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Effect of nicotine on blood flow, oxygen consumption and glucose uptake in the canine small intestine

J. Grayson & D.D.O. Oyebola[1]

Department of Physiology, Medical Sciences Building, University of Toronto, Toronto, Ontario M5S 1A8, Canada

1 Resting blood flow, arterio-venous glucose and oxygen $(A-V)O_2$ differences, glucose uptake and oxygen consumption by a segment of the upper jejunum were measured in anaesthetized dogs. Systemic arterial pressure was also measured.

2 The effect of nicotine infusion (25 $\mu g\,kg^{-1}$ i.v., over 10 min) on these measurements was recorded in untreated dogs, in dogs treated with propranolol (0.5 $mg\,kg^{-1}$) to produce β-adrenoceptor blockade and in dogs after α_1-adrenoceptor blockade with prazosin (0.2 $mg\,kg^{-1}$).

3 Nicotine cause a significant pressor response during infusion and a hypotensive response during the post infusion period. Propranolol did not significantly affect these results. Jejunal blood flow increased in the first half of nicotine infusion in both the untreated and β-blocked animals. Vascular resistance was reduced during nicotine infusion and the decrease persisted post infusion in the β-blocked group.

4 In the untreated group $(A-V)O_2$ was significantly reduced during the first 5 min of nicotine infusion, thereafter it returned to control levels, then rose significantly above control level, post infusion. β-Adrenoceptor blockade had little effect on these responses to nicotine. When oxygen consumption was calculated it was found that nicotine had little effect during or after infusion.

5 Nictine caused significant hyperglycaemia during and for about 1 h after infusion. Tissue release of glucose was occasionally observed following the infusion. β-Adrenoceptor blockade reduced the hyperglycaemia caused by nicotine. β-Blockade alone increased glucose uptake and nicotine caused a further three to four fold increase. Prazosin abolished the effects that were observed in the untreated and the α-blocked animals.

6 The present findings, related to our previous observations on the effects of catecholamines on glucose uptake by the bowel, are consistent with the hypothesis that nicotine has its action on bowel glucose uptake or release through its well-established action in releasing catecholamines and in activating β-adrenoceptors. The responses are not related to oxygen utilization.

Introduction

Nicotine has been widely studied especially as it relates to the smoking habit and carcinogenesis (Euler, 1965; Wynder & Hoffmann, 1967; 1968). It is not often realized that nicotine is used by man in many other ways than smoking. Thus, over the years it has had wide medicinal applications of which Larson & Silvette (1965) gave a detailed review. In Nigeria it is an important constituent of a widely consumed panacea for convulsive seizures of any origin but particularly in children, cow's urine concoction (Oyebola & Elegbe, 1975). For other medicinal purposes it is usually taken orally. Even when smoking, a large amount is actually swallowed rather than inhaled. The nicotine present in ingested medicament or swallowed cigarette smoke is absorbed from the gastro-intestinal tract. Nicotine therefore reaches the tissues of the gastro-intestinal tract not only via the blood following its absorption in the lungs but also by direct contact with gut tissues during absorption. Yet, in spite of the frequent exposure of gut tissues to nicotine, reports in the literature which deal with its effects on the gastro-intestinal blood flow or metabolism are inadequate and contradictory. The present study was carried out in order to investigate further the effects of systemically administered nicotine on blood flow, oxygen consumption and glucose uptake in the dog upper jejunum. It was a study which paralleled a similar

[1]Present address: Department of Physiology, College of Medicine, University of Ibadan, Nigeria.

investigation concerning the effects of catecholamines on the same variables (Grayson & Oyebola, 1983).

Methods

Mongrel dogs of either sex weighing 13–18 kg were used for the experiments. Each animal was fasted for 18–24 h before the start of an experiment. The procedure has been described in detail elsewhere (Grayson & Oyebola, 1983).

A summary of the method is as follows: blood pressure was monitored via a cannula in the carotid artery. A cannula was placed in the jejunal vein draining the intestinal segment to be studied. The femoral artery and femoral vein were connected in an extra-corporeal circuit. The effluent from the jejunal segment was passed through a cannulating electromagnetic flow meter, 3 mm i.d. (Zepeda) to measure jejunal blood flow. Abdominal aortic blood (via the femoral arterial cannula) and jejunal venous effluent were passed in the extra-corporal circuit through the cuvettes of an AVOX machine (Avox Systems, San Antonio, Texas) for the measurement of arterio-venous oxygen difference, $(A-V)O_2$. Heparin ($2\,mg\,kg^{-1}$) was administered, i.v. hourly, to prevent blood clotting.

Experimental procedures

Following surgery, a period of 1 h was allowed for stabilization in all animals.

Untreated group (Group I): Seven dogs were studied. Blood pressure, blood flow and $(A-V)O_2$ were recorded. Then nicotine (B.D.H.) $25\,\mu g\,kg^{-1}$, diluted in 0.15 M saline was infused intravenously through a cannula in a femoral vein for a period of 10 min in a volume of 10 ml (i.e. $1\,ml\,min^{-1}$). A Harvard infusion pump was used. Blood flow, blood pressure and $(A-V)O_2$ were recorded during the infusion and for 1 h post-infusion.

Pretreatment with β-adrenoceptor blocker (Group II): Seven dogs were first given propranolol before nicotine infusion. Each dog was injected with propranolol, $0.5\,mg\,kg^{-1}$ given intravenously (i.v.). Forty minutes was allowed for the drug to take effect. Then basal recordings of blood pressure, blood flow and $(A-V)O_2$ were made. After basal recordings, nicotine $25\,\mu g\,kg^{-1}$ was infused i.v. for 10 min as in the untreated group and blood pressure, blood flow and $(A-V)O_2$ were similarly monitored.

Pretreatment with α-adrenoceptor blockers (Group III): Two dogs were first injected with phenoxybenzamine (dibenzyline, $2\,mg\,kg^{-1}$, i.v.). One hour after the injection, basal recordings were made and the effect of nicotine $25\,\mu g\,kg^{-1}$ on blood pressure, blood flow and $(A-V)O_2$ was studied as in the untreated group. To ascertain if the changes observed in the animals treated with phenoxybenzamine are specific α-adrenoceptor-mediated responses, the experiment was repeated in seven more dogs treated with prazosin, a specific α-adrenoceptor blocker (Graham *et al.*, 1977). Prazosin, $0.2\,mg\,kg^{-1}$, was injected i.v.; 40 min was allowed for the drug to take effect before nicotine ($25\,\mu g\,kg^{-1}$) was infused. Similar measurements to those used in the other groups were made.

Estimation of glucose and oxygen consumption: Jejunal venous and abdominal aortic blood samples for glucose estimation were taken simultaneously at 5 min intervals via three way stop-cocks placed in the jejunal and arterial lines of the extracorporeal circuit. Glucose was measured with a Beckman glucose analyser. Oxygen consumption was calculated as the product of $(A-V)O_2$ and flow, while glucose uptake was the product of arterio-venous glucose difference and flow.

The area of the venous drainage of the jejunal vein cannulated was identified using a retrograde injection of trypan blue. Blood flow per 100 g intestinal tissue was calculated as described earlier (Grayson & Oyebola, 1983). The values obtained agreed well with published values.

A one-way analysis of variance was carried out on the data. The data, measured at corresponding 5 min intervals in the untreated and β-adrenoceptor blocked groups studied, were tested for statistically significant differences using the F-test. Also, data measured before and for 5 min after injection in the same group were assessed for statistically significant differences using the Q test for significance (Snedecor & Cochran, 1967). P values of 0.05 or less were taken as statistically significant.

Results

Effect of β-blockade on blood pressure, flow, oxygen and glucose uptake

Figures 1, 2 and 3 and Table 1, give the effects of β-adrenoceptor blockade alone (i.e. before giving nicotine) on blood pressure, blood flow, $(A-V)O_2$, oxygen consumption, (A–V) glucose and glucose uptake. They also show the effect of a β-blocker on these basal parameters. β-Blockade alone had no effect on blood pressure, flow, $(A-V)O_2$ or oxygen uptake. But it did have a marked and highly significant effect on (A–V) glucose (Table 1) and on glucose uptake, both of which it raised.

Table 1 Effect of nicotine infusion on jejunal (A – V) glucose (mg 100 ml^{-1}), glucose uptake (mg min^{-1}) and vascular resistance (mmHg min ml^{-1}) in untreated and β-blocked dogs

Time (min)		*(A – V) glucose in untreated dogs*	*(A – V) glucose in β-blocked dogs*	*Glucose uptake in untreated dogs*	*Glucose uptake in β-block dogs*	*Vascular resistance in untreated dogs*	*Vascular resistance after β-block*
Control	0	3.4 ± 1.9	9.4 ± 4.3	0.37 ± 0.16	0.96 ± 0.28	12.6 ± 2.7	12.5 ± 1.6
Period of	5	16.3 ± 4.3*	18.7 ± 3.9	2.53 ± 0.80*	3.49 ± 1.01*	11.6 ± 2.7	12.5 ± 2.6
infusion	10	−6.6 ± 11.8	4.5 ± 4.2	− 0.09 ± 0.49	0.59 ± 0.50	16.9 ± 4.5	7.56 ± 2.7*
	15	5.3 ± 11.8	11.2 ± 4.4	0.28 ± 0.41	1.19 ± 0.48	14.1 ± 0.5	6.3 ± 2.3*
Post	20	8.0 ± 3.2	13.0 ± 3.0	0.22 ± 0.28	1.12 ± 0.24	12.8 ± 1.1	7.6 ± 2.3*
infusion	25	3.2 ± 5.5	20.0 ± 4.6*	− 0.07 ± 0.18	1.84 ± 0.50	11.0 ± 2.5	6.3 ± 2.7*
	30	− 8.5 ± 4.5*	28.0 ± 7.0*	− 0.66 ± 0.34*	2.53 ± 0.61*	11.1 ± 3.3	6.2 ± 2.7*
	45	− 3.0 ± 3.0	18.0 ± 4.7	0.46 ± 0.27	1.86 ± 0.53	11.0 ± 3.4	7.3 ± 2.3*
	60	7.5 ± 5.5	17.5 ± 7.0	0.92 ± 0.44	1.79 ± 0.72	10.1 ± 2.5	7.7 ± 2.2*
	70	13.0 ± 5.0	16.7 ± 9.4	1.00 ± 0.31	1.92 ± 1.08	10.7 ± 2.0	8.2 ± 2.1*

The values are given as the mean ± s.e.mean for 7 determinations.
* $P < 0.05$ when compared with control value (analysis of variance).

Effect of nicotine on blood pressure

The effects of infusion of nicotine 25 μg kg^{-1} for 10 min on blood pressure in the untreated and in the β-blocked animals are shown in Figure 1a. The response is characterized by an initial pressor response which was significant in the 5th minute of infusion in the two groups. This was followed by post-infusion hypotension with a blood pressure significantly lower than control for most of the 1 h post-infusion observation period. In the β-blocked animals the pressor response in the 5th minute was more pronounced and the difference in blood pressure compared with the untreated animal was statistically significant ($P < 0.05$). Also, post-infusion blood pressure values were significantly lower than control values for this group for 60 min after infusion.

Effect of nicotine on blood flows

Jejunal blood flow increased during the first half of nicotine infusion in the untreated and in the β-blocked groups; the increase was significant in both groups (Figure 1b). In the untreated group, blood flow fell and was significantly lower than control values at 5, 10, 15 and 20 min after infusion. In the β-blocked animals, blood flow after the infusion, was not significantly different from control values. When the two groups were compared statistically there were significant differences in blood flow apparent from the 10th minute of infusion until the end of the post infusion period.

Effect of nicotine on vascular resistance

Vascular resistance was calculated by dividing arterial pressure by flow. Central venous pressure was not always recorded, but when it was, it varied between 0 and 5 mmHg, values regarded as too low to make any important difference to the resistance calculations. Thus, although the values of resistance obtained in this work, were not absolute, they were sufficient to indicate the occurrence of large or small changes in vascular resistance. The results are given in Table 1. It will be seen that in animals which were not pretreated by receptor blockers there was no significant rise in resistance during the infusion period. After β-blockade, the effect was changed, and towards and after the end of the infusion, resistance fell significantly, the fall persisting throughout the post infusion period. Vascular resistance in the β-blocked group remained significantly lower than control throughout the post infusion period, which was 1 h.

Effects of nicotine on (A – V)O_2 and on oxygen consumption

These are shown in Figure 2. In the untreated group, it will be seen that initially nicotine caused a significant fall in (A – V)O_2. However, this was only temporary and (A – V)O_2 had returned to near resting levels by the 10th minute of infusion. The rise continued and maximum levels, significantly higher than controls ($P < 0.05$) were reached 10 min after infusion ceased. β-Blockade, had no significant effects on (A – V)O_2 nor on the responses to nicotine. The late rise in (A – V)O_2 which continued after the infusion of nicotine had ended, still occurred, maximum levels being reached 25 and 30 min after stopping the infusion.

Nicotine had no effect on oxygen consumption in the untreated and β-blocked animals either during or after infusion. However, during the post infusion period, oxygen consumption in the β-blocked group of

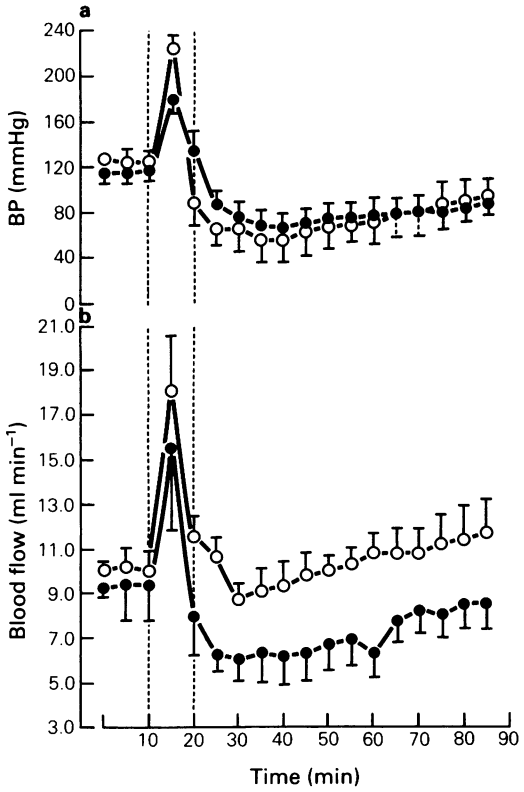

Figure 1 The effect of intravenous infusion of nicotine ($25\,\mu g\,kg^{-1}$) on blood pressure (a) and blood flow (b) in untreated dogs (●) and in β-blocked dogs (○). β-Blockade was by means of propranolol ($0.5\,mg\,kg^{-1}$, i.v.). Nicotine was infused between 10 and 20 min (vertical broken lines). Note the increase in pressure during the infusion followed by a decline which began during the infusion but continued for 10 or 15 min after infusion. Note, also, the initial rise which occurred in flow, followed also by a decline more marked in the untreated animals. The points are the mean of 7 determinations with the bars representing 1 s.e.mean.

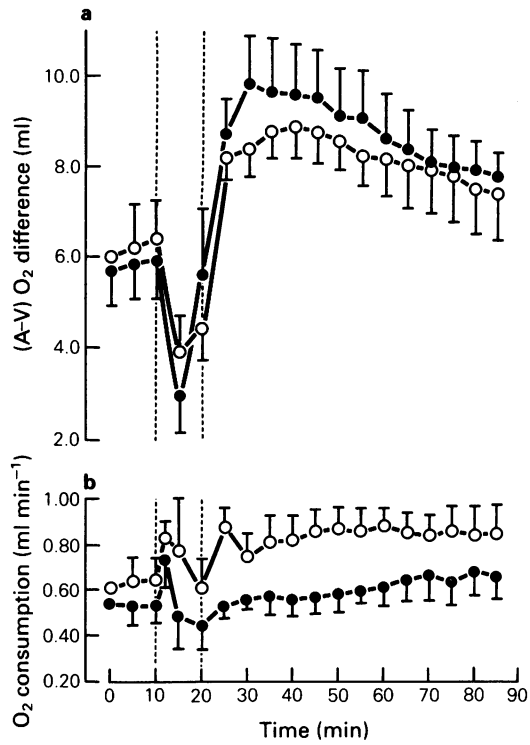

Figure 2 The effect of intravenous infusions of nicotine ($25\,\mu g\,kg^{-1}$) over a 10 min period on arterio-venous oxygen differences $(A-V)O_2$ (a) and on oxygen consumption calculated as $(A-V)O_2$ flow. Effects are shown before (●) and after (○) β-blockade with propranolol ($0.5\,mg\,kg^{-1}$, i.v.). Note the initial fall in $(A-V)O_2$ reaching a maximum decline in about 5 min, thereafter rising markedly to maximum levels reached about 10 min after infusion. The results were the same in treated and untreated animals. Nicotine had little effect on oxygen consumption. The points are the mean of 7 determinations with the bars representing 1 s.e.mean.

animals was significantly higher than in the untreated group until the last 10 min of the period.

Effect of nicotine on blood glucose, (A – V) glucose and glucose uptake

The effect of nicotine on blood glucose levels in the untreated group is shown in Figure 3(a). Figure 3(a) shows that the hyperglycaemic response was sustained throughout the infusion and blood glucose remained significantly higher than control values for 20 min post-infusion. β-Blockade significantly reduced the hyperglycaemic response to nicotine (Figure 3b).

The effects on glucose uptake are given in Table 1. In the untreated animals, glucose uptake increased almost seven fold in response to nicotine infusion. However, the effect was short lived and uptake returned to control levels or even below while the infusion was still in progress. In some dogs negative values were recorded for glucose uptake showing that these was actually a net tissue output of glucose. The decline continued after the infusion and in some dogs, negative values for glucose uptake were also recorded between the 10th and 45th minutes post-infusion. Three dogs produced negative values for glucose uptake of $-0.87 \pm 0.48\,mg\,min^{-1}$. These were highly significant changes compared with the control values and indicated a signficant tissue glucose output. Even in the pooled data, values obtained at the 30th minute

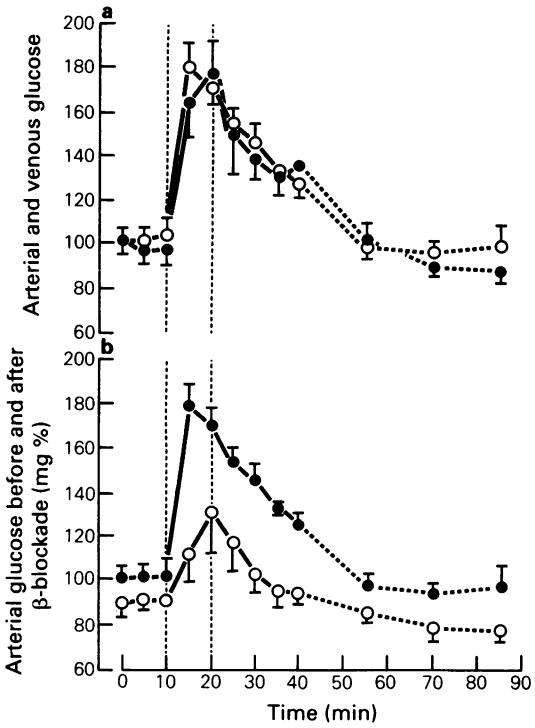

Figure 3 (a) The effect of intravenous infusions of nicotine (25 μg kg^{-1} over a 10 min period) on arterial (●) and venous (○) blood glucose levels in unblocked animals. Note the marked hyperglycaemia which reached maximum levels between 5 and 10 min of infusion, thereafter arterial and venous levels declining together. The points are the mean of 7 determinations with the bars representing 1 s.e.mean. (b) This shows arterial glucose levels alone before (●) and after (○) β-blockade with propranolol (0.5 mg kg^{-1} i.v.). Note, the hyperglycaemic effect of nicotine is greatly reduced by β-blockade. This result was highly significant (see, also, Table 1). The points are the means of 7 determinations with the bars representing 1 s.e.mean.

indicated that nicotine usually caused a net glucose output.

a-Adrenoceptor blockade alone increased glucose uptake approximately three times. This finding was highly significant. Infusion of nicotine caused a further three to four fold increase in this group. The maximum effect wore off quickly even during continued infusion. However, although glucose uptake after the infusion was stopped, was not significantly higher than its own control levels, it was always higher than in the untreated group. Tissue release of glucose was also never seen after β-blockade.

Glucose uptake in the post-infusion period in the β-blocked animals rose to higher levels than in the untreated animals. The differences in corresponding values in the two groups were significant, 10, 15, 20 and 35 min after the infusion.

Effect of α-adrenoceptor blockers on the response to nicotine infusion

Since the β-adrenoceptor blocker, propranolol, had such profound effects on many of the data measured, the effect of α-adrenoceptor blockade was also investigated. When phenoxybenzamine was administered to two dogs, the changes in blood pressure, blood flow, arterio-venous oxygen differences and oxygen consumption which had been previously found to occur both in the untreated (Group I) and β-blocked dogs (Group II) during and after the nicotine infusion were markedly reduced. Also the hyperglycaemic response to nicotine was greatly reduced. However, in contrast to the findings in Group I and II, blood glucose in the phenoxybenzamine-treated dogs not only remained elevated after nicotine infusion but showed progressive increase throughout the post infusion period.

The results of further experiments in seven dogs using a more specific α-adrenoceptor antagonist, prazosin, are summarized in Table 2. When nicotine

Table 2 Effect of nicotine infusion in dogs given prazosin (0.2 mg kg^{-1}) before nicotine infusion

Time (min)		*Blood pressure* (mm Hg)	*Flow* (ml min^{-1})	*Vascular resistance*	$(A-V)O_2$ (ml 100 ml^{-1})	*Oxygen consumption* (mg 100 ml^{-1})	*Arterial glucose* (mg min^{-1})	*Glucose uptake*
Control	0	66.3 ± 10.8	5.2 ± 1.6	13.4 ± 3.8	8.1 ± 2.2	0.43 ± 0.12	107.6 ± 10.2	0.47 ± 0.50
Period of	5	67.8 ± 13.9	5.4 ± 1.7	13.4 ± 3.6	8.1 ± 2.2	0.43 ± 0.12	111.0 ± 11.9	0.48 ± 0.40
infusion	10	65.7 ± 13.8	5.2 ± 1.8	14.0 ± 4.7	8.4 ± 2.2	0.41 ± 0.13	111.5 ± 12.1	0.36 ± 0.18
	15	64.6 ± 10.3	5.5 ± 1.3	12.3 ± 3.2	8.0 ± 2.2	0.42 ± 0.11	112.5 ± 14.5	0.66 ± 0.71
Post	20	64.0 ± 11.0	5.4 ± 1.4	12.6 ± 3.6	8.1 ± 2.0	0.42 ± 0.11	112.1 ± 9.9	0.52 ± 0.64
infusion	25	64.3 ± 10.0	5.4 ± 1.3	21.1 ± 2.2	8.4 ± 2.1	0.44 ± 0.08	115.1 ± 11.5	0.80 ± 0.98
	30	65.4 ± 9.6	5.6 ± 1.5	12.3 ± 2.9	8.3 ± 1.9	0.45 ± 0.12	116.1 ± 11.4	0.77 ± 0.98
	45	67.6 ± 9.9	5.4 ± 1.8	13.9 ± 4.5	8.2 ± 1.7	0.43 ± 0.14	117.1 ± 13.5	0.72 ± 1.08
	60	71.0 ± 8.4	5.6 ± 1.8	13.7 ± 3.6	7.8 ± 1.7	0.42 ± 0.11	115.8 ± 14.8	0.34 ± 1.02
	75	72.4 ± 8.2	5.5 ± 1.7	14.0 ± 3.2	7.8 ± 1.7	0.41 ± 0.09	118.8 ± 14.6	0.61 ± 0.66

The values are the mean ± s.e.mean of 7 determinations.

was infused into prazosin-treated dogs, the decrease in $(A-V)O_2$ and the increases in blood pressure and blood flow observed during nicotine infusion in the untreated and β-blocked animals were abolished (Table 2). Moreover in the recovery period, $(A-V)O_2$ did not rise above control levels. This was in contrast to the increases in $(A-V)O_2$ in the untreated and β-blocked animals. Also, blood pressure, blood flow, vascular resistance and oxygen consumption remained stable in the post infusion period.

The large increases in arterial and venous glucose levels seen during and after nicotine infusion in Group I and Group II dogs were abolished in the prazosin-treated animals. Although glucose uptake exhibited considerable variability in this group, the difference in glucose uptake, before, during and after nicotine was not significant.

Discussion

In this study we used different dogs to study the effects of nicotine before and after the administration of adrenoceptor blockers. This was because of the pharmacological action of nicotine which first stimulates autonomic ganglia, then blocks them. Since many of the effects of nicotine are mediated via its ganglion stimulating action, varying degrees of ganglion blockade arising from the first infusion would confuse the results of a second. Moreover $(A-V)O_2$ remained significantly elevated for several hours after the first infusion of nicotine in the untreated dog. It was, therefore, not possible to use the same dog to study the effects of adrenoceptor blocking agents on $(A-V)O_2$ in a second infusion.

The systemic hypertensive effect of nicotine in the present study is consistent with earlier observations in dogs (Papacostas & Reed, 1966; Mandel *et al.*, 1973; Downey *et al.*, 1977; 1980; 1981). The effect of propranolol in this study is also similar to some earlier reports (Papacostas & Reed, 1966; Sutton & Isaac, 1973; Downey *et al.*, 1977; 1980), but does not agree with the findings of Mandel *et al.*, (1973). The latter reported a 'blunting' of nicotine-induced hypertension by treatment of conscious dogs with propranolol. Our dogs were not conscious and we cannot be sure how the results might have been affected by anaesthesia. The hypertensive effect is clearly not due to gastrointestinal vasoconstriction since the initial local response to nicotine at the time the hypertensive effect was maximum was nil. Later there was some increase in vascular resistance in the gastrointestinal tract indicating vasoconstriction – probably compensatory. The effect of β-blockade, which had no effect in itself, was to convert the nicotine action into a vasodilator effect. It should be noted, moreover, that after α-adrenoceptor blockade, this vasodilator effect was abolished. These findings seem to indicate that β-mediated mechanisms are implicated in vasoconstrictor activity and that α-mechanisms are implicated in vasodilator activity. The results are hard to interpret.

The reduced arterio-venous oxygen difference during the first 5 min of nicotine infusion, in the untreated and β-blocked animals, can probably be explained mainly on the basis of increased blood flow during this period. The significant increase which occurred in oxygen extraction post-infusion (especially before β-blockade) may be explained on the basis of the combined effects of a reduction (though not significant) in blood flow which allowed more time for extraction and the ability of the nicotine to decrease 2,3 diphosphoglycerate in red blood cells (Oski *et al.*, 1972) thereby causing a shift in the oxyhaemoglobin dissociation curve to the right. In spite of the significant increases in oxygen extraction before β-blockade, oxygen consumption was not increased during or after nicotine infusion. Since oxygen extraction rose, this has to be due to the fall in blood flow that occurred. β-Blockade raised oxygen consumption slightly. After β-blockade, nicotine seemed to cause a further slight rise in consumption. There was a slight, post-infusion rise. The small effect of β-blockade in the bowel may indicate some β-mediated activity in reducing oxygen consumption.

The increased jejunal blood flow during nicotine infusion in the untreated dogs observed in this study contrasts with the results of Downey *et al.* (1980) who first reported no significant change, then in later work the same workers (Downey *et al.*, 1981) showed an actual fall in blood flow to the duodenum during nicotine infusion. Using the radioactive microsphere technique, Downey *et al.* (1980; 1981) measured blood flow to splanchnic organs including the duodenum. They found that nicotine caused a significant decrease in duodenal blood flow in propranolol-treated dogs. In contrast, in our experiments, nicotine caused an even greater increase in jejunal blood flow in propranolol-treated dogs compared with the untreated dogs. Gallavan *et al.* (1984) reported transient increases followed by a net decline in arterial pressure and mesenteric blood flow, results similar to the present findings.

In our studies we found that treatment with α-adrenoceptor blocking agents (phenoxybenzamine or prazosin) prevented the rise in blood flow previously caused by nicotine. This, again, is in contrast to the findings of Downey *et al.* (1981) who observed that after selective α-adrenoceptor blockade with phenoxybenzamine, nicotine caused a marked increase in duodenal blood flow. Downey and his co-workers made their observations at the peak of the hypertensive response; it is of interest to observe that our maximum flow increments also occurred at the peak of the hypertensive effect. We have no explanation for these discrepancies. It may be that the duodenum is functionally different from the jejunum. However, we

should note that duodenal and jejunal blood flows are comparable (Delaney & Custer, 1965). Our own work also indicates that resting heat production is similar in the two regions (Durotoye & Grayson, 1971). However, these observations may not be relevant.

The hyperglycaemic effect of nicotine found in this study is consistent with the findings of earlier workers in other species (Larson *et al.*, 1961; Tsujimoto *et al.*, 1965). The mechanism of nicotine-induced hyperglycaemia is well-documented (Tsujimoto *et al.*, 1965; Milton, 1966). Essentially it involves stimulation of the sympathetic ganglion and release of adrenaline from the adrenal medulla by nicotine.

When the large changes in $(A-V)O_2$, blood flow and blood glucose levels which occur in the first half of a nicotine infusion are examined in relation to one another, the following points emerge. In the first 5 min of the infusion, while $(A-V)O_2$ decreased sharply, there were also sharp increases in the arterial and venous blood glucose levels and also in blood flow. When these changes were expressed as oxygen consumption and glucose upake it will be seen that whilst glucose uptake had increased by as much as nearly 400% and 700% in the β-blocked and untreated animals, the increase in oxygen consumption in the β-blocked animal was only 50%. In the untreated animals the oxygen consumption had returned to resting levels by the 10th min of infusion; glucose uptake was actually negative by the 10th min of infusion and remained so at 15 min and 20 min post infusion. Gallavan *et al.* (1984) reported smaller increments in oxygen uptake caused by nicotine.

Thus glucose uptake did not match oxygen consumption either in magnitude or direction. This is similar to our earlier findings concerning the effects of catecholamines. Adrenaline, too, caused increase in glucose uptake and oxygen consumption, in the bowel but there was no temporal or quantitative relation between the two, (Grayson & Oyebola, 1983). Indeed, we feel that there may well be a direct link between those observations and the present findings.

The effects of prazosin on blood pressure in the present study is in agreement with earlier findings (Oates *et al.*, 1976) and with the findings of Downey *et al.* (1981) who showed that α-adrenoceptor blockade prevented the hypertensive response to nicotine.

The abolition of the large hyperglycaemic response to nicotine infusion by prazosin was a matter of great interest. Although studies in normal hypertensive patients receiving prazosin have not revealed abnormalities in carbohydrate metabolism (Thulin *et al.*, 1974; Pitts, 1974; Wibell *et al.*, 1980), there is evidence which indicates that hepatic glycogenesis is mediated by α-adrenoceptors (Sherline *et al.*, 1972; Hutson *et al.*, 1976; Blair *et al.*, 1979). Thus, Sherline *et al.* (1972), using the isolated perfused liver, showed that adrenaline, noradrenaline and isoprenaline caused activation of glycogen phosphorylation and increased hepatic glucose output. The effects of all these agents were blocked by the α-blocker, phentolamine, whereas propranolol inhibited only the effects of noradrenaline. Hutson *et al.* (1976) using rat isolated liver cells also showed that adrenaline-induced glycogenolysis and gluconeogenesis were blocked by phentolamine and phenoxybenzamine but not β-blocking agents including propranolol. Blair *et al.* (1979) reported that glycogenolysis from hepatocytes of mature rats was blocked by phenoxybenzamine, but not by propranolol. These authors concluded that the effects of adrenaline on carbohydrate metabolism in the rat liver parenchymal cells are mediated predominantly by α-adrenoceptors.

These observations probably relate to our own findings with respect to the effect of catecholamines on glucose uptake. In a previous paper, we showed that adrenaline and noradrenaline produce a six fold increase in glucose uptake. We have also observed that β-blockers alone had a marked effect on glucose uptake (Grayson & Oyebola, 1983). In that work we proposed a hypothesis to explain the marked effect of catecholamines on glucose uptake. This was that the primary event was a catecholamine action on the liver such as to raise blood glucose levels greatly. It was proposed that the bowel action was primarily compensatory, a non-oxidative uptake of glucose having the effect of modulating the high arterial blood levels (Grayson & Oyebola, 1983) induced by a primary hepatic response. We proposed that the action involved α- and β-receptor interaction. Thus, β-blockers had a tonic effect in lowering glucose uptake, whereas α-receptors had the opposite effect.

It is worth noting in the general context of glucose homeostasis that glucose uptake by the bowel can occasionally be negative, that is to say the bowel actively releases glucose into the blood stream, presumably to correct a hypoglycaemia. This action was not seen after β-blockade, neither was hypoglycaemia. Similar observations were made in the present work which is a further link between the two sets of observations.

It has been shown that the glycaemic effects of nicotine are mediated by the release of adrenaline from the adrenal medulla. Our results in the prazosin-treated group strongly suggest that the effects of nicotine on blood glucose, blood pressure, blood flow, $(A-V)O_2$ and oxygen consumption are predominantly α-mediated. Since the present results with nicotine are thus essentially similar to our earlier findings with adrenaline, it seems reasonable to propose that in the present experiments, too, the effects of nicotine on blood glucose are secondary to its action on the adrenal gland. The present findings are consistent with the hypothesis that nicotine has its action on bowel glucose uptake or release through its well-established action in releasing catecholamines and in activating α-receptors.

References

BLAIR, J.B., JAMES, M.E. & FOSTER, J.L. (1979). Adrenergic Control of Glucose output and adrenosine 3'5' monophosphate levels in hepatocytes from juvenile and adult rats. *J. biol. Chem.*, **254,** 7579–7584.

DELANEY, J.P. & CUSTER, J. (1965). Gastrointestinal blood flow in the dog. *Circulation Res.*, **17,** 394–402.

DOWNEY, H.F., BASHOUR, C.A., BOUTROS, I.S., BASHOUR, F.A. & PARKER, P.E. (1977). Regional mycardial blood flow during nicotine infusion: effects of beta adrenergic blockade and acute coronary arterial occlusion. *J. Pharmac. exp. Ther.*, **202,** 55–68.

DOWNEY, H.F., CRYSTAL, G.J. & BASHOUR, F.A. (1980). Regional, renal and splanchnic blood flows during nicotine infusion; effects of beta adrenergic blockade. *J. Pharmac. exp. Ther.*, **216,** 363–367.

DOWNEY, H.F., CRYSTAL, G.J. & BASHOUR, F.A. (1981). Regional, renal and splanchnic blood flows during nicotine infusion: effects of combined alpha and beta adrenergic blockade. *J. Pharmac. exp. Ther.*, **220,** 375–381.

DUROTOYE, A.O. & GRAYSON, J. (1971). Heat production in the gastrointestinal tract of the dog. *J. Physiol.*, **214,** 417–426.

EULER, U.S. VON. (1965). Ed. *Tobacco Alkaloids and Related Compounds.* London, New York, Paris: Pergamon Press.

GALLAVAN, R.H., TSUCHIYA, Y. & JACOBSON, E.D. (1984). Effects of nioctine on canine intestinal blood flow and oxygen consumption. *Am. J. Physiol.*, **246, G195–G202.**

GRAHAM, R.M., OATES, H.F., STOKER, L.M. & STOKES, G.S. (1977). Alpha Blocking Action of the Antihypertensive Agent, Prazosin. *J. Pharmac. exp. Ther.*, **201,** 747–752.

GRAYSON, J. & OYEBOLA, D.D.O. (1983). The effect of catecholamines on intestinal glucose and oxygen uptake in the dog. *J. Physiol. (Lond.)*, **343,** 311–322.

HUTSON, N.J., BRUMLEY, F.T., ASSIMACOPOULOS, F.D., HARPERS, C. & EXTON, J.H. (1976). Studies on alpha adrenergic activation of hepatic glucose output. *J. biol. Chem.*, **251,** 5200–5208.

LARSON, P.S. HAAG, H.B. & SILVETTE, H. (1961). *Tobacco: Experimental and Clinical Studies.* pp. 324–332. Baltimore: William & Wilkins.

LARSON, P.S. & SILVETTE, H. (1965). Medical uses of tobacco (past and present). In *Tobacco Alkaloids and Related Compounds.* ed. Euler, U.S. von. pp. 3–13. London, New York: Pergamon Press.

MANDEL, W.J., LAKS, M., HAYAKAWA, J., OBAYASHI, K. & McCULLEN, A. (1973). Cardiovascular effects of nicotine in the conscious dog. *Am. J. Cardiol.*, **32,** 947–955.

MILTON, A.S. (1966). The effect of nicotine on blood glucose levels and plasma non-esterified fatty acid levels in the intact and adrenalectomized cat. *Br. J. Pharmac.*, **26,** 256–263.

OATES, H.F., GRAHAM, R.M., STOKER, L.M. & STOKES, G.S. (1976). Haemodynamic Effects of prazosin. *Archs Int. Pharmacodyn.*, **224,** 239–247.

OYEBOLA, D.D.O. & ELEGBE, R.A. (1975). Cow's urine poisoning in Nigeria. Experimental observations in mice. *Trop. Geogr. Med.*, **27,** 194–202.

OSKI, F.A., DELIVORIA-PAPADOPOULOS, M., MANCHESTER, J.H. & SHELBURNE, J.C. (1972). Oxygen affinity in red cells: changes induced in vivo by propranolol. *Science*, **175,** 1372–1373.

PAPACOSTAS, C.A. & REED, J.P. (1966). Influence of beta receptor blockade on certain cardiovascular actions of nicotine. *Archs Int. Pharmacodyn.*, **164,** 167–172.

PITTS, N.E. (1974). The clinical evaluation of parzosine hydrochloride, a new antihypertensive agent. *Excerpta Medica Int. Cong. Ser. No. 17.*, **331,** 149–163.

SHERLINE, P., LYNCH, A. & GLINSMANN, W.H. (1972). Cyclic AMP and adrenergic receptor control of rat liver glycogen metabolism. *Endocrinology*, **91,** 680–690.

SNEDECOR, G.W. & COCHRAN, W.G. (1967). In *Statistical Methods.* 6th Edition. Ames, Iowa, U.S.A.: The Iowa State University Press.

SUTTON, I. & ISAAC, P.E. (1973). The cardiovascular actions of nicotine in the rat. *Archs Int. Pharmacodyn.*, **202,** 5–16.

THULIN, T., SAETRE, H., VICKESDAHL, O., WARMENIUS, S., PERSSON, G. & SHERSTON, B. (1974). Multicentre study of the antihypertensive effect of prazosin hydrochloride on mild and moderate hypertension. *Excerpta Medica Int. Congr. Ser. No.* **331,** 126–137.

TSUJIMOTO, A., TANIMO, S. & KUROGOCHI, Y. (1965). Effect of nicotine on serum potassium and blood glucose. *Jap. J. Pharmac.*, **15,** 415–422.

WIBELL, L., BERNE, C., WAERN, A.U. & LITHELL, H. (1980). Prazosin influence on carbohydrate and lipoprotein metabolism. *R. Soc. Med. Int. Congr. Symp. Ser. No.* **41,** 85–89.

WYNDER, E.L. & HOFFMANN, D. (1967). *Tobacco and Tobacco Smoke: Studies in Experimental Carcinogenesis.* New York, London: Academic Press Inc.

WYNDER, E.L. & HOFFMANN, D. (1968). (ed). Towards a Less Harmful Cigarette. *U.S. National Cancer Institute Monograph,* 28.

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