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Research Article

Role of nitric oxide in glucose-, fructose and galactose-induced increases in intestinal glucose uptake

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ABSTRACT

Previous studies have shown that the infusion of glucose, fructose and galactose resulted in significant increases in intestinal glucose uptake (IGU) and the role of nitric oxide in these responses was not known. The present study was designed to investigate the role of nitric oxide in the observed increases in IGU. Experiments were carried out on thirty-five (35) fasted male anaesthetized Nigerian local dogs divided into seven groups (5 dogs per group). Group I dogs served as control and received normal saline, groups II-IV dogs were infused with glucose (1.1 mg/kg/min), fructose (1.1 mg/kg/min) or galactose (1.1mg/kg/min) while groups V-VII were pretreated with L-Nitro-Arginine-Methyl-Esther (L-NAME) (35 mg/kg) after which they were infused with glucose (1.1 mg/kg/min), fructose (1.1 mg/kg/min) or galactose (1.1mg/kg/min). Through a midline laparatomy, the upper jejunum was cannulated for blood flow measurement and blood samples were obtained for measurement of glucose content of the arterial blood and venous blood from the upper jejunal segment. Glucose uptake was calculated as the product of jejunal blood flow and the difference between arterial and venous glucose levels (A-V glucose). Blood pressure was recorded continuously. The results showed that pretreatment of the animal with L-NAME, caused significant reductions in jejunal blood flow with complete abolition of glucose-, fructose- and galactose-induced increases in IGU. The results suggest that only glucose-induced IGU was nitric oxide-dependent through the induced hyperemia while the increases in IGU caused by fructose and galactose were not mediated by nitric oxide.

INTRODUCTION

In a recent study, Salman et al;(2014a), reported that intravenous infusion of glucose, fructose or galactose in dogs produced significant increases in blood glucose and intestinal glucose uptake. This report is similar to earlier observations in dogs (Alada and Oyebola, 1996, Alada et al;2005) and rabbits (Oyebola et al; 2009, 2011) whereby hyperglycemia induced by adrenaline, nicotine and glucagon caused significant increases in intestinal glucose uptake. It was therefore concluded that the gastro-intestinal tract will increase its glucose uptake in response to hyperglycemia irrespective of its cause. Hence, the gastrointestinal tract plays a modulatory role in glucose homeostasis

The mechanism(s) by which the hyperglycemia induced by the hexoses causes a rise in the amount of glucose taken up by the intestine is not fully elucidated. One of the important regulatory signalling molecules produced by the endothelium is nitric oxide (NO), which is synthesized from L-arginine by the action of three isozymes of Nitric Oxide synthase (NOS) (Moncade and Higgs, 1993). Nitric oxide is a well known mediator of glucose transport in skeletal muscle

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during the resting and postexercise state (Balon and Nadler, 1997). Nitric oxide-stimulated glucose transport is associated with an activation of the α1 catalytic subunit of AMPK (Higaki et al; 2001). Studies by Bian et al; (2001) showed that different isoforms of NOS are expressed in the gastro-intestinal tract. Although, the complete physiological function of NO in the gastro-intestinal tract is not known, a study by Kibourn and Griffith (1992) showed increased intestinal permeability in response to high NO concentration. A study by Powell et al; (2004) has also shown that presence of high blood glucose concentration in human upregulates nitric oxide synthase gene-expression in intestinal epithelial cells. There is a compelling data from animal studies (Alemany et al; 1997, Matheson et al; 1997) showing that nitric oxide is involved in the regulation of splanchnic blood flow.

The aim of this study therefore is to assess the role of nitric oxide in the observed increases in intestinal glucose uptake following hyperglycemia induced by glucose, fructose or galactose.

MATERIALS AND METHODS

Experiments were carried out on male, adult mongrel dogs weighing 10 – 15 Kg. Each animal was fasted for 18 – 24h before the start of an experiment. Anaesthesia was induced by i.v. Sodium pentobarbitone, 30mg/kg. Light anaesthesia was maintained with supplementary doses of i.v. sodim pentobarbitone as necessary. The trachea was intubated using a Y-piece cannula and the animal was allowed to breathe room air (temp 25^{0}C) spontaneously. Cannulae were placed in the right femoral veine and right femoral artery. The later was advanced to the level of the superior mesenteric artery.

Through a midline laparatomy, the jejunum was identified and a vein draining the proximal segmenrt of the jejunum was cannulated using a 1.8 mm (i.d) polyethylene tubing (P.E 260). The jejunal vein cannula was moved into an extra-corporeal position and a non-crushing clamp was applied to its free end. Sodium heparin, 300 units per kg was administered i.v. to prevent blood clotting . The abdomen was closed in two layers with interrupted sutures.

Experimental procedure

Following surgery, a period of 60 min was allowed for stabilization of all animals. After stabilization, basal measurements of jejenual venous flow, arterial and venous glucose levels were made at 5 min interval over 15 min. The mean was taken as the control. Jejunal blood flow was determined by timed collection of blood as previously described (Alada et al; 2005). Blood pressure was continuously monitored through the right femoral artery connected to physiographic two channel recorder (Gemini Model 7070, Ugo Basil, Italy).

Arterial and venous blood samples for glucose estimation were obtained from the femoral artery and jejunal venous cannulae, respectfully. After the basal measurements, a 20 min infusion of glucose (1.1 mg/kg/min), fructose (1.1 mg/kg/min) or galactose (1.1 mg/kg/min) intravenously. Another group was pretreated with L-Nitro-Argenine-Methyl-Ester (L-NAME, Sigma, USA) 35 mg/kg followed by infusion of glucose (1.1 mg/kg/min), fructose (1.1 mg/kg/min) or galactose (1.1 mg/kg/min). Five dogs were used for each dose of all the sugars studied. Infusion was carried out using an infusion pump (Palmer, England). Measurement of blood flow and blood sample collection were carried out at 0 min, 5 min, 10 min, 15 min, 20 min, 25 min, 30 min, 45 min, 60 min, 75 min and 90 min during and post infusion period.

Another group of five dogs were studied for the effects of normal saline (0.2 ml/kg/min) on jejunal blood flow, arterial and venous glucose levels as in other groups. This served as the control. Blood glucose was determined by modified glucose oxidase method (Trinder, 1969). Intestinal glucose uptake was calculated as the product of arterio-venous glucose difference (A – V) and jejunal blood flow per minute, intestinal vascular resistance was also calculated as the blood pressure divided by the intestinal blood flow.

Statistical analysis

All values given are the means ± SEM of the variable measured. Significance was assessed by the Student t-test for two Means of independent variables. P values of 0.05 or less were taken as statisticall significant.

RESULTS

Effects of Glucose

The effects of glucose infusion on arterial and venous blood glucose levels, arterio-venous glucose difference, jejunal blood flow and intestinal glucose uptake before and after pretreatment of the animal with L-NAME are shown in table 1 and fig 1. Infusion of glucose produced significant increases in arterial and venous blood glucose levels. There was also a corresponding increase in arterio-venous glucose difference in response to infusion of glucose. Pretreating the animal with L-NAME caused significant decrease in both arterial and venous blood glucose levels. However, there was no change in the basal blood glucose before and after pretreatment with L-NAME (table 1). Infusion of glucose produced a slight but significant increase in jejunal blood flow which lasted for about twenty minutes (Fig. 1b). This increase in jejunal blood flow was completely abolished following pretreatment of the dog with L-NAME and the vascular resistance

Table 1: Effects of intravenous infusion of glucose on arterial and venous glucose Concentrations (mg/dl) before and after pretreatment with L-Nitro-Arginine-Methyl-Ester

Treatment		0min	5min	10min	15min	20min	25min	30min	45min	60min	75min	90min
Glu	Arterial blood glucose	99.40 ±0.87	115.80 ±1.32**	119.60 ±2.42**	126.00 ±1.70**	131.80 ±4.79***	134.40 ±5.85**	141.20 ±5.65***	131.60 ±7.37**	132.40 ±6.42**	119.80 ±1.71**	113.20 ±1.85**
L-NAME+Glu		98.00 ±3.63	107.25 ±3.82*	108.75 ±2.69*	112.25 ±2.29*	121.00 ±5.45*	116.50 ±1.19*	113.25 ±2.93*	114.50 ±1.94*	110.50 ±4.11*	108.25 ±3.45*	105.50 ±4.73
Glu	Venous blood glucose	95.20 ±1.02	101.20 ±1.53*	101.40 ±2.89*	102.00 ±2.19*	107.60 ±3.50*	112.20 ±4.05*	118.40 ±4.75*	113.20 ±4.31*	116.40 ±5.24*	105.80 ±1.39*	99.00 ±1.97
L-NAME+Glu		94.00 ±3.92	90.00 ±3.51#	89.75 ±2.84#	91.75 ±2.06#	100.75 ±5.22	95.50 ±1.50#	93.25 ±2.72#	96.75 ±2.21#	94.25 ±4.33#	95.00 ±3.49#	93.25 ±2.87

*P<0.05, **P<0.01; ***P<0.001 vs basal; #p<0.05 vs Glu

Table 2: Effects of intravenous infusion of fructose (Fru) (1.1 mg/kg/min) on arterial and venous glucose Concentrations (mg/dl) before and after pre-treatment with L-Nitro-Arginine-Methyl-Esther (L-NAME) (35 mg/kg).

Treatment		0min	5min	10min	15min	20min	25min	30min	45min	60min	75min	90min
Fru	Arterial blood glucose	97.60 ±1.78	110.60 ±1.25**	112.00 ±2.72**	108.80 ±3.01**	114.20 ±1.88**	103.60 ±3.70	110.80 ±1.28	103.40 ±2.18	109.60 ±1.21	107.40 ±1.78	98.80 ±2.31
L-NAME+Fru		96.25 ±2.69	107.50 ±3.28*	106.25 ±1.49*	101.50 ±0.65	102.25 ±1.31#	101.00 ±1.96	101.00 ±2.42#	101.25 ±1.31	97.75 ±1.25#	95.25 ±1.44#	94.25 ±2.10
Fru	Venous blood glucose	94.20 ±2.06	88.80 ±1.36	89.80 ±4.65	90.60 ±1.12	101.40 ±1.60	91.60 ±2.25	85.80 ±2.91	91.40 ±0.93	89.80 ±0.86	85.40 ±1.21	94.00 ±2.39
L-NAME+Fru		92.25 ±2.66	92.00 ±3.37	90.75 ±2.32	89.25 ±1.18	91.50 ±1.76#	89.50 ±1.89	85.25 ±1.03*	89.75 ±1.49	85.00 ±0.58*#	80.00 ±1.47*#	83.00 ±1.73*#

*p<0.05, **p<0.01 vs basal; #p<0.05 vs Fru

increased by about four fold (table 4). Glucose infusion produced a highly significant increase in intestinal glucose uptake. This increase in intestinal glucose uptake could be as high as 700%. When the animal was pretreated with a NOS inhibitor, L-NAME, the rise in intestinal glucose uptake was completely abolished (Fig. 1c).

Effects of Fructose.

The effects of frucose on arterial and venous blood glucose, arterio-venous glucose difference, jejunal blood flow and intestinal glucose uptake are shown in table 2 and Fig. 2. Infusion of fructose produced slight but significant increases in arterial and venous glucose levels which lasted for about twenty minutes. There were also significant increases in arterio-venous glucose levels. However, pretreatment of the animal with L-NAME had no effect on the blood glucose response to fructose infusion. Though, fructose had no effect on the jejunal blood flow, pretreating the animal with L-NAME significantly decreased the blood flow throughout the period of the experiment (Fig 2a). The significant increase of about 600% in intestinal glucose uptake caused by fructose infusion was also completely abolished when the animal was pretreated with L-NAME before fructose infusion (Fig 2c).

Effects of Galactose

The effects of infusion of galactose on arterial and venous blood glucose levels, arterio-venous glucose difference, jejunal blood flow and intestinal glucose uptake are

Table 3: Effects of intravenous infusion of galactose (Gal) (1.1 mg/kg/min) on arterial and venous glucose Concentrations (mg/dl) before and after pre-treatment with L-Nitro-Arginine-Methyl-Esther (L-NAME) (35 mg/kg).

Treatment		0min	5min	10min	15min	20min	25min	30min	45min	60min	75min	90min
Gal	Arterial blood glucose	96.00 ±1.47	102.75 ±1.93	106.25 ±1.65*	109.75 ±1.84*	105.25 ±1.80*	102.00 ±1.63	99.00 ±1.35	91.75 ±1.18	90.25 ±1.03	86.00 ±0.71	86.00 ±1.47
L-NAME+Gal		99.50 ±2.90	100.75 ±2.87	108.25 ±2.29*	112.50 ±2.63*	107.75 ±3.52	99.75 ±0.85	99.00 ±1.78	98.00 ±2.48	96.00 ±0.82	98.75 ±4.21	96.50 ±0.65
Gal	Venous blood glucose	92.00 ±1.29	96.50 ±1.50	98.50 ±0.87*	97.75 ±2.39*	90.00 ±1.47	90.00 ±2.68	91.25 ±1.11	82.75 ±1.80	82.50 ±1.50	80.25 ±2.02	79.75 ±1.80
L-NAME+Gal		93.00 ±1.53	93.33 ±2.03	102.00 ±0.58*	105.33 ±1.20*	96.67 ±1.20	93.67 ±1.45	92.33 ±0.88	90.00 ±1.73	90.00 ±1.53	89.00 ±2.52	90.67 ±0.33

*P<0.05 compared to basal

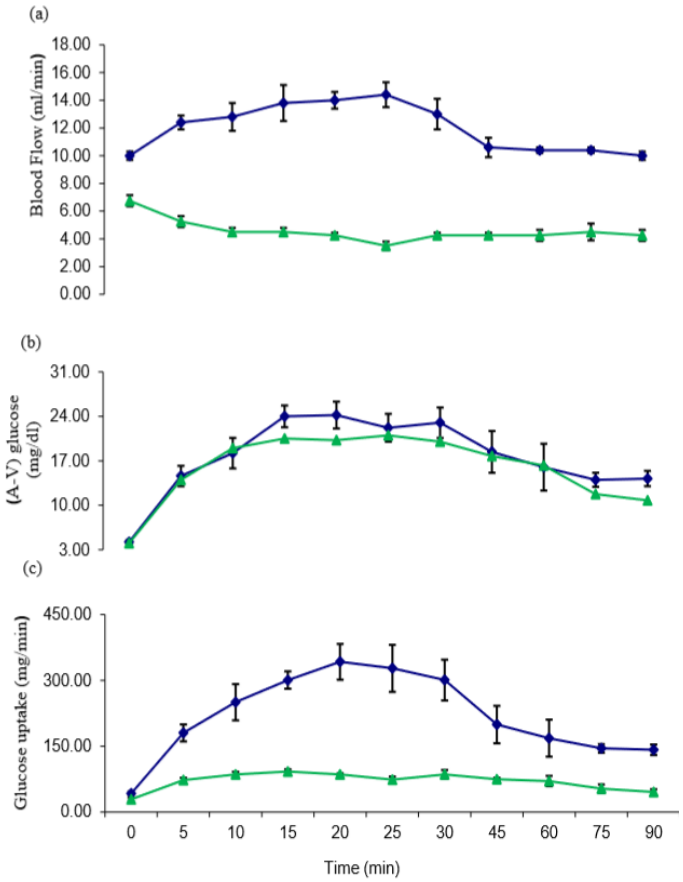

Fig. 1: Effects of intravenous infusion of glucose on blood flow (a), (A-V) glucose (b) and glucose uptake (c) in untreated ( ) and dogs pretreated with L-NAME ( )

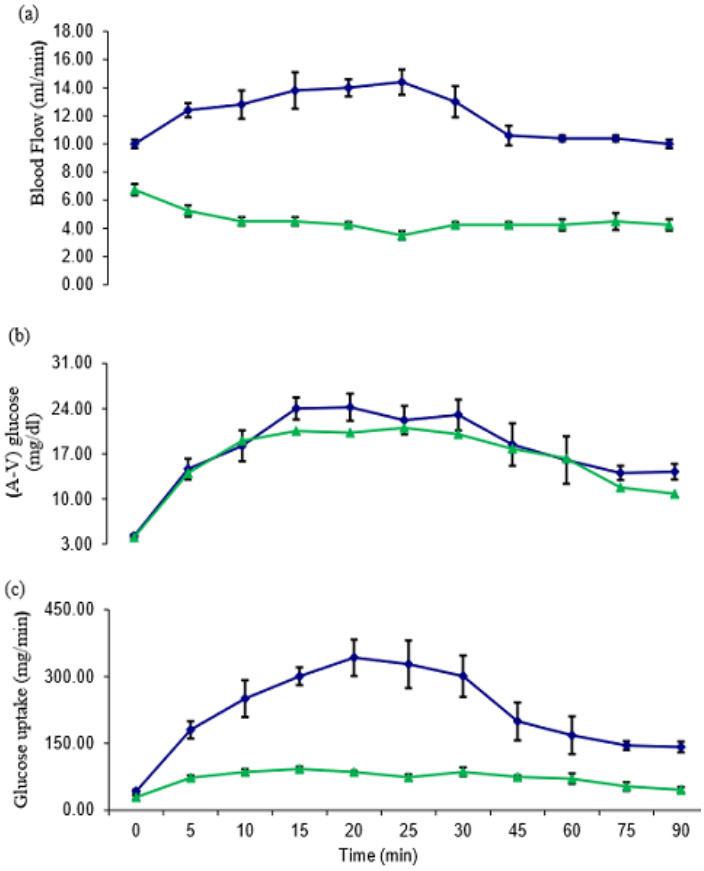

Fig. 2: Effects of intravenous infusion of fructose on blood flow (a), (A-V) glucose and glucose uptake in untreated ( ) and in dogs treated with L-NAME ( )

shown in table 3 and figure 3. Galactose also caused slight but significant increases in blood glucose levels. Arterio-venous blood glucose difference also increased significantly for about twenty minutes during infusion of galactose. Pretreatment of the animal with L-NAME had no effect on the blood glucose levels and the

Table 4: Vascular changes in response to Glucose, Fructose and Galactose before and after L-NAME treatment.

Treatment	ABP (mmHg)	IBF (ml/min)	Vascular Resistance (RU)
Glucose	88.44 ± 1.24	14.4 ± 0.93	6.14 ± 0.49
L-NAME + Glucose	95.67 ± 1.14	3.5 ± 0.25	27.33 ± 1.67
Fructose	85.65 ± 0.67	10.8 ± 0.37	7.95 ± 0.91
L-NAME + Fructose	98.83 ± 1.45	3.4 ± 0.18	29.06 ± 3.13
Galactose	82.10 ± 1.33	9.75 ± 0.48	8.42 ± 0.66
L-NAME + Galactose	95.81 ± 0.82	3.23 ± 0.22	29.67 ± 3.83

arterio-venous glucose levels. Galactose had no effect on jejunal blood flow, but following pretreatment of the animal with the NOS inhibitor, there were significant reductions in the jejunal blood flow which was sustained during the infusion and post infusion period (Fig 3a). Pretreatment of the animal with a NOS inhibitor significantly reduced the galactose – induced increase in intestinal glucose uptake from 150 mg/min to about 50 mg/min.

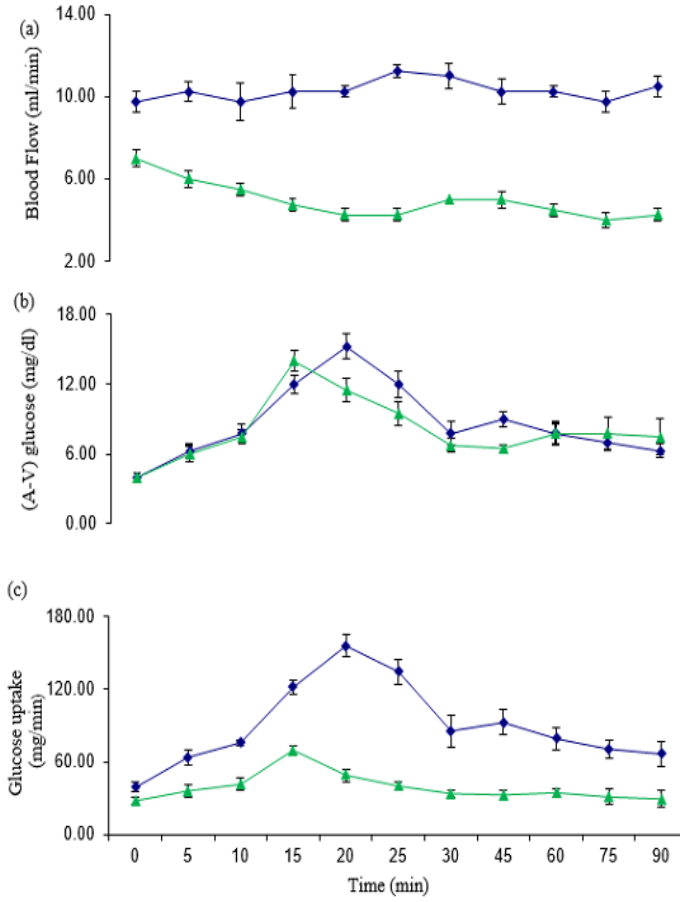

Fig. 3: Effects of intravenous infusion of galactose on blood flow (a), (A-V) glucose (b) and glucose uptake (c) in untreated ( ) and in dogs pre-treated with L-NAME ( ).

Effect of normal saline

Normal saline had no effect on the arterial and venous blood glucose levels and arterio-venous glucose diference. It also had no effect on the jejunal blood flow and intestinal glucose uptake. The resting jejunal blood flow was 10.60 ± 0.75 ml/min and the resting intestinal glucose uptake was 36.80 ± 8.26 mg/min.

DISCUSSION

The observed increases in intestinal glucose uptake in response to glucose, fructose or galactose in this study are consistent with our earlier reports (Salman et al; 2014) in similar dog experiments. Salman et al; (2014) had earlier concluded that the increased intestinal glucose uptake was a metabolic response to the hyperglycemia induced by glucose, fructose or galactose. A major observation in this study is the significant reduction or complete abolition of the induced increases in intestinal glucose uptake by the three sugars following pretreatment of the animal with NOS inhibitor, L-NAME. Since L-NAME had no effect on blood glucose levels and arterio-venous glucose difference, it would be difficult therefore, to suggest that nitric oxide is involved in intestinal glucose extraction. A plausible explanation for the effect of L-NAME on the intestinal glucose uptake in this study is its effect on blood flow and other vascular parameters as seen on table 4. For instance, L-NAME produced a slight rise in blood pressure but a tremendous increase in vascular resistance which significantly reduced intestinal blood flow in all the experiments bringing about such a decrease in intestinal glucose uptake.

There was only a slight but significant increase in intestinal blood flow in response to infusion of glucose. Interestingly, the other two sugars; fructose and galactose did not produce such hyperemia. This observed glucose-induced hyperemia had earlier been reported in dogs (Alada and Oyebola, 1996, Pencek et al; 2004) and is most probably due to secretion of insulin which has been reported to possess vasodilatory properties (Scherrer and Sartori, 1997). In other words, glucose infusion causes hyperinsulinemia which could be responsible for the increase in blood flow. The involvement of nitric oxide in insulin secretion remains controversial (Gentilcore et al; 2005). The reason why fructose and galactose did not induce increase in intestinal blood flow inspite of their similarities to

glucose in structure is not clear. Perhaps, the difference in their vascular responses may be related to their isomerism. Further studies may throw more light on this.

Determination of intestinal glucose uptake was based on indirect Fick's law which is calculated as the product of Intestinal Blood Flow (IBF) and Arterio-Venous glucose difference ((A – V) glucose). In other words, the intestinal glucose uptake was determined by both the blood flow and arterio-venous glucose difference. Thus, in the present study, glucose infusion significantly increased both the intestinal blood flow and (A – V) glucose, thereby causing a significant rise in intestinal glucose uptake. The observed abolition of the glucose –induced hyperemia in the jejunum by the NOS inhibitor, L-NAME suggests the involvement of nitric oxide in glucose-induced hyperaemia in the canine jejunum. This result agrees with previous reports which showed that nitric oxide mechanisms are important in splanchnic blood flow. In pigs, L-NAME attenuates the increase in mesenteric blood flow after meal (Alemany et al; 1997) and in rats, intestinal arteriolar distension induced by topical application of glucose is blocked by L-NAME (Matheson et al; 1997). Since fructose and galactose had no effect on intestinal blood flow, it is reasonable to conclude that the effect of the two sugars on intestinal glucose uptake is essentially due to their effects on glucose extraction by the gut. Again, since L-NAME had no effect on intestinal glucose extraction, it is not unreasonable to conclude that nitric oxide is not involved in increasing intestinal glucose uptake induced by infusion of fructose or galactose.

In conclusion, these results show that nitric oxide may have played a vasodilatory role in increasing blood flow which contributed significantly to increase intestinal glucose uptake induced by glucose. However, nitric oxide did not play any role in the increased intestinal glucose uptake following administration of fructose and galactose. These results show that the increased intestinal glucose uptake induced by glucose is mediated, at least in part, by nitric oxide- dependent vasodilation which increases blood flow; however, fructose or galactose-induced increase in intestinal glucose uptake is nitric oxide- independent.

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