PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 178, 585–590 (1985)

Actions of Nicotine on Renal Function in Dogs (42046)

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Abstract. Renal excretory and circulatory responses to nicotine were investigated in anesthetized dogs under three sets of conditions: (a) infusion of nicotine into the left renal artery (ia) at a dose of 0.5 $\mu g \cdot min^{-1} \cdot kg$ body $wt^{-1} \times 15$ min; (b) ia nicotine after 1.0 mg/kg ia propranolol; and (c) ia nicotine after bilateral adrenalectomy. Measured and calculated left and right renal excretory variables included sodium, potassium, and chloride excretion rates ($U_{Na}V$, U_KV, and $U_{Cl}V$, respectively), total solute excretion ($U_{Os}V$), glomerular filtration rate (GFR), fractional sodium excretion (FE_{Na}), and urine flow rate. Systemic arterial pressure and left renal artery blood flow (RBF) were also measured. In seven intact dogs administered nicotine alone, there were significant increases in $U_{Na}V$, $U_{Cl}V$, $U_{Os}V$, GFR, and urine flow rates from both kidneys. However, nicotine did not significantly affect U_KV, FE_{Na}, arterial pressure, or RBF. The lack of circulatory effects of nicotine was also observed after either propranolol or adrenalectomy. However, when nicotine was administered after propranolol, the drug evoked significant decreases in $U_{Os}V$, $U_{Na}V$, $U_{Cl}V$, and GFR, compared with prenicotine values. When nicotine was administered after bilateral adrenalectomy, the drug evoked decreases in the excretory parameters similar to those observed after propranolol. These findings seem to support several inferences: (a) nicotine stimulates renal excretory functions—the alkaloid is saluretic and diuretic; (b) the action of nicotine on the kidney is mediated mainly by the release of catecholamines from the adrenal medulla; (c) catecholamines released by nicotine act mainly on β-adrenergic receptors; and (d) the saluresis prompted by the release of catecholamines in response to nicotine is due to a subsequent increase in GFR.

Nicotine is an important constituent of the pharmacological burden imposed on the body during the consumption of tobacco products. In recent investigations we have explored the hemodynamic effects of nicotine on the canine intestine and stomach when the alkaloid was administered into the circulation in doses which would result in circulating concentrations approximating those experienced by smokers. In the gut nicotine evoked a transient hyperemia followed by a decrease in mesenteric blood flow which reflected corresponding changes in arterial blood pressure and a subsequent increase in vascular resistance (1). These effects of nicotine appeared to be mediated indirectly through adrenergic receptors. In the stomach nicotine caused initial increases in gastric blood flow and oxygen consumption which were also mediated indirectly through adrenergic receptors (2).

Surprisingly, there have been few reports concerning the effects of nicotine on renal function or on renal hemodynamics. Antidiuretic effects of relatively large doses of nicotine (100–2500 μg/kg) have been reported in rats (3) and in dogs (4) undergoing a water diuresis. In the latter study (4) it was also reported that the nicotine-induced antidiuresis was associated with increases in the glomerular filtration rate (GFR), no change in renal blood flow (RBF), and an increase in the excretion rate of sodium and potassium. Effects of nicotine on renal function in animals not subjected to a water diuresis and in doses more likely to reflect those obtained during cigarette smoking have not been reported.

Therefore, in the current study we have examined the effects of relatively low doses of nicotine both on renal hemodynamics and on renal excretory function. The possible role of adrenergic mediation was examined in an effort to further elucidate the mechanism of action of this widely used drug.

Methods. Seventeen mongrel dogs of either sex weighing 15–25 kg were anesthetized with sodium pentobarbital (30 mg/kg, iv) and supplemented with anesthetic as needed throughout the experiment. An endotracheal tube was inserted and the animals were al-

0037-9727/85 $1.50

lowed to breathe spontaneously. Body temperature was sustained with a heating pad connected to a temperature-controlled system (Yellow Springs, Model 63RC). Mean arterial blood pressure was measured through a right femoral arterial catheter (PE-100) connected to a pressure transducer (Physiograph, Model P-1000A). Another catheter was placed in the left femoral artery for withdrawal of blood samples.

After infusing saline at 1.0 $ml \cdot kg^{-1} \cdot min^{-1}$ for 15 min, a permanent infusion rate of 0.25 $ml \cdot kg^{-1} \cdot min^{-1}$ was established and delivered throughout each experiment via a catheter placed in the right femoral vein. The left femoral vein was also catheterized for infusion of saline containing creatinine (3%) at a rate of 0.2 ml/min.

Both ureters were exposed and catheterized through a small abdominal incision. The left renal artery was exposed and isolated through a flank incision. Renal blood flow was measured with an electromagnetic blood-flow meter (Narco Biosystems Model RT 400 with digital display meter Model DD 350). An electromagnetic blood-flow transducer (i.d. 3–3.5 mm) was positioned on the renal artery. At the beginning and end of each experiment, zero blood flow was obtained by occlusion of the renal artery distal to the transducer. A curved 25-gauge needle connected to PE-50 tubing and a syringe infusion pump system (Harvard Apparatus Model 975) was inserted into the renal artery proximal to the transducer for intraarterial infusion of nicotine (Sigma) or propranolol (Ayerst) dissolved in saline. During the control periods, saline alone was infused into the renal artery at a rate of 0.2 ml/min. Mean arterial pressure and renal blood-flow values were monitored continuously on a polygraphic recorder (Physiograph Model 4).

Following surgery, the dogs were allowed adequate time for stabilization (60–90 min) prior to commencing the experiment. The criterion used to determine when an animal was in a steady state was a constant urine flow rate (V) and urine osmolality (U_{Os}) during a 30-min time interval. When urinary flow rate and osmolality were stabilized, a control renal clearance (C) was begun. Immediately following this control period, infusion of nicotine or propranolol was started or the animal was bilaterally adrenalectomized. In seven dogs, nicotine was infused as the only treatment. In five dogs, the alkaloid was infused after 1 mg/kg ia propranolol. In five other dogs nicotine was infused after bilateral adrenalectomies had been performed. The dose of nicotine infused into the renal artery was 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 15 min.

Plasma and urinary concentrations of creatinine and chloride (Cl^-) were measured by the method of Folin and Wu (5) and amperametric titration with silver (Buchler-Cotlove chloridometer), respectively. Sodium (Na^+) and potassium (K^+) concentrations in urine (U) and plasma were determined by flame photometry (Advanced Instruments). The clearance (C) of creatinine (cr) was equated with the GFR. Fractional excretion (FE) was calculated by Cion/Ccr. Urinary osmolality was measured by freezing-point depression (Precision Systems). At the end of each experiment the right and left kidneys were excised and weighed; results are expressed per gram kidney weight.

Experimental data have been presented as means ± standard error of the mean. Statistical significance was determined by using Student's t test for paired data, assuming significant change at a probability of less than 5%.

Results. In the first series of seven animals only nicotine was tested. Control values for GFR, urine flow rate, $U_{Os}V$, $U_{Na}V$, U_KV, $U_{Cl}V$, FE_{Na}, FE_K, and FE_{Cl} from both kidneys are summarized in Table I. There was no significant difference in any value between the two organs. Nicotine significantly increased GFR, urine flow rate, $U_{Os}V$, $U_{Na}V$, and $U_{Cl}V$, but did not affect the fractional excretion of the latter two ions. These effects on excretory function were observed in both kidneys. Nicotine had no significant effect on RBF, U_KV, FE_K, or systemic arterial pressure. However, in six of the seven control animals nicotine increased U_KV in both kidneys.

In the second series of five animals the effects of nicotine on renal function were evaluated following antagonism of β-adrenergic receptors with propranolol. The dose of propranolol employed (1 mg/kg injected into the left renal artery) prevented the renal dilator response to isoproterenol (1 μg/kg ia).

TABLE I. EFFECTS OF NICOTINE ON RENAL FUNCTION

	Control		Nicotine	
	R	L	R	L
RBF (ml/min · g kidney wt)	—	3.50 ± 0.20	—	3.54 ± 0.20
GFR (ml/min · g kidney wt)	0.67 ± 0.08	0.75 ± 0.08	0.75 ± 0.10*	0.85 ± 0.09*
Urine flow rate (ml/min · g kidney wt)	0.031 ± 0.006	0.039 ± 0.006	0.040 ± 0.007*	0.052 ± 0.008*
$U_{Os}V$ (μOsm/min · g kidney wt)	17.0 ± 2.8	18.5 ± 3.3	19.4 ± 2.6*	23.7 ± 4.2*
$U_{Na}V$ (μeq/min · g kidney wt)	5.90 ± 1.42	6.91 ± 1.47	6.88 ± 1.32*	8.56 ± 1.65*
U_KV (μeq/min · g kidney wt)	0.92 ± 0.09	1.04 ± 0.13	1.00 ± 0.10	1.19 ± 0.19
$U_{Cl}V$ (μeq/min · g kidney wt)	3.93 ± 0.91	4.52 ± 0.92	4.67 ± 0.83*	5.85 ± 1.02*
FE_{Na} (%)	5.75 ± 1.10	5.99 ± 1.09	6.59 ± 1.45	6.54 ± 1.40
FE_K (%)	53.2 ± 12.9	53.6 ± 12.6	55.4 ± 15.9	56.5 ± 16.9
FE_{Cl} (%)	6.04 ± 1.09	6.24 ± 1.10	7.13 ± 1.46	7.60 ± 1.39
Systemic arterial pressure (mm Hg)	123 ± 3.0		126 ± 3.0	

* $P < 0.05$ compared with corresponding value in preceding period.

Propranolol alone caused significant decreases in RBF of the left kidney and in $U_{Na}V$ and $U_{Cl}V$ from the right kidney. However, there were decreases in nearly all of the excretory parameters from both kidneys after propranolol, although these declines were not significant. Nicotine, after propranolol, had no effect on RBF of the left kidney, but significantly decreased GFR, $U_{Na}V$, and $U_{Cl}V$, bilaterally (compared with propranolol alone), and decreased $U_{Os}V$ in the left kidney. These findings are shown in Table II.

In the third series of five dogs, adrenalectomy was performed before administering nicotine. Compared with values obtained with adrenalectomy alone, nicotine significantly decreased GFR and $U_{Na}V$ bilaterally and decreased urine flow rate, $U_{Os}V$, U_KV, and $U_{Cl}V$ in the left kidney. As in series I and II, there was no effect of nicotine on RBF. These data are summarized in Table III. When one compares hemodynamic values after adrenalectomy alone with control values for the intact animals in Tables I and II, it appears that the procedure significantly lowered RBF but did not alter systemic arterial blood pressure.

Discussion. The current studies demonstrate that, under our experimental conditions, nicotine is a diuretic and saluretic agent. Effects of the drug on renal function were not associated with changes in either renal hemodynamics or in arterial blood pressure but did include a nicotine-induced increase in the glomerular filtration rate. The effects of nicotine appear to be largely indirect since virtually identical responses were obtained in both the kidney into which nicotine was infused and in the contralateral organ.

The fact that fractional excretion of sodium was unaffected by nicotine indicates that changes in the GFR are a major factor contributing to the nicotine-induced natriuresis. This conclusion is further supported by the finding that following either treatment with propranolol or adrenalectomy, infusion of nicotine was associated with a decrease in the GFR and a decrease in sodium excretion. Whether the actions of nicotine following propranolol or adrenalectomy represent direct effects of the alkaloid on renal function or are related to other indirect actions of the drug such as induction of α-adrenergic activity will require further experimentation.

TABLE II. EFFECTS OF PROPRANOLOL PLUS NICOTINE ON RENAL FUNCTION

	Control		Propranolol		Nicotine after propranolol	
	R	L	R	L	R	L
RBF (ml/min · g kidney wt)	—	3.66 ± 0.3	—	3.24 ± 0.2*	—	3.35 ± 0.4
GFR (ml/min · g kidney wt)	0.74 ± 0.11	0.65 ± 0.12	0.65 ± 0.09	0.57 ± 0.09	0.57 ± 0.08*	0.51 ± 0.08*
Urine flow rate (ml/min · g kidney wt)	0.048 ± 0.009	0.038 ± 0.007	0.043 ± 0.008	0.039 ± 0.009	0.046 ± 0.008	0.036 ± 0.007
$U_{Os}V$ (μOsm/min · g kidney wt)	15.5 ± 1.7	12.8 ± 3.1	12.5 ± 1.9	11.2 ± 1.6	10.7 ± 0.8	8.1 ± 0.8*
$U_{Na}V$ (μeq/min · g kidney wt)	6.74 ± 1.01	5.54 ± 1.60	5.26 ± 0.99*	4.60 ± 0.79	4.63 ± 0.96*	3.69 ± 0.83*
U_KV (μeq/min · g kidney wt)	1.01 ± 0.07	0.80 ± 0.07	0.87 ± 0.01	0.65 ± 0.04	0.86 ± 0.04	0.69 ± 0.07
$U_{Cl}V$ (μeq/min · g kidney wt)	4.81 ± 0.60	3.96 ± 1.16	3.87 ± 0.72*	3.31 ± 0.65	3.53 ± 0.74*	2.78 ± 0.71*
FE_{Na} (%)	5.91 ± 0.71	5.29 ± 0.88	5.04 ± 0.80	4.95 ± 0.60	5.18 ± 0.72	4.49 ± 0.46
FE_K (%)	43.4 ± 7.9	39.7 ± 6.4	41.2 ± 7.90	34.6 ± 6.0	46.9 ± 8.1	39.6 ± 5.5*
FE_{Cl} (%)	7.02 ± 0.96	6.17 ± 1.13	6.14 ± 1.13	5.72 ± 0.78	6.45 ± 1.04	5.38 ± 0.72
Systemic arterial pressure (mm Hg)	128 ± 3.0		127 ± 3.0		127 ± 3.0	

* $P < 0.05$ compared with corresponding value in preceding period.

TABLE III. EFFECTS OF NICOTINE ON RENAL FUNCTION FOLLOWING ADRENALECTOMY

	Adrenalectomy		Nicotine after adrenalectomy	
	R	L	R	L
RBF (ml/min · g kidney wt)	—	2.55 ± 0.33	—	2.52 ± 0.33
GFR (ml/min · g kidney wt)	0.60 ± 0.05	0.59 ± 0.07	0.54 ± 0.04*	0.45 ± 0.06*
Urine flow rate (ml/min · g kidney wt)	0.008 ± 0.002	0.022 ± 0.003	0.010 ± 0.002	0.017 ± 0.002*
$U_{Os}V$ (μOsm/min · g kidney wt)	6.35 ± 0.99	8.30 ± 1.12	5.48 ± 0.65	6.34 ± 0.69*
$U_{Na}V$ (μeq/min · g kidney wt)	2.03 ± 0.40	2.91 ± 0.51	1.66 ± 0.28*	2.25 ± 0.38*
U_KV (μeq/min · g kidney wt)	0.46 ± 0.16	0.48 ± 0.14	0.40 ± 0.14	0.40 ± 0.12*
$U_{Cl}V$ (μeq/min · g kidney wt)	1.46 ± 0.34	2.20 ± 0.35	1.23 ± 0.22	1.67 ± 0.26*
FE_{Na} (%)	2.13 ± 0.23	3.15 ± 0.30	1.98 ± 0.17	3.02 ± 0.38
FE_K (%)	20.4 ± 5.4	21.7 ± 4.5	19.3 ± 4.9	22.1 ± 4.5
FE_{Cl} (%)	2.24 ± 0.32	3.56 ± 0.37	2.18 ± 0.22	3.43 ± 0.53
Systemic arterial pressure (mm Hg)	128 ± 6.0		128 ± 6.0	

* $P < 0.05$ compared to corresponding value in preceding period.

The similar effects of propranolol and of adrenalectomy on the changes in renal function induced by nicotine provide information regarding the mechanism of action of the alkaloid on renal function. It would appear, then, that a nicotine-induced release of adrenal medullary catecholamines (6) with subsequent stimulation of β receptors could account for our observations. Indeed, infusion of the β agonist, isoproterenol, directly into the renal artery results in an increase in the GFR and a natriuresis and diuresis (7, 8). However, since an intravenous infusion of isoproterenol or epinephrine (which may reflect conditions in our experimental protocol) causes a decrease in urine flow rate and sodium excretion (7–9) further experiments will be required to elucidate the involvement of β receptors in the renal response to nicotine infusion.

The amount of nicotine infused in the current study was clearly within the range expected to be attained by individuals smoking a single cigarette (1). In previous studies we have found that somewhat higher doses of nicotine act on the circulation of splanchnic organs and that, as in the kidney, the action appears to be largely mediated by the adrenergic system. In the canine small intestine intravenously infused nicotine prompted a transient hyperemia but this effect coincided with an increase in systemic arterial blood pressure; calculated vascular resistance was not reduced during infusion of the drug (1). In the same preparation close intraarterial or intraluminal infusion of nicotine evoked a transient vasodilation which was prevented by the ganglion blocker, hexamethonium. Nicotine contracted mesenteric vascular smooth muscle *in vitro,* an effect which was blocked by the α-adrenergic antagonist, phentolamine. Thus, the acute hemodynamic response to nicotine in the gut appears to be transient and indirectly mediated.

In the stomach intraarterially administered nicotine also prompted a hyperemia which was prevented by β-adrenergic blockade with propranolol (2). In addition, intravenous nicotine produced a transient increase in gastric blood flow which coincided with a systemic pressor response and was prevented by propranolol. As in the case of the kidney and the small intestine the effects of nicotine on the stomach were indirect.

In summary, the results of this study suggest that a sequence of events mediates the actions of nicotine on the kidney. Nicotine probably evokes the release of catecholamines (especially epinephrine) from the adrenal medulla which stimulates mainly β-adrenergic receptors, thereby directly or indirectly inducing an increase in the GFR and a resultant diuresis and saluresis. To a lesser extent, nicotine may also stimulate α-adrenergic receptors perhaps via renal sympathetic nerves or via changes in circulating norepinephrine concentrations, since both β-adrenergic antagonism and adrenalectomy converted the renal excretory response to nicotine from an increase to a decrease in function.

The authors are grateful to Mrs. Reiko Tanaka for expert technical assistance. This work was supported by a grant from the Smokeless Tobacco Research Council, Inc.

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Received September 4, 1984. P.S.E.B.M. 1985, Vol. 178.
Accepted December 19, 1984.