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Effect of adrenaline on glucose uptake in the rabbit small intestine.

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Summary

Objectives: Previous study had shown that nicotine acts on blood glucose through release of adrenaline. While there are reports on the hyperglyceic effect of adrenaline in rabbits, there is no information on the effect of adrenaline on intestinal glucose uptake of rabbits. The present study was carried out to find out if adrenaline has any effect on glucose uptake in the rabbit small intestine.

Materials and Methods: Experiments were carried out on fasted anaesthetized male rabbits. Five groups of rabbits (6 rabbits per group) were studied. A vein draining a segment of the upper jejunum was cannulated for blood flow and venous glucose measurements. The left femoral artery and vein were cannulated for arterial blood sampling and drug infusion respectively. Glucose uptake was calculated as a product of jejunal blood flow and the glucose difference between arterial (A) and venous (V) blood.

Results: The fasting venous blood glucose levels were 151.8±4.4mg/dl and 164.0 ± 2.3mg/dl in Groups I and V that were not given adrenoceptor blockers. The upper jejunum had a resting (or basal) glucose uptake of 38.3 ± 1.6mg/min in the control group. When adrenaline (2ug/kg) was injected intravenously, arterial blood glucose rose from a basal value of 245.5±4.6mg/dl to 307.5±4.7mg/dl at the peak of response while venous glucose rose from 151.8±4.4mg/dl to 275.8±4.2mg/dl at the peak of response. Glucose uptake increased to 107.4±2.5mg/min at the peak of response. The hyperglycaemic response to adrenaline injection was abolished by propranolol but not by prazosin indicating that this effect of adrenaline is mediated through beta adrenoceptor. Both prazosin and propranolol reduced considerably adrenaline-induced increase in blood flow and glucose uptake, prazosin being more potent in flow reduction.

Conclusion: This study showed that the resting small intestine of rabbits took up large amounts of glucose. The intestinal glucose uptake was markedly increased by adrenaline injection. The response to adrenaline was mediated through alpha and beta adrenoceptors. The responses to adrenaline are different in many respects from those induced by nicotine in rabbits in our earlier study. The reason for the differences is obscure.

Keywords: *Adrenaline, rabbit, intestine, glucose uptake, beta-blocker, alpha-blocker*

Résumé

Les expériences étaient évaluées sur les lapins males à jeune anesthésiés classés en cinq groupes de six lapins. L'artère et la veine fémorale gauche étaient canulé par prendre un échantillon du sang artériel/veineux et l'infusion du médicament respectivement. L'absorption du glucose était calculée comme produit de l'écoulement du sang jéjunal et la différence entre le sang artériel (A) et veineux (V). Les taux du glucose veineux sanguin à jeune etaient de 151.8+4.4mg/dl et 164.0 + 2.3mg/dl en groupe I et V qui ne recevaient pas des bloqueurs d'adrenocepteurs. Le jéjunum supérieur avait un taux d'absorption au repos de 38.3 ± 1.6mg/min chez le groupe de contrôle. Lorsque l'adrénaline (2ug/kg) était injectée par voie intraveineuse, le taux du glucose artériel augmentait de la valeur de base de 245.5±4.6mg/dl à 307.5±4.7mg/dl à la réponse maximale tandis que le glucose veineux augmentait de 151.8±4.4mg/dl à 275.8±4.2mg/dl à la réponse maximal. L'absorption du glucose augmentait de 107.4±2.5mg/min à la réponse maximale. La réponse d'hyperglycémique à l'injection de adrénaline était abolit par le propranolol mais pas par la prazosine indiquant que cet effet de l'adrénaline est medié par les adrenorecepteurs beta. La prazosine et le propranolol réduisaient considérablement augmentation induit par l'adrénaline dans l'écoulement du sang et l'absorption du glucose, prazosine étant plus puissant dans la réduction de l'écoulement. Cette étude démontrait qu'au niveau des intestines greles des lapins au repos

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s'effectuent une large absorption du glucose. La réabsorption du glucose intestinal était augmentée par l'injection de l'adrénaline. La réponse de l'adrénaline était medié par les adrenorecepteurs alpha et beta. Les réponses à l'adrénaline sont différentes dans plusieurs respects de ceux induits par la nicotine aux lapins dans nos études antérieures. La raison de ces différences est obscure.

Introduction

Previous studies in dogs have shown that the post-absorptive gut is capable of taking up large quantities of glucose [1- 8]. A recent study also showed that there is uptake of glucose, similar to that reported in dogs, in the small intestine of rabbits [9]. In the rabbit, nicotine caused a marked increase in glucose uptake by the small intestine. This response was however abolished when the rabbits were pretreated with an alpha adrenoceptor blocker, prazosin and almost totally abolished by pretreatment with a beta adrenoceptor blocker, propranolol. It was therefore concluded in that study [9] that the effect of nicotine on glucose uptake in the gut of rabbits was mediated through the release of adrenaline from the adrenal glands. Adrenaline has been reported to cause large increases in glucose uptake in the canine jejunum [2], terminal ileum [4] and large intestine [10].

Although Tsujimoto and his coworkers [11] provided unassailable evidence that nicotine indeed mediates its hyperglycaemic effect in cats by causing release of adrenaline from the adrenal glands, this cannot be accepted as foolproof evidence that the effect of nicotine on blood glucose changes in the rabbit is entirely due to adrenaline release. Therefore, apart from the possibility of species differences, the following questions arise: (i) does adrenaline have an effect on glucose uptake in the rabbit small intestine? (ii) Is the effect of adrenaline the same as that of nicotine on blood glucose and glucose uptake in the rabbit small intestine? While there are reports on the hyperglycaemic effect of adrenaline in rabbits [12,13,14], there is no report in the literature, as far as we know, on the effect of adrenaline on glucose uptake in the intestine of rabbits.

The present study was carried out to find out if adrenaline has any effect on glucose uptake in the rabbit small intestine. The study also aims at finding out if the effect (if any) is the same as those of nicotine in rabbits reported earlier from our laboratory [9]. The receptor(s) that mediate the effect of adrenaline on glucose uptake in the rabbit intestine (if any) will also be investigated.

Materials and methods

The design and the materials and methods of this experiment are similar to those in our recent study on the effect of nicotine on glucose uptake in the rabbit small intestine [9]. In the present study, however, instead of nicotine, adrenaline is used. The experimental design and the materials and methods which have been described in detail earlier [9] will be summarized here in relation to the present study.

Thirty-two male white rabbits, weighing 1.6–2.5kg and aged 9-10 months were used for the experiments. The rabbits were divided into five groups of six rabbits per group. Each animal was fasted for 18-24 hours before the start of an experiment but was allowed free access to drinking water. Anaesthesia was induced with sodium thiopentone, 30 mg/kg given intraperitoneally (ip). Light anaesthesia was maintained with supplementary doses of ip sodium thiopentone. Each animal was surgically prepared as earlier described [9] for measurement of jejunal blood flow, arterial and venous blood sampling for glucose estimation and an intravenous (iv) route for injections. The left femoral artery and vein were secured and cannulated for collection of arterial blood samples and intravenous injections respectively.

Through a midline laparotomy, the jejunum was identified, secured and a vein draining the proximal segment of the jejunum was cannulated using polyethylene tubing. The jejunal vein cannula was moved into an extracorporeal position and a non-crushing clamp was applied to its free end. Sodium heparin, 300 iu/kg was administered intravenously to prevent blood clotting. The abdomen was closed in two layers with interrupted sutures. Following surgery, a period of about 1h was allowed for stabilization. Jejunal blood flow was measured by timed collection using a modified 1cc or 2cc syringe for collecting the blood flowing out of the jejunal venous cannula as earlier described [9]. After the flow has been recorded, the blood collected was taken up with a needle and syringe and returned slowly into the animal through the cannula placed in the femoral vein.

Blood glucose was determined with ONE TOUCH BASIC – plus glucometer (Life Scan data file 2000). The meter was checked against the glucose standard solution at regular intervals to ensure accuracy. Previous studies have shown that the values of blood glucose obtained using a glucometer correlate excellently with those from the use of standard biochemical methods [15, 16]. In this study, one large drop of blood (about 5 microlitres), was enough for

blood glucose measurement. For the jejunal venous sample, this drop of blood was obtained directly from the jejunal cannula as soon as the flow measurement by timed collection was completed. The sample for measurement of arterial blood glucose level was obtained from the cannula in the femoral artery in the same way as in the venous cannula. Care was taken to avoid blood loss since arterial blood is under high pressure.

Experimental procedure

The groups were treated as shown in the protocol in Table 1. Only two rabbits were used in what would have been the sixth group on which further work was discontinued for the reason stated below under adrenaline, 4ug/kg.

Table 1: Treatment given to rabbits in groups I to V

Group	Treatment given
I	Adrenaline injection, 2μg/kg
II	Prazosin, 0.2mg/kg + Adrenaline, 2ì g/kg
III	Propranolol, 0.5mg/kg + Adrenaline 2ì g/kg
IV	Prazosin (0.2mg/kg) + Propranolol (0.5mg/kg) + Adrenaline 2ì g/kg
V	Normal saline, 0.2ml/kg

Adrenaline injection (Group I)

After the 1h stabilization following surgery, basal measurements of jejunal blood flow rate, arterial and venous glucose levels were first made. Then, a bolus injection of adrenaline, 2ug/kg, was given intravenously through the femoral vein cannula. Measurements of jejunal blood flow rates, arterial and venous blood glucose levels were repeated at 5, 10, 15, 30, 45, 60, 75 and 90 minutes respectively from the time of injection. Glucose uptake was calculated as the product of the blood flow and the arterio-venous glucose difference [2, 3, 5].

Adrenaline and prazosin (Group II)

Rabbits in this group were first injected (pretreated) with prazosin, 0.2mg/kg, given intravenously. Forty minutes were allowed for the drug to take effect. After basal measurements of blood flow, arterial and venous glucose levels, a bolus injection of adrenaline (2ug/kg) was given as in group I and all the measurements were repeated at the intervals indicated in Group I.

Adrenaline and propranolol (Group III)

The rabbits in this group were pretreated with propranolol, 0.5mg/kg given intravenously. Forty minutes were allowed for the drug to take effect. After basal measurements have been taken as in group I, a bolus injection of adrenaline (2ug/kg) was given intravenously as in group I and all the measurements were repeated at 5, 10, 15, 30, 45, 60, 75 and 90 minutes respectively as in group I.

Adrenaline and prazosin and propranolol (Group *IV*)

Rabbits in this group were pretreated with both prazosin (0.2mg/kg) and propranolol (0.5mg/kg). Forty minutes were allowed for the drugs to take effect. After all basal measurements have been made, adrenaline injection (2ug/kg) was given and all measurements were repeated as in group I.

Normal saline injection (Group V)

After basal measurements have been taken as in group I, 0.2ml/kg normal saline (0.9% saline) was given as a bolus injection, the same volume as the adrenaline injections. All measurements were repeated at 5, 10, 15, 30, 45, 60, 75 and 90 minutes respectively as in group I. Glucose uptake was calculated in this and all the other groups as in group I.

Table 2: Effect of adrenaline (2ug/kg) on arterial and venous glucose, (A-V) glucose, blood flow and glucose uptake (Group I).

Time (min)	0"	5"	10"	15"	30"	45"	60"	75"	90"
Arterial Glucose	245.5	283.0	307.5	283.4	264.6	234.0	231.0	224.7	217.7
(mg/dl)	±4.6	±4.8**	±4.7**	±4.9**	±4.7	±4.6	±4.4	±4.3	±4.7*
Venous Glucose	151.8	193.5	275.8	248.7	223.8	215.8	218.5	182.7	160.7
(mg/dl)	±4.4	±3.8*	±4.2**	±3.9**	±4.2*	±4.2*	±4.3*	±4.1	±4.0
(A-V) Glucose	94.7	89.5	31.7	34.7	40.8	18.2	12.5	42.0	57.0
(mg)	±2.9	±2.7	±2.1**	±3.0**	±1.8*	±1.6***	±1.1***	±1.7**	±2.1**
Blood flow	0.72	1.2	1.35	1.3	1.35	1.35	1.25	1.35	1.37
(ml/min)	±0.3	±0.3	±0.3*	±0.3*	±0.3*	±0.3*	±0.5	±0.5*	±0.3*
Glucose uptake	68.1	107.4	42.8	45.1	55.0	24.5	15.6	56.7	78.1
(mg/min)	±2.6	±2.5**	±2.3	±3.1	±1.9	±1.8**	±1.1**	±1.7	±1.5*

*(n=6; *p<0.05; **p<0.01; ***p<0.001); (A-V) Glucose is Arterial minus Venous glucose.*

Table 3: Effect of prazosin (0.2mg/kg) and adrenalin (2ug/kg) on arterial and venous glucose, blood flow, (A-V) glucose and glucose uptake (Group II)

Time (min)	0"	5"	10"	15"	30"	45"	60"	75"	90"
Arterial Glucose (mg/dl)	263.5 ±8.5	270.0 ±31.6	315.5 ±9.1**	346.0 ±8.1**	351.5 ±19.1*	393.2 ±29.3*	342.0 ±41.4	421.0 ±40.7*	386.2 ±23.7*
Venous Glucose (mg/dl)	226.5 ±25.02	207.2 ±25.8	216.5 ±8.4	249.5 ±32.2	282.7 ±31.7	313.7 ±35.8*	320.5 ±26.8*	375.0 ±23.3*	371.0 ±21.3*
Blood flow (ml/min)	0.28 ±0.02	0.28 ±0.01	0.26 ±0.02	0.21 ±0.02*	0.18 ±0.01**	0.16 ±0.01*	0.18 ±0.02*	0.16 ±0.02*	0.16 ±0.01*
(A-V) Glucose (mg)	37.0 ±17.2	62.8 ±21.8	99.0 ±9.7*	96.5 ±24.8*	68.8 ±38.5	79.5 ±12.4*	21.5 ±14.8	46.0 ±22.5	15.2 ±6.8
Glucose uptake (mg/min)	10.5 ±5.4	18.4 ±6.4	25.5 ±0.7*	22.1 ±6.7	14.4 ±8.1	13.0 ±2.4	4.9 ±3.8	8.2 ±4.1	2.6 ±1.3**

*(n=6; *p<0.05; **p<0.01)*

Injection of adrenaline, 4ug/kg

Two rabbits were given a higher dose of adrenaline, 4ug/kg and this caused immediate death of the rabbits. Use of more rabbits at this dose was therefore stopped. The mean ± S.E.M of all measurements were computed. Significance was assessed by the Student's t-test for two means of independent variables or a one way analysis of variance (ANOVA) as was appropriate. p values of 0.05 or less were taken as statistically significant.

Results

The results are shown in Tables 2 to 6. All values given are Mean ± S.E.M of the variables measured. The asterisks in the tables indicate the levels of significance of the variables measured compared with their basal (zero minute) values.

The effects of adrenaline on rabbits in group I are shown in Table 2. Adrenaline caused significant increase in arterial blood glucose level between 5min and 15 min post-injection. After this, arterial glucose level fell and it fell significantly below basal level at 90min. There was also a significant increase in venous glucose level above the basal value of 151.8 ± 4.4mg/dl from 5min to 60 minutes post-injection. Venous blood glucose has, however, returned to resting level at 90min post-injection. Adrenaline caused a decrease in glucose extraction (A-V glucose). Glucose extraction decreased significantly from 10min post-injection to the end of the 90min post-injection observation period. Adrenaline caused a significant increase in jejunal blood flow above the basal value of 0.72 ± 0.3ml/min from 10min to 90min post-injection. Adrenaline also caused a significant but biphasic increase in glucose uptake, at 5min and 90min post-injection. After the initial increased uptake at 5min, glucose uptake decreased significantly below basal value at 45min and 60min post-injection.

Table 3 shows the results of rabbits pre-treated with prazosin and then challenged with adrenaline.

Table 4: Effect of propranolol (0.5mg/kg) and adrenaline (2ug/kg) on arterial and venous glucose, blood flow, (A-V) glucose and glucose uptake (Group III)

Time (min)	0"	5"	10"	15"	30"	45"	60"	75"	90"
Arterial Glucose (mg/dl)	270.2 ±39.9	276.7 ±33.5	238.5 ±24.8	280.7 ±57.4	222.5 ±34.3	205.0 ±35.9	190.0 ±40.2	161.5 ±19.7*	151.2 ±17.1*
Venous Glucose (mg/dl)	236.7 ±127.6	246.0 ±107.1	223.2 ±106.6	256.5 ±99.9	215.0 ±95.2	196.0 ±91.6	150.0 ±90.4	122.7 ±89.1	116.5 ±89.1
Blood flow (ml/min)	0.63 ±0.1	0.72 ±0.1	0.99 ±0.1*	0.97 ±0.1**	0.92 ±0.1**	0.77 ±0.2	0.65 ±0.2	0.55 ±0.2	0.47 ±0.1*
(A-V) Glucose (mg)	33.5 ±19.4	30.7 ±18.02	15.3 ±5.1	24.2 ±6.6	7.5 ±3.2*	9.0 ±4.2	15.0 ±3.8	38.8 ±16.7	34.7 ±17.0
Glucose uptake (mg/min)	30.0 ±23.1	30.0 ±23.2	15.6 ±6.7	23.5 ±6.5	8.2 ±4.5	9.0 ±6.3	17.6 ±8.6	14.7 ±4.4	11.6 ±4.5

*(n=6; *p<0.05; **p<0.01)*

There was a significant increase in arterial blood glucose from a basal value of 263.5±8.5mg/dl at 10min post-injection and this persisted till the end of the 90min post-injection period. Similarly, venous glucose increased from the 226.5 ± 25.02mg/dl basal level and the increases were significant from 45min to 90min post-injection. Adrenaline caused a significant increase in glucose extraction (A – V glucose) at 10min, 15min and at 45min post-injection. Prazosin administration resulted is a marked decrease in basal jejunal blood flow. A comparison of the results in Table 3 with those in Table 6 (control group) shows the following differences. Basal blood flow decreased from 1.01 ± 01ml/min in the control group (Group V) to a mere 0.28 ± 0.02ml/min after prazosin injection. Adrenaline injection produced a further decrease in blood flow in this group with the decreases becoming significant from 30min to 90min post-injection (Table 3). Glucose uptake was reduced by prazosin administration from the basal value of 38.3 ± 1.6mg/min in the control group to a basal value of 10.5 ± 5.4 mg/min in this group. After adrenaline injection, glucose uptake increased from a basal value of10.5 ± 5.4mg/min to 25.5 ± 0.7mg/min at 10min post-injection. This increase was significant. Glucose uptake values in this group were however significantly lower than corresponding values in the control group and in group I in which no adrenoceptor blocker was administered. At 90min post-injection, glucose uptake was 2.6 ± 1.3mg/min and this was significantly lower than the control value for the group.

Table 5: Effect of prazosin (0.2ug/kg) and propranolol (0.5mg/kg) and adrenaline (2ug/kg) on arterial and venous glucose, blood flow, (A-V) glucose and glucose uptake (Group IV).

Time (min)	0"	5"	10"	15"	30"	45"	60"	75"	90"
Arterial Glucose (mg/dl)	279.0 ±47.9	268.5 ±48.3	249.5 ±41.6	254.5 ±51.8	231.5 ±53.4	191.0 ±12.8	179.5 ±8.3	148.0 ±12.2*	147.7 ±4.2*
Venous Glucose (mg/dl)	248.0 ±50.8	241.0 ±49.1	225.0 ±41.7	232.5 ±46.9	215.0 ±46.2	178.0 ±17.3	151.2 ±17.6*	102.0 ±19.3*	115.7 ±9.0*
Blood flow (ml/min)	0.83 ±0.2	0.92 ±0.1	1.05 ±0.1	1.1 ±0.1	0.97 ±0.1	0.8 ±0.1	0.7 ±0.2	0.61 ±0.1	0.62 ±0.1
(A-V) Glucose (mg)	31.0 ±3.0	27.5 ±3.3	24.5 ±2.2	24.5 ±4.5	16.5 ±8.9	13.0 ±6.0*	28.3 ±9.2	46.0 ±9.8	32.0 ±6.2
Glucose uptake (mg/min)	27.8 ±8.9	25.6 ±7.5	25.8 ±4.5	25.7 ±2.8	15.4 ±6.9	11.75 ±6.5*	205 ±6.1	28.5 ±9.1	17.8 ±2.7

*(n=6; *p<0.05)*

Table 4 shows that in rabbits pre-treated with propranolol, adrenaline injection failed to cause an increase in arterial blood glucose level. Arterial blood glucose level actually decreased progressively post – injection. At 75min, arterial glucose level has fallen to 161.5±19.7mg/dl which is significantly lower than the 270.2±39.9mg/dl basal value in this group. The

Table 6: Effect of normal saline (0.2ml/kg) on arterial and venous glucose, blood flow, (A-V) glucose and glucose uptake (Group V)

Time (min)	0"	5"	10"	15"	30"	45"	60"	75"	90"
Arterial Glucose (mg/dl)	201.0 ±1.2	206.8 ±3.4	203.5 ±1.5	202.3 ±0.8	199.0 ±1.5	197.5 ±2.9	196.5 ±3.5	191.5 ±4.6	192.0 ±4.9
Venous Glucose (mg/dl)	164.0 ±2.3	171.0 ±0.5	172.2 ±1.6	170.8 ±2.4	165.5 ±2.5	164.2 ±4.1	158.0 ±2.5	160.2 ±4.2	161.0 ±3.3
Blood flow (ml/min)	1.01 ±0.1	0.95 ±0.08	0.90 ±0.1	0.92 ±0.1	1.04 ±0.09	1.02 ±0.1	1.05 ±0.08	1.25 ±0.12	1.15 ±0.09
(A-V) Glucose (mg)	38.0 ±1.6	35.8 ±0.6	31.3 ±3.1	31.5 ±3.7	33.5 ±4.7	33.3 ±3.6	38.5 ±3.5	31.3 ±4.7	31.0 ±2.6
Glucose Uptake (mg/min)	38.3 ±1.6	33.9 ±2.5	28.1 ±2.8	28.9 ±3.8	34.8 ±2.6	33.6 ±4.4	40.4 ±4.6	39.0 ±5.9	35.6 ±5.4

(n=6)

venous glucose levels showed a similar pattern to the arterial glucose levels; that is, there was no increase in venous glucose level but a progressive decrease after the injection of adrenaline. Basal blood flow in this group was reduced to 0.63 ± 0.1ml/min by propranolol administration when flow is compared with the control group value of 1.01 ± 0.1ml/min (Table 6) but the decrease was not as severe as in group III rabbits pre-treated with prazosin (Table 3). After adrenaline injection, blood flow increased significantly from 10min to 30min post-injection. Thereafter, blood flow decreased to basal level. Glucose extraction (A-V glucose) which was 33.5±19.4mg decreased after adrenaline injection and the decrease was significant at 30min post-injection. Adrenaline injection did not result in any significant change in glucose uptake in the propranolol- treated rabbits.

Table 5 shows the results of rabbits given a combination of prazosin and propranolol before adrenaline injection. The pattern of the glycaemic response was similar to that of propranolol and adrenaline in Table 4, that is, a decrease in blood glucose levels following adrenaline injection. There was no significant change in blood flow but the decreases in (A-V) glucose and glucose uptake from basal values of 31.0±3.0mg and 27.8±8.9mg/min respectively to 13.0 ± 6.0mg and 11.8 ± 6.5mg/min respectively at 45min post-injection were significant.

Normal saline injection had no effect on blood glucose levels, (A – V) glucose, blood flow and glucose uptake (Table 6). When a higher dose of adrenaline (4ug/kg) was administered, the two rabbits given this dose died post-injection thereby making post-injection observation impossible.

Discussion

This study showed, like our recent study [9], that a substantial amount of glucose is extracted from the arterial blood by the rabbit small intestine as blood passes through the tissues of the intestine. Basal glucose extraction (A-V glucose) in the control group was as high as 38.0 ±1.6mg. When glucose uptake was computed, it was quite substantial, with a value of 38.3 ± 1.6mg/min in the control (0.9% saline) group. This confirms our earlier finding [9] that the bowel of the rabbit also takes up large quantities of glucose similar to what had been reported in dogs [2-8].

The rise in blood glucose following adrenaline injection is consistent with its known pharmacological effect on blood glucose. Since 0.9% saline injection had no effect on blood glucose, the hyperglycaemic effect of adrenaline could not be ascribed to the stress of the injections. In any case, the animals were fully anaesthetized and were unlikely to be stressed by injection of the very small volumes of normal saline or the drugs used. This result is similar to the hyperglycaemia reported following adrenaline injection in rabbits by earlier workers [12,13]. The significant increase in glucose uptake following adrenaline injection in this study is similar to the increase in glucose uptake caused by nicotine in rabbits [9] and by adrenaline in dogs [2,4]. There are, however, marked differences in the glycaemic effects of adrenaline in rabbits in the present experiments and those caused by nicotine in rabbits [9].

In the nicotine study, the increases in arterial and venous blood glucose levels were marked, progressive and lasted throughout the 90 minutes post-injection observation period. In the present study, arterial glucose rose only between 5min and 30minutes with its peak at 10min after which it returned to basal levels. Although the rise in venous glucose levels lasted longer than those of the arterial levels, the increase in venous glucose also peaked at 10 minutes post-injection. After this, venous glucose level started falling gradually so that at 90 minutes post-injection, venous blood glucose level had returned to basal values. This is in contrast to the nicotine experiments in which venous glucose level was still rising even at 90min post-injection.

Another notable difference between the present study and the nicotine experiment is that while pre-treatment with prazosin totally abolished the hyperglucaemic response to nicotine in both arterial and venous blood, in the present study, pretreatment with prazosin followed by adrenaline injection resulted in marked and sustained increases in both arterial and venous blood glucose levels throughout the 90 minutes of post-injection observation. This result is similar to the findings in rats in which prazosin potentiated adrenaline-induced hyperglycaemia [17] but contrasts with the nicotine experiments in which both arterial and venous blood glucose levels fell significantly below basal levels when nicotine was administered after pretreatment with prazosin. This result was a big surprise and we have no explanation for this difference. This result suggests however that the mechanism of nicotine-induced hyperglycaemia in rabbits is different from that of adrenaline-induced hyperglycaemia. While the hyperglycaemic effect of nicotine is mediated mainly through alpha receptors that of adrenaline seems to be mediated mainly through beta receptors. The present findings also contrast with those of Moratinos *et al* [18] who reported that phenoxybenzamine, an alpha adrenoceptor blocker, attenuated the blood

glucose elevation observed when adrenaline was infused into conscious fasted rabbits.

When rabbits were pretreated with propranolol, in the nicotine experiments, the rise in arterial and venous blood glucose levels was almost abolished. Blood glucose did not however fall below basal values. In the adrenaline experiments, not only did pretreatment with propranolol abolish the hyperglycaemic response to adrenaline, blood glucose levels actually fell significantly below resting levels post-injection. This result confirms our earlier suggestion that adrenaline-induced hyperglycaemia in rabbits is medicated mainly through beta adrenoceptors. This result is similar to the effect of propranolol on adrenaline-induced hyperglycaemia in dogs [4]. Again, the findings in the present study contrasts with those of Moratinos *et al* [18,19] and Potter *et al* [20] in conscious rabbits. These workers showed that propranolol failed to antagonize the increase in blood glucose elicited by adrenaline and noradrenaline. Interestingly, in another study, yohimbine, but not prazosin attenuated the hyperglycaemic effect of adrenaline in a dose-related manner [13].

There are many but conflicting reports concerning the type of adrenoceptor mediating the hyperglycaemic response to adrenaline [21]. It has been observed that catecholamine - induced hyperlycaemia should be considered as a complex integrated response including increased liver and muscle glycogenolysis, increased gluconeogenesis, decreased peripheral glucose utilization, inhibition of insulin and stimulation of glucagon secretion [18]. All these components should therefore be kept in mind when analysing the nature of adrenoceptors involved in the hyperglycaemic effects of catecholamines. Apart from the now well-established species variation in the adrenoceptors mediating cathecholamine-induced hyperglycaemia [21], it is becoming increasingly clear that different alpha- and beta-adrenoceptor subtypes play different roles in this response [17,22]. The nutritional state of the animal also plays an important role in glycaemic response [12]. For example, isoprenaline is hyperglycaemic in fasted but not in fed rats [23]. The relative contribution of each of these components may differ in different species and under different nutritional conditions [24] thus accounting, at least partly, for the conflicting reports.

The increase in jejunal blood flow caused by adrenaline injection (Group I) was abolished by prazosin. Indeed, prazosin caused a highly significant reduction in basal jejunal blood flow when flow in this group (Group II) is compared with basal flow in the control group (Group V). The fact that injection of adrenaline after prazosin resulted in further decrease in blood flow suggests that the increased blood flow due to adrenaline is medicated largely through alpha receptors. Although pretreatment with propranolol also resulted in a decrease in blood flow, the decrease was not as profound as in group II pretreated with prazosin. This suggests that alpha receptors play a dominant role in the control of blood flow in the rabbit jejunum. The increase in small intestinal blood flow caused by adrenaline in this study is similar to the increase in blood flow caused by nicotine in the rabbit intestine [9]. The effects of adrenoceptor blockers followed by administration of agonists on blood flow in the two studies are however, different. While blood flow in propranolol treated rabbits fell significantly below basal values following administration of nicotine [9], it was in the prazosin-pretreated group in the present study that blood flow fell below basal values following adrenaline injection. In the nicotine study [9], blood flow increased significantly from 10min to 90min following nicotine injection in prazosin treated rabbits whereas, the reverse occurred in the present study. The reasons for these differences are not clear.

With respect to glucose uptake, the effect of adrenaline injection in this study is similar to its effect in dogs [2, 4]. It is interesting to note that glucose uptake values in all pretreated rabbits were far below the basal values in animals not given adrenoceptor blockers (Groups I and V). Again, glucose uptake after adrenaline injection in the present study is different from that induced by nicotine. In the nicotine experiment, glucose uptake was above basal level throughout the 90min post-infusion period and the values were significantly higher than basal values at 10, 30 and 60 minutes whereas, only a transient significant increase at 5min post-injection occurred in the present study. The effect of prazosin or propranolol in attenuating glucose uptake in the present experiment is however similar to the results in the nicotine study [9].

Previous studies in dogs [2,10], cats [25] and rats [26] showed that the hyperglycaemia induced by nicotine is mainly due to adrenaline released from the adrenal medulla. The fact that both alpha and beta adrenoceptor blockers modified the effects of nicotine and adrenaline on blood glucose level, blood flow and glucose uptake in the rabbit small intestine lend support to this assertion. Nonetheless, the big differences in the effects of adrenaline and nicotine on glucose kinetics as highlighted above suggest that adrenaline alone does not account for all the effects

of nicotine. There seems to be more to nicotine action than just the release of adrenaline. Additional mechanisms are most probably involved. In this respect, it should be noted that nicotine is a well-known potent stimulant of the sympatho-adrenal system. Thus, apart from causing adrenaline release from the adrenal medulla, it stimulates the sympathetic ganglia leading to marked increase in sympathetic nerve activity. Studies have shown that increased activity of the sympathetic nerves supplying the pancreas causes inhibition of insulin secretion [27]. This results in an increase in nicotine-induced hyperglycaemia. Thus, adrenaline release and sympathetic nerve-induced inhibition of insulin release act synergistically leading to a more profound nicotine-induced hyperglycaemia. Previous studies have shown that the higher the blood glucose level, the greater is the glucose uptake in the gut [8].

The recent study of Battram *et al* [28] also seems to lend support to the suggestion that adrenaline alone does not account for all the effects of nicotine. In their study, Battram and her colleagues assessed the influence of adrenaline on the effect of caffeine on glucose kinetics in humans. The study aimed at finding out whether adrenaline can account for all of the effects of caffeine. In a very elegant study, they measured the plasma concentration of adrenaline caused by ingestion of caffeine, the rate of endogenous glucose production and whole-body glucose uptake rates among other metabolic indices. They followed with an infusion of adrenaline at a rate that produced a plasma concentration of adrenaline equal to that caused by ingestion of caffeine and repeated all the measurements of metabolic indices. They found that caffeine and infusion of adrenaline at a plasma concentration similar to that caused by caffeine ingestion resulted in different effects on glucose kinetics. From the results, they concluded that adrenaline alone does not account for the effects of caffeine and that additional mechanisms must be involved.

The death of the rabbits in this study when 4ug/kg of adrenaline was injected prevented investigation of the effects of higher doses of adrenaline. It also suggests that rabbits are killed by adrenaline more readily than other animals. In previous studies, 5ug/kg and 50ug/kg of adrenaline were given to dogs [4] and rats [26] respectively and the animals did not die throughout experiments of even longer duration than this study.

In conclusion, we have demonstrated in this study that adrenaline has an effect on blood glucose and glucose uptake in the rabbit small intestine. Furthermore, this study has shown that release of adrenaline alone cannot account for the effects of nicotine on blood glucose and glucose uptake observed in our earlier study [9]. This study also demonstrated that both alpha and beta receptors are involved in mediating the effects of adrenaline. The beta receptors appear dominant in the control of the glycaemic response while the alpha receptors seem dominant in the control of blood flow.

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