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ORIGINAL CONTRIBUTION

Evidence for the role of α_{1A}-adrenoceptor subtype in the control of renal haemodynamics in fructose-fed Sprague–Dawley rat

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Abstract
Aim To explore the hypothesis that high fructose intake results in a higher functional contribution of α_{1A}-adrenoceptors and blunts the adrenergically and angiotensin II (Ang II)-induced renal vasoconstriction.
Methods Twelve Sprague–Dawley rats received either 20% fructose solution [FFR] or tap water [C] to drink ad libitum for 8 weeks. The renal vasoconstrictor response to noradrenaline (NA), phenylephrine (PE), methoxamine (ME) and Ang II was determined in the presence and absence of 5-methylurapidil (5-MU) (α_{1A}-adrenoceptor antagonist) in a three-phase experiment (pre-drug, low- and high-dose 5-MU). Data, mean ± SEM were analysed by ANOVA or Student's unpaired *t*-test with significance at $P < 0.05$.
Results FFR exhibited insulin resistance (HOMA index), hypertension and significant increases in plasma levels of glucose and insulin. All agonists caused dose-related reductions in cortical blood perfusion that were larger in C than in FFR while the magnitudes of the responses were progressively reduced with increasing doses of 5-MU in both C and FFR. The degree of 5-MU attenuation of the renal cortical vasoconstriction due to NA, ME and Ang II was significantly greater in the FFR compared to C.
Conclusions Fructose intake for 8 weeks results in smaller vascular response to adrenergic agonists and Ang II. The α_{1A}-adrenoceptor subtype is the functional subtype that mediates renal cortical vasoconstriction in control rats, and this contribution becomes higher due to fructose feeding.

Keywords Renal vasoconstriction · Noradrenaline · 5-methylurapidil, fructose, α_{1A}-adrenoceptors

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Introduction

Fructose intake produces an elevation in blood pressure [1], hypertriglyceridaemia [2] and hyperinsulinaemia [3]. Insulin resistance and hyperinsulinaemia in fructose-fed rats impair endothelial function and thereby contribute to the elevated blood pressure in this model [4]. Furthermore, an activation of the sympathetic nervous system due to fructose intake in the rat [5] has been associated with insulin resistance and may contribute to the onset and maintenance of cardiovascular and renal complications [6].

α_1-Adrenoceptors have been suggested to be the functionally relevant adrenoceptor subtype in the renal vasculature of the rat [7, 8]. Three α_1-adrenoceptor subtypes have been identified (α_{1A}, α_{1B} and α_{1D}), all from the G protein-coupled receptor family [9–11]. The α_{1A}-adrenoceptor subtype has been reported to be the major functional subtype mediating adrenergically induced vasoconstriction in the kidney [12–14], and there is a shift in the functional contribution of α_1-adrenoceptor subtypes in certain

vascular beds in pathophysiological conditions. There is uncertainty in the literature regarding rat models of insulin resistance induced by fructose feeding in that there is either an enhancement [15] or inhibition [16, 17] of adrenergically induced vasoconstrictions, which was largely mediated by α_1-adrenoceptors.

The effects of insulin resistance on the functional contribution of α_1-adrenoceptor-mediated vasoconstriction of resistance vessels have not been fully elucidated. We have shown previously that fructose feeding induces an insulin resistance associated with an attenuation of α_1-adrenoceptor-mediated cortical vasoconstriction. The present investigation aimed to provide evidence for the contribution of α_1-adrenoceptor subtypes in the fructose-fed rat and to explore the hypothesis that the α_1-adrenoceptor-mediated renal vasoconstrictor responses were shifted to the α_{1A}-adrenoceptor subtype.

Materials and methods

Animals

Twelve male Sprague–Dawley [SD] rats (160–190 g) were procured from the Animal Facility at Universiti Sains Malaysia, Penang, Malaysia. The rats were allowed to acclimatize for 3 days in the new environment (controlled conditions of temperature and humidity and on a 12:12-h light–dark cycle) and were permitted free access to tap water and standard rodent chow (Gold Coin Sdn. Bhd. Penang, Malaysia). The rats were randomly assigned into two groups ($n = 6$), viz. control [C] that received ad libitum a standard rodent chow and tap water and fructose-fed rats [FFR] that were fed ad libitum a standard rodent chow and fructose was administered as a 20% solution (prepared freshly everyday) in the drinking water for 8 weeks. All the procedures and experiments were approved by the Ethics Committee of Universiti Sains Malaysia.

Animal surgical preparation

Renal vasoconstrictor responses

The surgical procedures for the acute renal vasoconstrictor response study were performed as previously described [16, 18, 19]. The rats were fasted for 12 h overnight prior to study and were anaesthetized with 60 mg/kg i.p. sodium pentobarbitone (Nembutal®, CEVA, Libourne, France), and then, the trachea was cannulated to ensure a clear airway. The left carotid artery was cannulated and attached to a fluid-filled pressure transducer (model P23 ID Gould, Statham Instruments, UK) connected to a computerized data acquisition system (PowerLab®, ADInstruments, Sydney, Australia) for continuous monitoring of mean arterial pressure (MAP) and heart rate (HR). The left jugular vein was cannulated for the infusion of maintenance doses of anaesthetic. The left kidney was exposed via a midline abdominal incision, and a laser Doppler probe (OxyFlo Probe, Oxford Optronix Ltd., Oxford, UK) was positioned in the outermost layer of the renal cortex and attached to a laser Doppler flowmeter (ADInstruments, Sydney, Australia) connected to a computerized data acquisition system (PowerLab®, ADInstruments, Sydney, Australia) for the recording of renal cortical blood flow (CBF) throughout the experiment. A cannula was inserted via the left common iliac artery with its tip facing the entrance of the renal artery to administer noradrenaline (NA), phenylephrine (PE), methoxamine (ME) and angiotensin II (Ang II) intrarenally. The cannula was kept patent by infusing saline (NaCl, 9 g/L) at a rate of 6 mL/kg/h. The iliac artery cannula was also attached to a pressure transducer (model P23 ID Gould, Statham Instruments, UK) further linked to data acquisition system (PowerLab®, ADInstruments, Australia) for baseline measurements of renal arterial pressure (RAP). The urinary bladder was cannulated to allow free passage of urine. Upon completion of the surgery, a stabilization period of 1 h was allowed before starting the experimental protocol.

Measurements

Body weight, fluid intake, food intake, urine output, fractional excretion of sodium, fasting plasma insulin and glucose levels and plasma levels of Ang II in each rat were measured at the end of the 8-week feeding period. Fluid and food intake for each rat was measured by subtracting the amounts remaining in the metabolic cages from the measured quantities provided. A blood sample (250 μL) was obtained from the rat tail, and the plasma was obtained by centrifugation and stored at −30 °C for measurement of glucose using ACCU-CHEK® advantage blood glucose monitoring system (Roche Diagnostics Corporation, Indianapolis, USA) and plasma insulin using a quantitative Ultra Sensitive Rat Insulin ELISA kit (Crystal Chem Inc., IL, USA). The Homeostasis Model Assessment index (HOMA index) was used as an index of insulin resistance and calculated using the following formula: [fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5] [20, 21]. A 24-hour urine sample was collected for the measurement of sodium and creatinine levels. Sodium was measured using flame photometry, while creatinine was measured using a spectrophotometric method. For plasma Ang II determination, a blood sample (500 μL) was collected from the carotid artery cannula during the acute study under sodium pentobarbital

anaesthesia just prior to renal vasoconstrictor experiment. The blood samples were collected in a pre-cooled eppendorf tubes containing 20 g/L ethylenediaminetetraacetic acid (EDTA) to prevent generation and/or degradation of Ang II. The samples were centrifuged, and the collected plasma was immediately stored at −30 °C. Ang II was determined by enzyme-linked competitive immunoassay using a commercial Kit (SPI-BIO Bertin Group, Montigny Le Bretonneux, France) following the procedure recommended by the manufacturer.

Renal vasoconstrictor response experimental protocol

The renal vasoconstrictor experiment consisted of three distinct phases as previously described [16, 22, 23]. Briefly, following a stabilization period, baseline values of MAP, HR, RAP and CBF were recorded. Dose–response curves to NA, PE, ME and Ang II were generated by injecting graded doses of these agonists into the renal artery (*NA*: 25, 50, 100, 200 ng; *PE*: 0.25, 0.50, 1, 2 μg; *ME*: 0.5, 1, 2, 4 μg; *Ang II*: 2.5, 5, 10, 20 ng) and assessing the renal cortical blood flow responses to each dose in the presence and absence of 5-methylurapidil (5-MU).

In the first phase (pre-drug), the rats received vehicle (normal saline, NaCl 9 g/L) at 6 mL/kg/h along with the adrenergic agonists and Ang II into the renal artery. In the second phase (low-dose 5-MU), a low bolus dose of 5-MU (5 μg/kg) was injected slowly over 30 s followed by a continuous infusion of 5-MU (1.25 μg/kg/h) into the renal artery line, and 15 min later, the second set of renal vasoconstrictor responses to NA, PE, ME and Ang II was performed. In the third and last phase (high-dose 5-MU), a high bolus dose of 5-MU (10 μg/kg) was injected slowly over 30 s followed by a continuous infusion of 5-MU (2.5 μg/kg/h). Upon reaching the steady state, 15 min later, the same procedure used in the first and second phases was repeated. The delivery of agonists was carried out in ascending followed by descending order of doses. The doses of agonist and antagonist (Table 1) were adapted from previous studies from this laboratory [23–25] and aimed to produce a local action without any significant effect on the systemic blood pressure. All drugs were prepared as stock solutions in saline on the day of experiment and stored at +4 °C.

Chemicals used

NA (Levophed®, Sanofi Winthrop, London, England) is a mixed agonist that acts on both the α_1 and α_2-adrenoceptors, PE (Phenylephrine, Knoll, Nottingham, UK) is a non-selective agonist of α_1-adrenoceptors with an ability to activate α_{1A}-, α_{1B}- and α_{1D}-adrenoceptor subtypes [22], Ang II (Hypertensin®, CIBA-GEIGY, Basel, Switzerland) and ME (Vasoxine®, Calmic Medical Division, Bristol, England) is a relatively selective α_{1A}-adrenoceptor-subtype agonist [26, 27]. 5-Methylurapidil (Research Biochemicals International, Natick, MA, USA) is a selective antagonist for the α_{1A}-adrenoceptor subtype [28]. Sodium chloride and fructose were obtained in pure powdered form from Sigma.

Statistical analysis

The maximum response in CBF following injection of Ang II and adrenergic agonists was calculated as the difference between the baseline value immediately prior to agonist administration and the maximum decrease in CBF and performed offline using the software (LabChart 6, ADInstruments, Sydney, Australia). The vasoconstrictor responses caused by Ang II and adrenergic agonists were taken as the average values caused by each dose of agonist administered in ascending and descending orders. The mean values for every phase (Figs. 1 and 2) are the overall mean calculated for all doses of each agonist and compared between high- and low-dose antagonist phases, and pre-drug phase. All data are expressed as mean ± SEM. The statistical analysis of the vasoconstriction responses data utilized two-way ANOVA followed by a Bonferroni *post hoc* test using the statistical package Super ANOVA (Abacus In. CA, USA). The analysis of the differences in the functional and metabolic parameters between C and FFR (Table 2) was performed by the Student's unpaired *t*-test while the differences in baseline haemodynamic parameters between the three phases of acute vasoconstrictor experiment (Table 3) were analysed using one-way ANOVA followed by Bonferroni *post hoc* test and the Student's unpaired *t*-test for the differences between C and FFR. The differences between the means were considered significant at the 5% level.

Table 1 Acute renal vasoconstrictor study protocol

Experimental group	Antagonist	Phase 1 (Pre-drug)	Phase 2 (Low-dose)		Phase 3 (High-dose)	
		Continuous	Bolus (μg/kg)	Continuous (μg/kg/h)	Bolus (μg/kg)	Continuous (μg/kg/h)
C	5-MU	Saline	5	1.25	10	2.5
FFR	5-MU	Saline	5	1.25	10	2.5

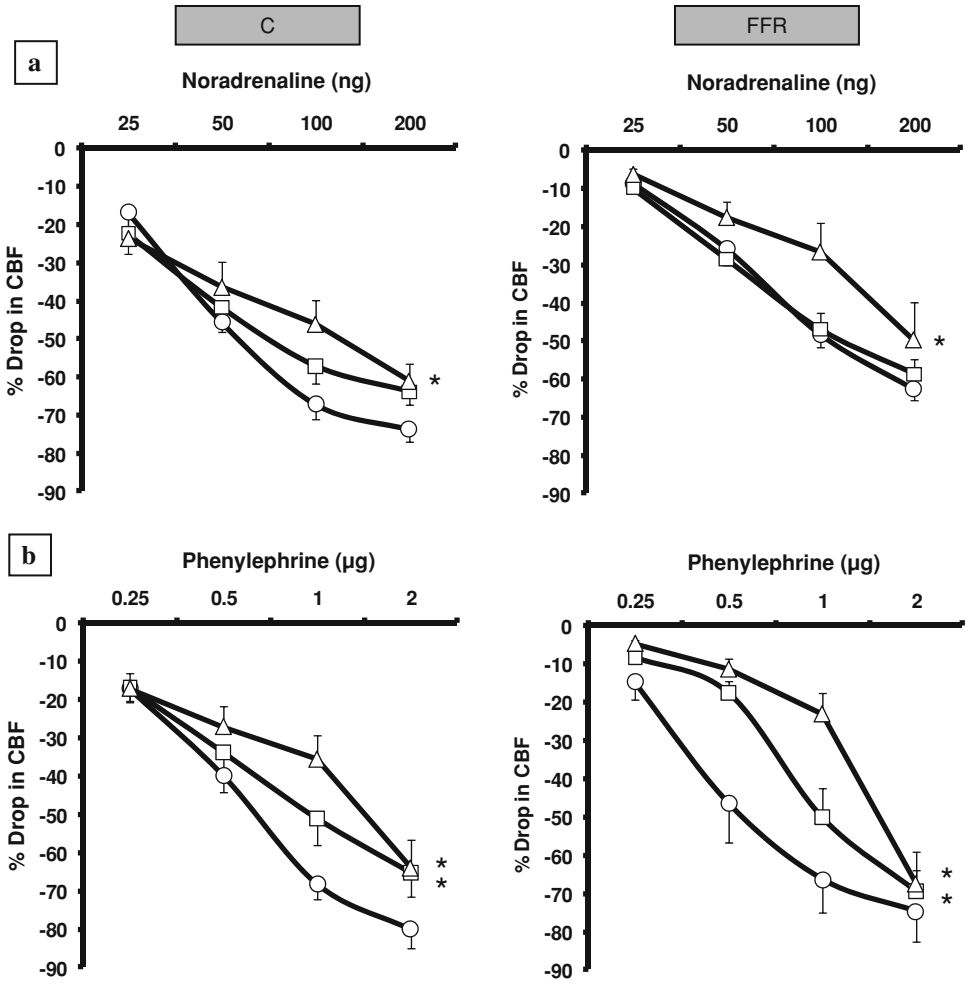

Fig. 1 Line graph shows dose–response curve of the renal vasoconstrictor responses to graded doses of NA (**a**) and PE (**b**) in control (*C*) and fructose-fed rats (*FFR*) during pre-drug phase (*circle*), low-dose 5-MU (*square*) and high-dose 5-MU (*triangle*). Values are mean ± SEM of $n = 6$ rats in each group. The significance is between the overall mean of responses due to 4 doses of agonist during each phase and compared to pre-drug phase. *$P < 0.05$ vs. pre-drug phase

Results

General observations

At the end of the 8 weeks feeding period, FFR had a higher body weight, lower food intake, unchanged fluid intake and urine output, and a lower fractional excretion of sodium ($P < 0.05$) compared to C. In addition, the fasting plasma insulin and glucose levels and the HOMA index of FFR were significantly ($P < 0.05$) higher than C. The plasma Ang II level in FFR at the end of the feeding period was higher ($P < 0.05$) than C (Table 2).

Basal haemodynamic parameters

Baseline values of MAP were significantly higher by about 17% ($P < 0.05$) in FFR as compared to that of the control rats (Table 3). Basal values of CBF, RAP and HR were similar in both experimental groups (Table 3). Moreover, the administration of the adrenoceptor antagonist had no effect on CBF or RAP in any of the C or FFR groups at either dose. MAP in FFR was significantly ($P < 0.05$) reduced after infusion of a low dose of 5-MU, while HR in both groups decreased significantly ($P < 0.05$) following the infusion of either a low or a high dose of 5-MU (Table 3).

Renal cortical vasoconstrictor responses

Adrenergic agonists

The exogenous administration of NA, PE and ME caused dose-dependent renal cortical vasoconstrictions in the pre-drug phase of both C and FFR groups (Figs. 1, 2). The vasoconstrictions induced by NA, PE and ME were decreased (all $P < 0.05$) by the low dose of 5-MU but to a greater extent (all $P < 0.05$) by the high dose of 5-MU in C rats relative to their corresponding pre-drug phase (Figs. 1, 2a). In the FFR, the NA-, PE- and ME-induced renal

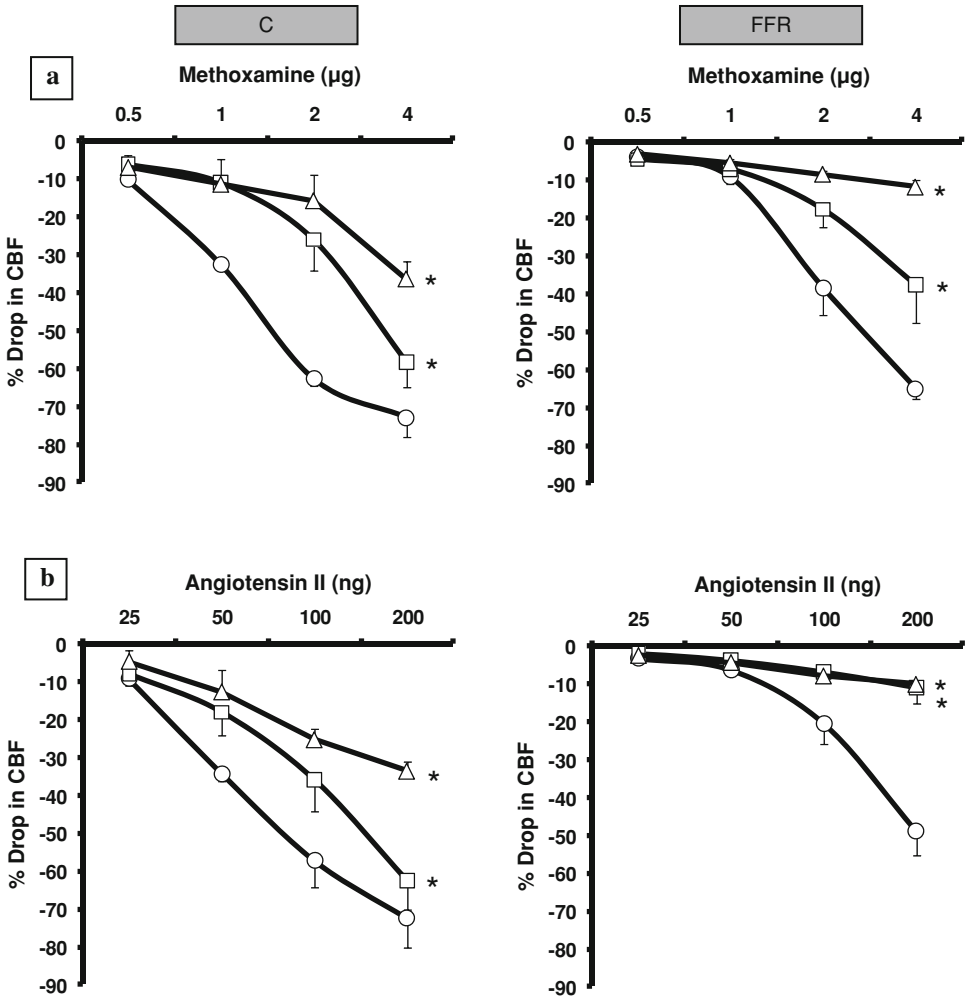

Fig. 2 Line graph shows dose–response curve of the renal vasoconstrictor responses to graded doses of ME (**a**) and Ang II (**b**) in control (*C*) and fructose-fed rats (*FFR*) during pre-drug phase (*circle*), low-dose 5-MU (*square*) and high-dose 5-MU (*triangle*). Values are mean ± SEM of $n = 6$ rats in each group. The significance is between the overall mean of responses due to 4 doses of agonist during each phase and compared to pre-drug phase. * $P < 0.05$ vs. pre-drug phase

Table 2 Effect of 8 weeks of fructose feeding on body weight, fluid and food intake, urine output, fractional excretion of sodium, fasting plasma glucose and insulin, HOMA index and plasma Ang II level

Parameters	Experimental group	
	C ($n = 6$)	FFR ($n = 6$)
Body weight (g)	273 ± 5	314 ± 3*
Fluid intake (mL/24 h)	44.5 ± 1.5	48.0 ± 4.4
Food intake (g/24 h)	17.6 ± 0.5	14.9 ± 0.6*
Urine output (mL/24 h)	14.4 ± 1.4	10.6 ± 2.6
Fractional excretion of sodium (%)	0.84 ± 0.16	0.26 ± 0.03*
Fasting plasma insulin (ng/mL)	1.93 ± 0.10	4.55 ± 1.13*
Fasting plasma glucose (mmol/L)	4.70 ± 0.31	6.80 ± 0.28*
HOMA index	9.87 ± 0.57	33.72 ± 2.62*
Plasma Ang II (pg/mL)	303.7 ± 11.2	509.6 ± 55.4*

Values are mean ± SEM, * $P < 0.05$ between FFR and C (Student's unpaired *t*-test)

vasoconstrictions were also attenuated significantly (all $P < 0.05$) by the high dose of 5-MU (Figs. 1, 2a). The low dose of 5-MU in the FFR resulted in no significant change in the magnitude of the renal cortical vasoconstriction response to NA, but caused smaller ($P < 0.05$) responses to PE and ME compared to the pre-drug phase (Figs. 1, 2a). The renal vasoconstrictions in response to NA and ME but not to PE in the pre-drug phase of FFR were significantly smaller than C (Fig. 3). Moreover, the magnitude of the 5-MU attenuation of the renal cortical vasoconstriction due to NA and ME in FFR was significantly higher than C (Fig. 3).

Angiotensin II

Exogenous Ang II produced dose-related decreases in cortical blood flow in the pre-drug phase of both C and FFR (Fig. 2b). Further, in the presence of the low and high doses of 5-MU in both FFR and C groups, the renal cortical vasoconstriction due to Ang II was smaller ($P < 0.05$) compared to the pre-drug phase (Fig. 2b). The renal vasoconstriction in response to Ang II in the pre-drug phase of FFR was significantly smaller than C (Fig. 3). In addition, the magnitude of the low- or high-dose 5-MU

Table 3 Baseline haemodynamic parameters measured during the acute renal vasoconstrictor experiment

Parameters	Experimental group	*n*	Saline (Pre-drug Phase)	5-MU (Low-dose Phase)	5-MU (High-dose Phase)
MAP (mmHg)	*C*	6	110 ± 4	102 ± 2	93 ± 4
	FFR	6	129 ± 4$^{\#}$	113 ± 4*	119 ± 5
HR (bpm)	*C*	6	300 ± 14	247 ± 15*	222 ± 7*
	FFR	6	309 ± 4	214 ± 1*	206 ± 19*
RAP (mmHg)	*C*	6	112 ± 4	111 ± 12	119 ± 29
	FFR	6	122 ± 4	111 ± 5	111 ± 5
CBF (bpu/min)	*C*	6	204 ± 19	159 ± 23	156 ± 18
	FFR	6	189 ± 9	163 ± 16	184 ± 11

Values are mean ± SEM, * $P < 0.05$ vs. pre-drug phase, $^{\#}$ $P < 0.05$ between FFR and C pre-drug phases

MAP mean arterial blood pressure, *HR* heart rate, *CBF* cortical blood flow, *RAP* renal arterial pressure, *bpm* beat per minute, *bpu* blood perfusion unit

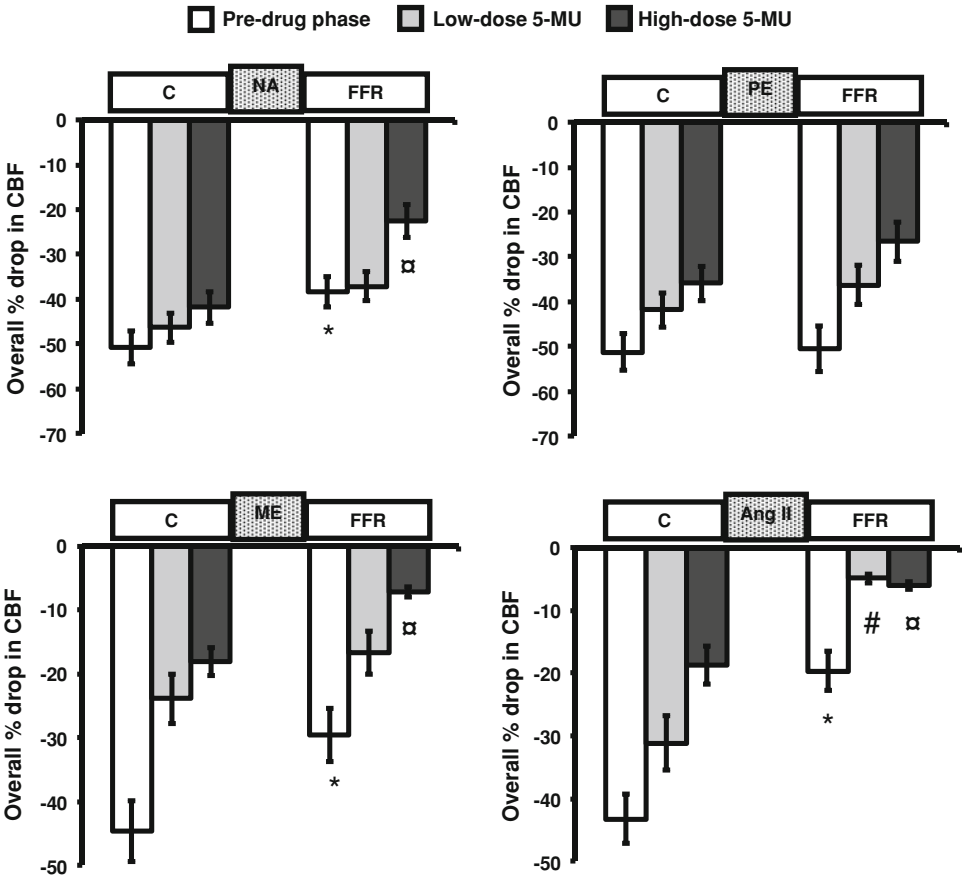

Fig. 3 Bar graph shows the overall % drop in the renal cortical blood flow in response to NA, PE, ME and Ang II in control (C) and fructose-fed rats (FFR) during pre-drug phase, low- and high-dose 5-MU. The overall mean is the mean of all responses due to 4 doses of each agonist during each phase. Values are mean ± SEM of $n = 6$ rats in each group. *$P < 0.05$ between pre-drug phases of C and FFR, $^{\#}P < 0.05$ between low-dose 5-MU phases of C and FFR, ¤$P < 0.05$ between high-dose 5-MU phases of C and FFR

attenuation of the renal cortical vasoconstriction due to Ang II in FFR was significantly higher than C (Fig. 3).

Discussion

The aim of the present study was to investigate whether any change in α_1-adrenoceptor subtype functionality occurred when insulin resistance was induced by 8 weeks of high fructose feeding with more concentration being on the functional contribution of α_{1A}-adrenoceptor subtype. Interestingly, high fructose intake resulted in a decrease in the renal vascular responsiveness to exogenously administered Ang II and α_1-adrenergic agonists, which was also reported in a previous study from this laboratory [16]. In relation to this, fructose feeding not only causes

hyperinsulinaemia [3], elevated blood pressure [5] and weight gain [29] but has also been reported to result in an activation of the sympathetic [30] and renin-angiotensin systems [31], impairment of endothelial function [32] in addition to a decreased contractile response to α-adrenoceptor agonists [17]. The decrease in vascular sensitivity to adrenergic agonists may have resulted as a compensatory mechanism that follows the enhancement of the activity of the sympathetic nervous system that will cause downregulation or desensitization of receptors [33, 34]. The three subtypes of α_1-adrenoceptors, α_{1A}-, α_{1B}- and α_{1D}-, have been shown to present in the kidney [11, 35, 36] with the α_{1A}-adrenoceptor subtype being reported as the predominant subtype in rat renal resistance vessels [37, 38], with smaller densities of α_{1B}- and α_{1D}-adrenoceptors [39]. Moreover, adrenergically induced renal vasoconstriction in normotensive and spontaneously hypertensive rats was found to be mediated by α_{1A}-adrenoceptors [14, 23, 40] although the functional contribution of the different α_1-adrenoceptor subtypes can vary in different pathophysiological states [8, 41, 42]. As discussed above, although there are a number of studies that have reported the functional contribution of α_1-adrenoceptor subtype in the rat renal vasculature, there is scarcity of information in metabolic syndrome model of rat fed with fructose. Interestingly, α_{1B}-adrenoceptors have been shown to make a smaller contribution to renal vascular tone in fructose-fed rats for 8 weeks [16].

At the end of 8 weeks of fructose administration, as used in this study, rats had an increased body weight and blood pressure which was in agreement with previous reports [3, 43]. Despite a report that showed that fructose feeding for 6 weeks did not cause any significant change in sodium, potassium or urine excretion [44], long-term feeding of high fructose in the present study resulted in a lower fractional excretion of sodium, which reflects a sodium retention that has also been reported in 3-week fructose-fed rat [45]. The finding that fructose feeding results in a reduction in sodium excretion has usually been linked to high blood pressure in this model [46], and it has been suggested that this significant antinatriuretic effect is due, in part, to the hyperinsulinaemia [45, 47, 48]. In addition, as fructose-induced hypertension is reported to be Ang II dependent [49], it is therefore possible that the sodium retention associated with hyperinsulinaemia in this model could be due, in part, to the action of Ang II [45]. The higher plasma insulin and Ang II levels in fructose-fed group compared to control in this study support this notion. Moreover, the daily urine excretion was lower, although not statistically significant, in fructose-fed rats compared to control at the end of treatment period which is indicative of disturbed water and electrolyte balance brought about by fructose feeding.

Basal CBF in the anaesthetized fructose-fed rats was not significantly different from control, yet the renal vasoconstrictor responses were almost always smaller compared with control rats (Figs. 1, 2, 3). The attenuation of the responses to Ang II and adrenergic agonists possibly resulted from higher circulating levels of Ang II and NA in fructose-fed rats [49, 50]. Interestingly, the eight-week FFR in this study exhibited higher plasma level of Ang II compared to C. It was observed that the α_{1A}-adrenoceptors antagonist had no effect on basal CBF in either fructose-fed rats or control; however, systemic blood pressure did fall during the course of the experiment, but this was unlikely due to the antagonist as the same pattern was observed in the time control study. The renal vasoconstrictor responses elicited by exogenously administered adrenergic agonists in fructose-fed rats and control were attenuated in the presence of 5-methylurapidil, but were not completely blocked by this antagonist. This would be suggestive of a contribution from multiple α_1-adrenoceptor subtypes. The observations were consistent with the involvement of both α_{1A}- and α_{1D}-adrenoceptor subtypes, which would be compatible with several earlier studies reporting the presence of multiple α_1-adrenoceptor subtypes in the renal vasculature [13, 22]. In the fructose-fed rats, 5-methylurapidil attenuated the adrenergically induced renal vasoconstrictor responses to a greater extent compared to the control rats, which would indicate the α_{1A}-adrenoceptor subtype being a functional receptor. We had shown previously that the α_{1B}-adrenoceptor subtype was contributing to the renal cortical vasoconstriction in control but not in fructose-fed Sprague–Dawley rats [16].

The renal cortical vasoconstriction to Ang II in the present study was significantly blunted following the administration of 5-methylurapidil in both control and fructose-fed rats. It has been suggested that α_1-adrenoceptors contribute to vascular response of Ang II [24, 51]. Interaction at both cellular and molecular levels between the AT_1 and α-adrenoceptors has been suggested due to the initiation of common signalling pathways by both receptors. Several in vivo studies from this laboratory and others have indicated that blocking of α_1-adrenoceptors attenuates renal vascular response to Ang II in rat and rabbit [24, 52, 53]. Moreover, long-term activation of α_1-adrenoceptors results in the downregulation of AT_1-receptors [54]. Thus, the possibility arises that there is a cross-talk relationship between AT_1-receptors and α_{1A}-adrenoceptors subtype, which may play an important role in mediating the renal vascular responses in fructose-fed rat.

In conclusion, the hypothesis was examined whether fructose feeding altered the contribution of the α_1-adrenoceptor subtypes in mediating adrenergically induced renal vasoconstrictions. Interestingly, fructose intake for 8 weeks blunted the renal vascular response to adrenergic

agonists and Ang II, but raised the contribution of α_{1A}-adrenoceptor subtype in mediating adrenergically induced vasoconstriction. We have shown previously that α_{1B}-adrenoceptors have lower contribution to renal vascular tone in fructose-fed rats [16]. The current study also reveals an important interaction between α_{1A}-adrenoceptor subtype and AT_1 receptors in the renal vasculature of fructose-fed rat. In this regard, blocking α_{1A}-adrenoceptor attenuates the AT_1 receptors sensitivity to Ang II.

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