacco-related cardiovascular disease.

In contrast to previous in vivo studies [27–29], we did not find an attenuation in blood flow responses to the endothelium-dependent vasodilation during nicotine administration. This disparity may be due to species differences [27] or to the study populations investigated [29]. Sarabi et al. [29] assessed the effects of nicotine supplementation in habitual smokers and reported a difference in a derived index of endothelial function. However, no direct comparisons were made of the blood flow responses to methacholine. In addition, nicotine treatment was associated with a change in systemic blood pressure and the authors conceded that this may have accounted for their findings. These contrasting observations may also be explained by the differing signal transduction pathways involved in muscarinic and substance P-induced vasodilatation [30,31]. Indeed, previous studies assessing endothelial function, using both substance P and acetylcholine administration, have documented either concordant [32,33] or discordant [34,35] responses that are, in part, dependent upon the disease processes under investigation. Moreover, we chose to use substance P as an endothelial cell stimulant because acetylcholine does not induce the acute release of t-PA in the human forearm [36]. These observations highlight the important differences between the various agents used to stimulate the endothelium as well as the differing manifestations of endothelial dysfunction that are dependent on the nature of the underlying cellular injury.

Another finding of the present study is that nicotine administration was associated with an increase in basal forearm blood flow suggesting a vasodilator effect of nicotine on the peripheral vascular bed. The cardiovascular effects of systemic nicotine administration are complex and include actions of nicotine on the central and peripheral nervous systems. Of the studies that have examined the direct effect of nicotine on vascular reactivity, all have suggested a vasodilator action. Ex vivo studies indicate that nicotine induces a neurally and nitric oxide-mediated, endothelium-independent, vasodilatation [37,38]. This has been confirmed by an in vivo canine model [39] that demonstrated that the intracarotid injection of nicotine increased cerebral blood flow through the release of nitric oxide from vagal nerve terminals. Moreover, Fewings et al. [40] have reported that intra-arterial nicotine infusion increases forearm blood flow in man. Our findings suggest that short-term nicotine administration does not impair endothelium-dependent vasomotion but does cause systemic vasodilatation as indicated by an elevation in resting forearm blood flow and heart rate.

In conclusion, we have demonstrated, for the first time, that nicotine administration alters specific aspects of endothelial function and enhances the acute endogenous fibrinolytic capacity in vivo. Future studies are now needed to assess the effects of long-term nicotine exposure, including the potential to cause depletion of endothelial t-PA stores, particularly in recent ex-smokers.

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This work was supported by a grant from the British Heart Foundation (PG/99110). Prof. Webb is supported by a Research Leave Fellowship from the Wellcome Trust (WT 0526330). We would like to thank Neil Johnston for his assistance with this study.

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[3] Celermajer DS, Adams MR, Clarkson P et al. Passive smoking and associated with a change in systemic blood pressure and the authors conceded that this may have accounted for their findings. These contrasting observations may also be explained by the differing signal transduction pathways involved in muscarinic and substance P-induced vasodilatation [30,31]. Indeed, previous studies assessing endothelial function, using both substance P and acetylcholine administration, have documented either concordant [32,33] or discordant [34,35] responses that are, in part, dependent upon the disease processes under investigation. Moreover, we chose to use substance P as an endothelial cell stimulant because acetylcholine does not induce the acute release of t-PA in the human forearm [36]. These observations highlight the important differences between the various agents used to stimulate the endothelium as well as the differing manifestations of endothelial dysfunction that are dependent on the nature of the underlying cellular injury.

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