

# Role of Adrenergic Receptors in Glucose, Fructose and Galactose-Induced Increases in Intestinal Glucose Uptake in Dogs

Salman T.M, Alada A.R.A\* and Oyebola D.D.O

Endocrinology and Metabolism Unit, Department of Physiology, College of Medicine, University of Ibadan, Ibadan, Nigeria

**Summary:** The study investigated the role of adrenergic receptors in glucose, fructose-, and galactose- induced increases in intestinal glucose uptake. Experiments were carried out on fasted male anaesthetized Nigerian local dogs divided into seven groups (with five dogs per group). Group I dogs were administered normal saline and served as control. Dogs in groups II, III and IV were intravenously infused with glucose (1.1 mg/kg/min), fructose (1.1 mg/kg/min) and galactose (1.1 mg/kg/min) respectively. Another three groups, V, VI and VII were pretreated with prazosin (0.2mg/kg), propranolol (0.5mg/kg) or a combination of prazosin (0.2mg/kg) and propranolol (0.5mg/kg) followed by glucose infusion, fructose infusion or galactose infusion respectively. Through a midline laparotomy, 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). The results showed that pretreatment of the animal with prazosin had no effect on glucose and galactose induced increases in glucose uptake. However, pretreatment with propranolol completely abolished glucose, fructose and galactose-induced increases in intestinal glucose uptake. Prazosin also significantly reduced galactose-induced increase in intestinal glucose uptake. The results suggest that the increases in intestinal glucose uptake induced by glucose and fructose are mediated mostly by beta adrenergic receptors while that of galactose is mediated by both alpha and beta adrenergic receptors.

**Keywords:** Hexoses administration, Adrenergic receptors, Glucose uptake, Dog.

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\*Address for correspondence: akinalada@gmail.com

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## INTRODUCTION

In previous studies, it was shown that the gastrointestinal tract (g.i.t) plays a role in glucose homeostasis. Thus, the g.i.t takes up large quantity of glucose from circulation following hyperglycemia induced by catecholamines (Grayson and Oyebola, 1983; Oyebola and Durosaiye, 1988; Alada and Oyebola, 1996; Oyebola et al, 2011); nicotine (Grayson and Oyebola, 1985); cow's urine concoction (Oyebola, 1982); glucagon (Alada and Oyebola, 1996); glucose (Alada and Oyebola, 1996) and diabetes mellitus (Alada et al; 2001). In addition, the g.i.t releases glucose into the blood stream in response to insulin induced hypoglycaemia. Recently, Salman et al; (2014) also showed that the canine intestine increased its glucose uptake significantly followings hyperglycaemia induced by glucose, fructose or galactose.

Although, Salman et al; (2014) did not report on the mechanisms of the increased intestinal glucose uptake in response to hyperglycaemia induced by

glucose, fructose or galactose, Grayson and Oyebola (1983) and Oyebola et al; (2011) had reported the involvement of alpha and beta adrenergic receptors in catecholamine induced increases in intestinal glucose uptake in dogs and rabbits respectively. Also, Alada and Oyebola (1997) reported that the increase in intestinal glucose uptake caused by glucagon or glucose is mediated through beta adrenergic receptors. It is however not clear if adrenergic receptors are involved in the increases in intestinal glucose uptake induced by fructose or galactose induced hyperglycaemia. The present study was therefore designed to investigate the role of adrenergic receptors in intestinal glucose uptake increases induced by hexoses such as glucose, fructose and galactose in the dog.

## MATERIALS AND METHODS

Male dogs weighing between 9-16 kg were used for the study. Each animal was fasted for 18-24 hours before the start of the experiment. Anaesthesia was

induced by an intravenous injection of 30mg/kg – body weight of sodium pentobarbitone. Light anaesthesia was maintained with supplementary doses of sodium pentobarbitone as necessary. The animal was laid supine and firmly secured on the dissecting table. The trachea was intubated using a Y-piece cannula and the animal was allowed to breathe room air (temp. 25C) spontaneously. A cannula was placed in the carotid artery to monitor arterial blood pressure (BP) using a pressure transducer connected to a channel recorder (Ugo Basil). Cannulae were also placed in the right femoral vein and right femoral artery. The latter was advanced to the level of the superior mesenteric artery.

Through a midline laparotomy, the jejunum was identified and a vein draining the proximal segment of the jejunum was cannulated using a 1.8 mm (i.d) polyethylene tubing (P.E). The jejunal vein cannula was moved into an extra-corporeal position and a non crushing clamp was applied to its free end. At the end of the surgical procedure, sodium heparin 300 i.u was administered intravenously to prevent blood clotting. The abdomen was then closed in two layers with interrupted sutures.

Following surgery, a period of 60 min was allowed for stabilization in all animals. Blood pressure and jejunal segment blood flow were continuously monitored throughout the duration of the experiment. Arterial and venous blood samples for glucose estimation were obtained from the femoral and jejunal venous cannulae respectively. Jejunal blood flow was determined by timed collection of the effluent from the jejunal venous cannula as previously described (Alada and Oyebola, 1996). Blood glucose was determined by the glucose oxidase method (Trinder, 1969). Arterio-venous glucose difference was calculated as the difference between arterial and venous blood glucose concentrations while intestinal glucose uptake (mg/min) was calculated as the product of the arterio-venous glucose difference and jejunal blood flow per minute.

### Experimental procedures

*Group I: Pre-treatment with alpha adrenergic receptor blocker.*

Five dogs were first given prazosin before glucose, fructose or galactose infusion. Each dog was injected i.v with prazosin, 0.2 mg/kg. Forty minutes was allowed for the drug to take effect. Then, basal recording of blood pressure, blood flow and collection of arterial and venous blood samples for glucose estimation were made. After the basal recordings and blood sample collection, glucose (1.1 mg/kg/min) infusion was given for twenty minutes. The blood pressure, blood flow, arterial and venous blood glucose were similarly monitored at intervals for 90 min during infusion and post-infusion observation period. The experiment was repeated in

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another two subgroups (with five dogs per subgroup) using fructose infusion (1.1 mg/kg/min) or galactose (1.1 mg/kg/min) in place of glucose.

*Group II: Pretreatment with beta adrenergic receptor blocker.*

Five dogs were also first injected with propranolol before glucose, fructose or galactose infusion. Each animal was given i.v injection of propranolol, 0.5 mg/kg. After forty minutes and basal recording of blood pressure, jejunal blood flow and sample collection for arterial and venous blood glucose, glucose (1.1 mg/kg/) infusion was administered intravenously for twenty minutes. Similar measurements to those used in group I were made. Another two subgroups (of five dogs per subgroup) were studied with propranolol pre-treatment but using fructose (1.1 mg/kg/min) or galactose (1.1 mg/kg/min) infusion instead of glucose.

*Group III: Pre-treatment with combined alpha and beta adrenergic receptor blockers.*

Five dogs were first given a combination of prazosin and propranolol before i.v infusion of glucose, fructose or galactose. Each animal was given an i.v injection of both prazosin, 0.2 mg/kg and propranolol, 0.5 mg/kg. After forty minutes and basal recording of blood pressure, jejunal blood flow and sample collection for arterial and venous blood glucose, glucose (1.1mg/kg/min) was intravenously infused for twenty minutes. Similar measurements to those used in group 1 were made. Again, another two subgroups (of five dogs per subgroup) were studied using fructose infusion (1.1 mg/kg/min) or galactose infusion (1.1 mg/kg/min) instead of glucose.

Blood glucose was determined by the modified glucose oxidase method (Trinder, 1969). Glucose uptake (mg/min) was calculated as the product of the arterio-venous glucose difference (A -V) and the jejunal blood flow.

### Statistical analysis:

All values given are the mean  $\pm$  S.E.M of the variable measured. Significance was assessed by the Students t-test for two means of independent variables. P values of 0.05 or less were taken as statistically significant

## RESULTS

### Effects of Glucose, Fructose and Galactose on Blood Glucose Levels.

The effects of the three sugars blood glucose levels are shown in tables 1, 2, and 3. Infusion of glucose, fructose or galactose causes significant increases in blood glucose levels. For instance, the blood glucose level increased from a basal level of  $97.4 \pm 0.87$  mg/dl to  $141.2 \pm 5.65$ ,  $114.2 \pm 1.88$  and  $109.75 \pm 1.84$  mg/dl following infusion of glucose, fructose and galactose respectively. Again, apart from the three sugars producing different degrees of

hyperglycemia, the maximum level of blood glucose was achieved at different times for the three sugars. The effects of adrenergic receptor blockade on the increases in blood glucose and intestinal glucose uptake are shown in tables 1,2 and 3 and figures 1, 2 and 3.

**Effects of alpha adrenergic blocker**

Prazosin pre-treatment caused significant reduction in glucose or fructose-induced increases in blood glucose levels. Prazosin however did not affect galactose induced hyperglycemia (tables 1 and 2). While prazosin had no effect on glucose or fructose-induced increases in intestinal glucose extraction and uptake, it however completely abolished the galactose-induced intestinal glucose uptake.

**Effects of beta adrenergic blocker**

Pre-treatment of the dog with propranolol followed by glucose infusion produced significant decreases in arterial blood glucose compared to infusion of glucose alone (Table 1). Pretreatment with propranolol also reduced significantly intestinal glucose uptake in response to glucose infusion. For instance, pretreatment with propranolol caused about 400% reduction in glucose-induced increase intestinal glucose uptake (figure 1). The increase in the

intestinal glucose uptake decreased from 670% for untreated dogs to 200% for propranolol-treated dogs (figure 1). Also, propranolol significantly reduced fructose-induced increases in arterial blood glucose. Figure 2 shows the effects of fructose infusion on intestinal glucose uptake in dogs pretreated with propranolol. Propranolol abolished the fructose-induced increase in intestinal glucose uptake (figure 2). Figure 3 shows the effects of galactose on intestinal glucose uptake in untreated and propranolol-treated dogs. Pretreatment of the dog with propranolol also completely abolished the galactose-induced increase in intestinal glucose uptake.

**Effects of combined alpha and beta adrenergic blockers**

A combination of propranolol and prazosin also caused significant decreases in arterial blood glucose levels (table 1) during and after glucose infusion. The blood glucose was also significantly reduced in the animal pre-treated with the two blockers and infused with fructose. (Table 2). However, a combination of the two adrenergic blockers had no effect on the blood glucose level induced by

**Table 1:** Effects of intravenous infusion of glucose (Glu) (1.1 mg/kg/min) on arterial glucose concentration (mg/dl) before and after pre-treatment with adrenergic blockers. Pro (Propranolol), Pra (Prazosin) , (\*p<0.05)

Treatment	0min	5min	10min	15min	20min	25min	30min	45min	60min	75min	90min
Glu	97.4	115.8	119.6	126	131.8	134.4	141.2	131.6	132.4	119.8	113.2
	±0.87	±1.32	±2.42	±1.70	±4.79	±5.85	±5.65	±7.37	±6.42	±1.71	±1.85
Pro+Glu	97.5	103.5	109.25	114	119	117.5	109.25	106.75	102.25	98.5	95.5
	±3.23	±2.53*	±1.49*	±2.16*	±4.04	±4.33	±5.65*	±4.77*	±3.22*	±1.55*	±1.66*
Pra+Glu	97.25	104.25	110	114.25	122.5	122.5	119.5	116.25	114.25	105.25	101.75
	±1.11	±2.17*	±1.41*	±2.17*	±2.63	±1.04	±0.50*	±1.03	±1.49*	±1.89*	±1.49*
Pro+pra+Glu	95.5	101.75	108.0	112.75	123.75	123.0	118.75	116.0	103.25	99.0	95.75
	±2.10	±2.69*	±1.41*	±1.60*	±2.39	±1.22	±2.39	±2.00	±1.97*	±0.58*	±0.75*

**Table 2:** Effects of intravenous infusion of fructose (Fru) (1.1 mg/kg/min) on arterial glucose concentration (mg/dl) before and after pre-treatment with adrenergic blockers. Pro (Propranolol), Pra (Prazosin) , (\*p<0.05)

Treatment	0min	5min	10min	15min	20min	25min	30min	45min	60min	75min	90min
Fru	97.6	110.6	112	108.8	114.2	103.6	110.8	103.4	109.6	107.4	98.8
	±1.78	±1.25	±2.72	±3.01	±1.88	±3.70	±1.28	±2.18	±1.21	±1.78	±2.31
Pro+Fru	95.25	97.75	106	101.75	98.5	97.25	97	95.5	90	91.75	94.5
	±2.32	±3.57*	±1.35	±4.44	±1.55*	±1.49	±0.71*	±0.65*	±3.54*	±2.02*	±0.65
Pra+Fru	99.75	100.75	99	97	102.75	100.75	94.75	94.5	92.75	93.5	94.75
	±2.32	±1.11*	±2.16	±3.58*	±2.10*	±1.49	±1.03*	±1.32*	±0.85*	±0.96*	±1.03
Pro+pra+Fru	98.25	100.75	116	104	106.25	102.5	101	98.5	100	100.25	99.25
	±2.78	±2.17*	±4.34	±2.48	±1.80*	±1.76	±0.58*	±2.47	±2.04*	±1.49*	±0.85

**Table 3:** Effects of intravenous infusion of galactose (Gal) (1.1 mg/kg/min) on arterial glucose concentration (mg/dl) before and after pre-treatment with adrenergic blockers. Pro (Propranolol), Pra (Prazosin) , (\*p<0.05)

Treatment	0min	5min	10min	15min	20min	25min	30min	45min	60min	75min	90min
Gal	96	102.75	106.25	109.75	105.25	102	99	91.75	90.25	86	86
	±1.47	±1.93	±1.65	±1.84	±1.80	±1.63	±1.35	±1.18	±1.03	±0.71	±1.47
Pro+Gal	96.25	107.75	112.25	114.75	101.5	98.5	92.75	94.25	96.25	96.75	94
	±1.75	±1.11	±1.03	±2.14	±2.53	±0.65	±3.92	±3.79	±0.48	±0.48	±1.68
Pra+Gal	96.67	107.33	110.33	114	105	101	92	91.33	94.67	94.67	94.67
	±0.88	±0.67	±0.33	±1.00	±2.08	±1.00	±1.53	±0.33	±0.33	±1.20	±1.33
Pro+pra+Gal	99.5	100.75	108.25	112.5	107.75	99.75	99	98	96	98.75	96.5
	±2.90	±2.87	±2.29	±2.63	±3.52	±0.85	±1.78	±2.48	±0.82	±4.21	±0.65

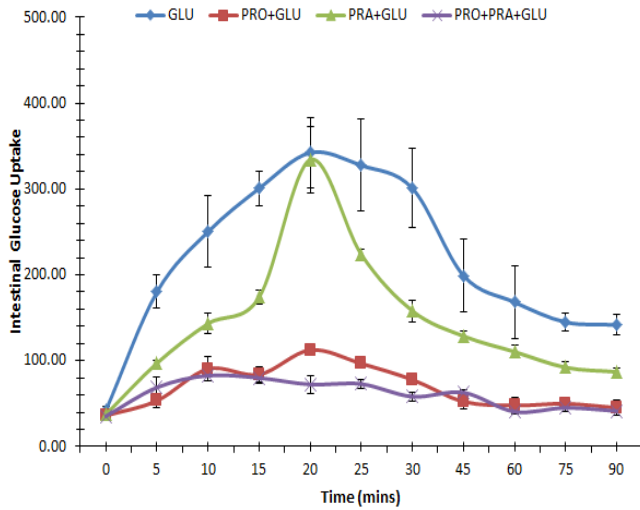


Fig 1: Effects of glucose (GLU) infusion on intestinal glucose uptake before and after pretreatment with prazosin (PRA) and propranolol (PRO).

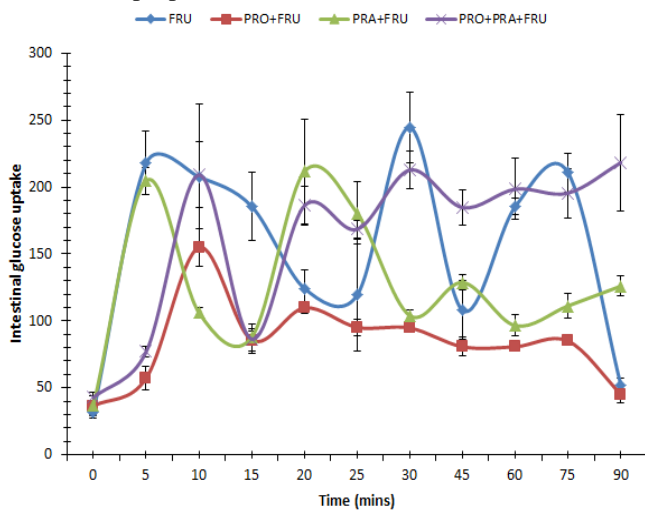


Fig 2: Effects of fructose (FRU) infusion on intestinal glucose uptake before and after pretreatment with prazosin (PRA) and propranolol (PRO).

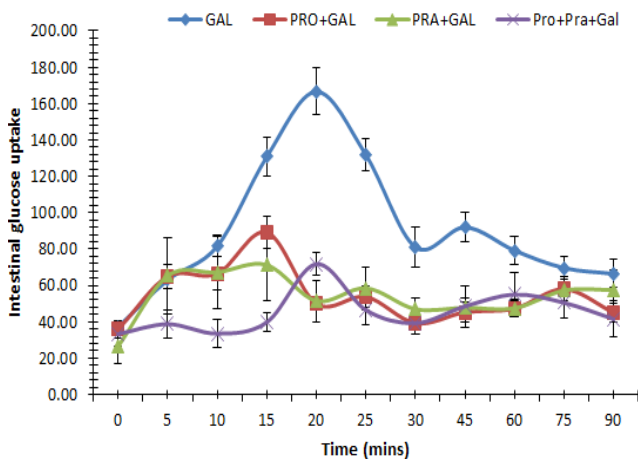


Fig 3 :Effects of galactose (GAL) infusion on intestinal glucose uptake before and after pretreatment with prazosin (PRA) and propranolol (PRO).

galactose. Interestingly, the combined prazosin and propranolol completely abolished the increases in intestinal glucose uptake following infusion of glucose, fructose or galactose. (Figures 1,2 and 3). The latter effect is essentially similar to that of propranolol.

## DISCUSSION

The observed increases in blood glucose levels and intestinal glucose uptake following the infusion of fructose, galactose and glucose have been well described in a recent report (Salman et al; 2014). The increased intestinal glucose uptake following hyperglycemia induced by glucose, fructose or galactose is also consistent with our recent findings (Salman et al; 2014). The increased glucose uptake by the gut is most probably a metabolic response to the induced hyperglycemia as earlier described in previous findings (Grayson and Oyebola, 1983, Alada and Oyebola, 1996). In other words, the gut responds to the hyperglycemia induced by hexoses such as glucose, fructose or galactose by increasing its glucose uptake.

The most significant observation on the role of adrenergic receptors in the increased intestinal glucose uptake following glucose infusion is the effect of beta adrenergic blocker. Prazosin had no effect on the glucose-induced increase in intestinal glucose uptake. However, propranolol completely abolished the glucose-induced increase in intestinal glucose uptake. These findings are consistent with earlier observation on the effects of alpha and beta adrenergic receptor blockers in similar dog experiments on the intestine (Grayson and Oyebola, 1983; Alada and Oyebola, 1997) and hindlimb (Salahdeen and Alada, 2009). The present study therefore showed that the increase in intestinal glucose uptake in response to the high blood glucose caused by glucose infusion is most probably mediated through beta adrenergic receptors alone.

The significant reduction in fructose-induced increased intestinal glucose uptake by propranolol seems to suggest that the fructose effect on intestinal glucose uptake is also mediated through beta adrenergic receptors. It is to be noted also that propranolol also reduced significantly the arterial blood glucose levels in this study. Therefore, the decrease in intestinal glucose uptake could as well be a consequence of the significant reduction in fructose-induced hyperglycemia. The significant reductions in blood glucose after pretreatment with propranolol are consistent with the reports that propranolol causes significant reduction of blood glucose in man and rat (Allison et al, 1969, Oyebola and Alada, 1993). However, the decrease in blood glucose level in animals pretreated with prazosin followed by infusion of fructose seems to suggest the involvement of alpha adrenergic receptors in fructose induced hyperglycemia. In spite of the role of alpha adrenergic receptors in fructose-induced hyperglycemia, prazosin had no effect on fructose induced increase in intestinal glucose uptake. That is, fructose induced increase in gut's glucose uptake is most probably due to activation of the beta adrenergic receptors since propranolol abolished the fructose

induced increase in the intestinal glucose uptake. The absence of any effect of prazosin pretreatment on fructose induced increase in intestinal glucose uptake suggests that the fructose effects are not mediated through alpha adrenergic receptors.

The absence of the effects of prazosin or propranolol on the hyperglycemia induced by galactose suggests that both alpha and beta adrenergic receptors are not involved in galactose induced hyperglycemia. Interestingly, the two adrenergic receptor blockers reduced considerably galactose-induced increase in the intestinal glucose uptake suggesting that both alpha and beta receptors are involved in galactose-induced increase in intestinal glucose uptake

In conclusion, the present study showed that beta adrenergic receptors are involved in the increased intestinal glucose uptake produced by glucose, fructose and galactose. It also showed that while alpha adrenergic receptors had no role in fructose- and glucose-induced increases in intestinal glucose uptake, they were involved in the increased intestinal glucose uptake caused by galactose.

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