Effect of pioglitazone on vasopressor responses to adrenergic agonists and angiotensin II in diabetic and non-diabetic spontaneously hypertensive rats

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Abstract: Pioglitazone, peroxisome proliferator-activated receptor (PPAR-γ) agonist, is a therapeutic drug for diabetes. Present study investigated the interaction between PPAR-γ and alpha adrenoceptors in modulating vasopressor responses to Angiotensin II (Ang II) and adrenergic agonists, in diabetic & non-diabetic Spontaneously Hypertensive Rats (SHRs). Diabetes was induced with an i.p injection of streptozotocin (40 mg/kg) in two groups (STZ-CON, STZ-PIO), whereas two groups remained non diabetic (ND-CO, ND-PIO). One diabetic and non-diabetic group received Pioglitazone (10mg/kg) orally for 21 days. On day 28, the animals were anaesthetized with sodium pentobarbitone (60mg/kg) and prepared for measurement of systemic haemodynamics. Basal mean arterial pressure of STZ-CON was higher than ND-CON, whereas following pioglitazone treatment, MAP was lower compared to respective controls. MAP responses to i.v administration of NA, PE, ME and ANG II were significantly lower in diabetic SHRs: STZ-CON vs ND-CON (35%). Pioglitazone significantly decreased responses to NA, PE, ME and ANG II in ND-PIO versus ND-CON by 63%. Responses to NA and ANG II were significantly attenuated in STZ-PIO vs. ND-PIO (40%). PPAR-γ regulates systemic hemodynamic in diabetic model and cross-talk relationship exists between PPAR-γ and α1-adrenoceptors, ANG II in systemic vasculature of SHRs.

Keywords: Diabetes, Spontaneously hypertensive rats, Pioglitazone, PPAR-γ, Angiotensin II, Adiponectin

INTRODUCTION

Hypertension and type 2 diabetes commonly go together with each other by; therefore, hypertensive individuals receive treatment of antihypertensive and antidiabetic drugs in combination. Thiazolidinediones, (TZDs), are hypoglycemic agents which act by attaching and triggering nuclear peroxisome proliferators-activated receptors-ã (PPAR-ã) and result in an enhanced insulin sensitivity and rise in peripheral glucose utilization (OVALLE and OVALLE-BERÚMEN 2002), through enhanced adiponectin levels, increased AMPK activation and lessening gluconeogenesis in liver, thus ameliorates insulin resistance (Kadowaki, Yamauchi *et al.,* 2006).

Pioglitazone, is a TZDs derivative and acts as ligand for PPAR-γ (Yki-Järvinen 2004) and is used therapeutically to improve insulin resistance through activation of PPAR-ã receptor in adipose tissue, thus results in increased number of small adipocytes which are responsive to insulin (Evans, Barish *et al.,* 2004). Elevated blood glucose levels and high blood pressure can damage vascular endothelial cells, resulting in increased oxidative stress, which may account for the increased vascular reactivity in diabetic patients (Lago, Singh *et al.,* 2007). Interestingly, endothelial dysfunction is also associated with atherosclerotic progression (Siasos, Tousoulis *et al.* 2009), which is increased in oxidative stress and occurs with diabetes and its complications. Diabetes can precipitate hypertension by activating sympathetic nervous system and rennin angiotensin aldosterone system, both of which promote sodium retention. Thus TZDs have the potential of modulating blood pressure by causing reduction in sympathetic over activity, improving endothelial function, or decreasing in intracellular Ca^{2+} content of vascular smooth muscle cells (Sarafidis and Lasaridis 2006). The antihypertensive effect of pioglitazone has also been ascribed to reduction in vascular sensitivity to Ang II together with endothelial dys-function (El-Mas, El-Gowelli *et al.,* 2011), through increased adiponectin levels which stimulates the production of nitric oxide (Wang and Scherer 2008). In addition, the cross talk between adrenergic neurotransmission and Ang II in rats has been shown to play vital role in determining the tone of vasculature in pathological states. Moreover, there is proof for interaction between α1-adrenergic receptors and Ang II receptors in vasculature of SHRs (Abdulla, Sattar *et al.,* 2009).

Consequently TZDs cause an increase in plasma adiponectin (ADN) levels by increasing glucose

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clearancein skeletal muscle by restraining gluconeogenesis in the liver, and improve insulin sensitivity *(Kubota, Terauchi et al.,* 2006). It is noteworthy that adiponectin also impacts on oxidative stress, thus, having anti-arteriosclerotic and anti-diabetic activity (Nakanishi, Yamane *et al.,* 2005). Therefore, treatment with a PPARγ- ligand is useful for insulin-resistant patients with vascular disorders and hypertension (Takatori, Zamami *et al.,* 2013).

However, it is not known whether the interaction between vascular α1-adrenergic, AT-1 receptors and Ppar-γ can modulate vasomotor function in STZ-induced diabetes in SHRs. With this background, we hypothesized that there is an interaction/cross talk exists between Ppar-γ and alpha-adrenoceptors subtypes in non-diabetic and diabetic model of SHR in regulation of systemic haemodynamics. Accordingly, present study was undertaken to address the issue of whether vasopressor responses to intravenous administration of adrenergic agonists and Ang II in diabetic rats receiving pioglitazone pre-treatment would modify in any way.

MATERIALS AND METHODS

Animals

Twenty four spontaneously hypertensive rats (SHR) (230-255g) body weight were housed in stainless metabolic cages for 3 days to acclimatize to the environment Commercial rat chow (Gold Coin Sdn. Bhd., Penang, Malaysia) and tap water were provided ad-libitum to the experimental animals. All procedures and animal handling were carried out in accordance with guidelines of Animal Ethics Committee, University Sains Malaysia, Malaysia. The animals were randomly divided into 4 groups (n=6)

Drugs

1. Pioglitazone, (±)-5[4[2(5-ethyl-2-pyridyl) ethoxy] benzyl]-thiazolidine-2,4-dione monohydrochloride), used as an antidiabetic drug, purchased from Searle, Pvt, Ltd., Pakistan
2. Streptozotocin (STZ), was used for induction of diabetes, purchased from Nova Laboratories, Sdn, Bhd., Selangor, Malaysia.

Adrenergic agonists

Noradrenaline, which acts on α1 and α2-adrenoceptors; whereas phenylephrine also acts on α1-adrenoceptors selectively to activate α1A-, α1B- and α1D-adrenoceptor subtypes and methoxamine is an only choosy for α1A adrenoceptors-subtype (Armenia, Munavvar *et al.,* 2004). All the agonists wee freshly prepared in saline before use for the experiment. Angiotensin II (ANG II) produces vasoconstriction due to binding to AT1 receptors.

Experimental protocol and streptozotocin, pioglitazone pre-treatment

Type 1 diabetes was induced using a single intra-peritoneal injection (I/P) of (STZ) (Nova Laboratories, Sdn, Bhd, Malaysia), 40mg/kg body weight, dissolved in citrate buffer (10mM, pH 4.5) (Ramesh and Pugalendi 2006). The injected rats were given glucose (5%) in drinking water for the first 48 hours after injection to offset the early hypoglycemic shock. Blood glucose levels were evaluated using a standard Glucometer (Free Style, Abbott, Malaysia) on day 7 of post-streptozotocin injection (between 9:00-9:30) and rats with glucose levels >300mg/dL at the 8th day were selected for the experiment. (Glucometer Free Style, Aabbott, Malaysia). Blood pressure of experimental rats was observed using the tail cuff method and rats with systolic blood pressure only higher than 150mmHg were selected and randomized into groups and used for the study. Diabetic and non-diabetic SHRs were divided as non-diabetic control (n=6, ND-CON), diabetic control (n=6, STZ-CON), non-diabetic with pioglitazone treatment (n=6, ND-PIO) and diabetic SHR with pioglitazone treatment (n=6, STZ-PIO) respectively. 10mg/kg/day pioglitazone was administered orally in treatment groups for 21 days. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) of all groups were measured, non invasively with tail-cuff plethysmography (NIBP Controller, AD Instruments, Sydney, Australia), along with their body weights on day 0, 8 and 29. Serum levels of adiponectin were measured on the acute surgery day (29) using an ELISA, (Chemtron Biotechnology Sdn, Bhd.) according to the manufacturer's protocol. To observe the effect of pioglitazone on altered vascular responsiveness in diabetic state in vivo, the vasopressor responses to vasoactive agents were examined in all the experimental groups. Sodium pentobarbitone was used with an overdose to sacrifice the animals at the termination of the experimental study.

Acute haemodynamics study

Overnight (≤12h) fasted (with water) rats were anaesthetized with 60mg/kg i.p. sodium pentobarbitone (Nembutal®, CEVA, Libourne, France). The trachea was exposed through a mid-line incision and cannulated (PP240, Protex, Kent, UK), whereas PE50 was used to cannulate the carotid artery and then connected to pressure transducer (P23 ID Gould, Statham Instruments, UK) coupled to a computerized data acquisition system (PowerLab®, ADInstruments, Sydney, Australia) for blood pressure measurement. Similarly left jugular vein was cannulated (PE50, Portex, Kent, UK) for infusion of doses of anaesthesia and vasopressor agonists for experiment (Perfusor secura FT 50ml, B. Braun) (Khan, Sattar *et al.,* 2014). Following an hour of stabilization, baseline systemic haemodynamics values were acquired, which comprised SBP, DBP, MAP and PP (Pulse pressure). The acute vasopressor responses to i.v administration of noradrenaline (NA; 200, 400 and 800 ng), phenylephrine (PE; 2, 4 and 8 μg), methoxamine (ME; 2, 4 and 8μg) and angiotensin II (Ang II; 5, 10 and 20ng) were recorded. The vasoactive agonists wereadministered intravenously in descending and

Table 1: Physiological and biochemical parameters in diabetic and non-diabetic, SHR control and Pioglitazone treated groups before treatment (initial) and after 3 weeks of treatment (final)

Groups	ND-CON	STZ-CON	ND-PIO	STZ-PIO
Blood glucose level (mg/dl)				
Initial	102±10	489±25a	86±05	505±17A
Final	94±07	508±19A	65±08b	470±20a
Body weight (g)				
Initial	212±11	211±08	231±09	202±14
Final	251±12	222±10	241±12	209±13

Values are expressed as Mean ±SEM.
a $p<0.05$, compared to ND-CON group.
b $p<0.05$, compared to STZ-CON group

Table 2: Baseline systemic haemodynamics values

Group	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	PP (mmHg)	HR (bpm)
ND-CON	136±3	100±3	112±3	28±2	321±7
STZ-CON	158±5*	118±5	131±5*	30±1	348±17
ND-PIO	117±7ρ	88±7 ρ	99±7 ρ	28±1	302±15
STZ-PIO	113±12#	86±14#	113±13#	27±3	308±19

Baseline systemic haemodynamics values measured during the acute vasopressor response experiment in ND-CONC, STZ-CON, ND-PIO and STZ-PIO SHRs. Values are mean ± SEM of n = 6 rats in each group. *, ρ Indicates $p<0.05$ vs. ND-CON, # indicates $p<0.05$ vs. STZ-CON. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; PP, pulse pressure; HR, heart rate; bpm, beat per minute

ascending order through left jugular vein to get dual response of
each agonist. A washout period of 15min was allowed between each agonist. The baseline blood pressure values were determined from the values at the beginning of each response.

STATISTICAL ANALYSIS

Average MAP values from basal to peak value caused by each dose of adrenergic agonists and Ang II were considered as vasopressor response. The overall mean response in MAP for each dose was taken as the average value of the vasopressor responses obtained at that dose. All data presented in this study are expressed as Mean ± SEM of vasopressor responses elicited by all doses of each agonist and comparisons were made between the treated and respective control groups. Data were compared using one-way ANOVA followed by Bonferroni *post- hoc* test using Superanova stat (Abacus In., CA, USA). Difference of 5% was considered significant between the mean values.

RESULTS

Physiological and biochemical indices

All STZ injected animals developed diabetes. There was no difference in blood glucose levels of non-diabetic control and pioglitazone treated groups, whereas blood glucose level in STZ treated SHRs was significantly higher ($p<0.05$). Treatment with pioglitazone did not cause an effect on blood glucose level of STZ-diabetic rats. There was a modest increase in body weight of ND-CON and STZ-CON groups. There was no significant effect on body weight of STZ-diabetic rats treated with pioglitazone, but upressed weight gain in ND-PIO group as shown in table 1.

Baseline systemic haemodynamics

Non-invasive techniques for the monitoring of conscious rat B.P were used in our study to measure the SBP, DBP and MAP respectively as shown in fig. 1. We observed significant ($p<0.05$) increase in SBP (142±11, mmHg), DBP (104±10, mmHg) and mean blood pressure (117±10, mmHg) in diabetic control group as compared to non-diabetic control groups. The treatment with pioglitazone (10mg/kg/day) for 21 days significantly decrease SBP (124±9, mmHg), DBP (94±9, mmHg) and mean blood pressure (107±9, mmHg) of the diabetic pioglitazone treated group in comparison to diabetic control group. At terminal part of our study significant decrease in SBP, DBP and mean blood pressure of non-diabetic pioglitazone group was observed, whereas heart rate decreased significantly with pioglitazone in the STZ-PIO SHRs ($P\leq0.05$). The baseline values of SBP, DBP, PP and MAP in pioglitazone treated SHRs were lower (all $p<0.05$) than ND-CON. Non-diabetic pioglitazone group had significantly ($p<0.05$) lower values of SBP and MAP versus diabetic control group as shown in table 2.

Vasopressor responses

The responses of the systemic vasculature were due to the vasopressor effect of the agonists administered during the

experiment. The intravenous injection of saline in the same volume with the one used for the agonist dose had no effect on the systemic blood pressure.

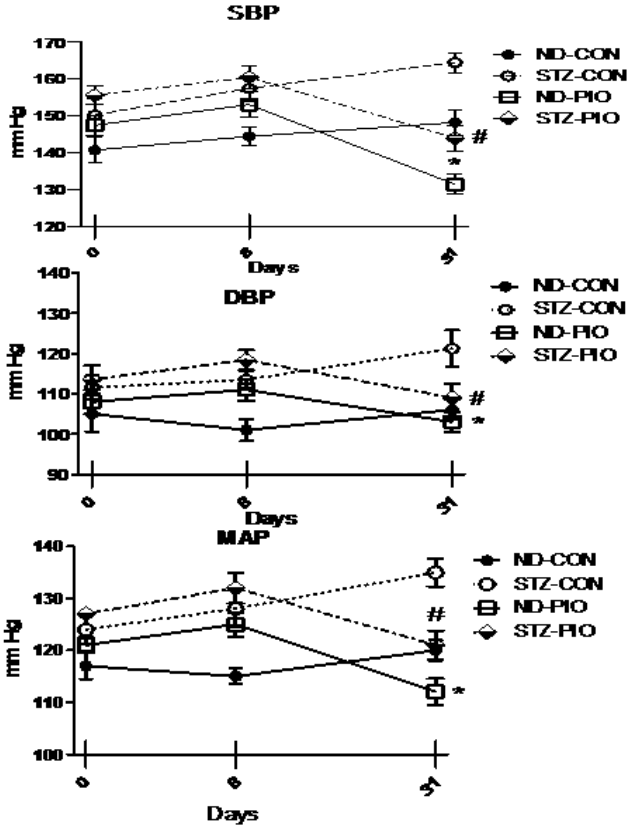

Fig. 1: Effect of pioglitazone treatment for 3 weeks on systolic, diastolic and mean blood pressure of conscious ND-CON, STZ-CON, ND-PIO and STZ-PIO groups (n=6), Values are expressed as mean ± SEM.*, #P<0.05, compared to STZ-CON

Alpha-adrenergic agonists

Noradrenaline (NA)

Dose-dependent increases in MAP were observed in all groups after exogenous administration of NAas shown in fig. 2. The overall mean percentage values for the responses elicited in the peripheral vasculature to all doses of NA in STZ-CON were significantly larger (all p<0.05) versus ND-CON (63±2% vs 52±2%), whereas pioglitazone treatment significantly blunted responses in non-diabetic and diabetic pioglitazone treated groups (35±2% vs 43±3%), as shown in fig. 3.

Phenylephrine (PE)

Phenylephrine also caused the same pattern of result as noradrenaline. It resulted in a dose-related vasopressor response in experimental groups(ND-CON; 84±3, STZ-CON; 86±3. The overall mean values for the changes in MAP produced by all doses of PE in the control rats were significantly blunted after pioglitazone treatment, ND-PIO:52±2 vs STZ-PIO: 50±3 as shown in fig. 3.

Methoxamine (ME)

As shown in fig. 2, ME was observed to cause peripheral vasoconstriction observed in dose-dependent manner in experimental groups. The overall mean percentage increase in MAP caused by all doses of ME in control rats were ND-CON; 65±5 vs. STZ-CON 65±5, whereas after treatment with pioglitazone the responses were as ND-PIO:23±1 vs. STZ-PIO: 26±3 as shown in fig. 3.

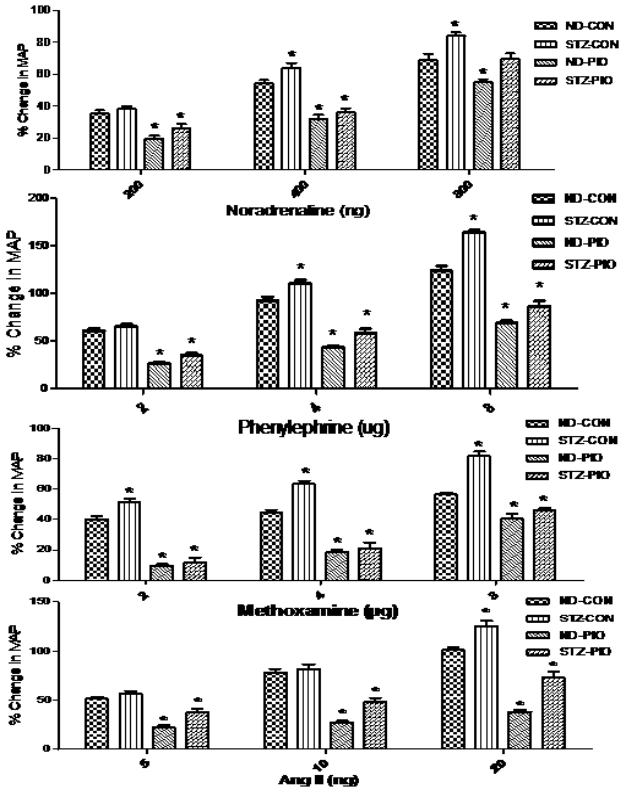

Fig. 2: Vasopressor response (expressed as (%) increase in MAP) to graded doses of NA, PE, ME and ANG II in control (ND-CON), (STZ-CON), and pioglitazone treated (ND-PIO, STZ-PIO) SHR. Data presented as mean ±SEM (n = 6). *indicates p<0.05 vs. control (SHR)

Angiotensin II (Ang II)

Ang II also caused similar pattern of results as alpha adrenergic agonists. It caused dose- related vasoconstriction in non-diabetic and diabetic control and pioglitazone treated groups as shown in fig. 2. The mean values for the increase in MAP produced by all doses of Ang II in the groups were as ND-CON; 77±1, STZ-CON 88±1, ND-PIO 30±1 and STZ-PIO 46±4 as shown in fig. 3.

Hormone measurement

Plasma adiponectin was significantly higher in ND-PIO and STZ-PIO (ND-PIO: 65.3±5, 54.6ng/ml) than in the placebo-treated groups. We observed that there was a significant difference between the plasma adiponectin levels observed in ND-CON vs STZ-CON (20.8±3 vs 9.89±4 ng/ml as shown in fig. 4. 10mg/kg pioglitazone

also significantly increased plasma adiponectin levels in the STZ-PIO, however the magnitude of the increase adiponectin levels in ND-PIO was significantly higher as compared to STZ-PIO SHR group.

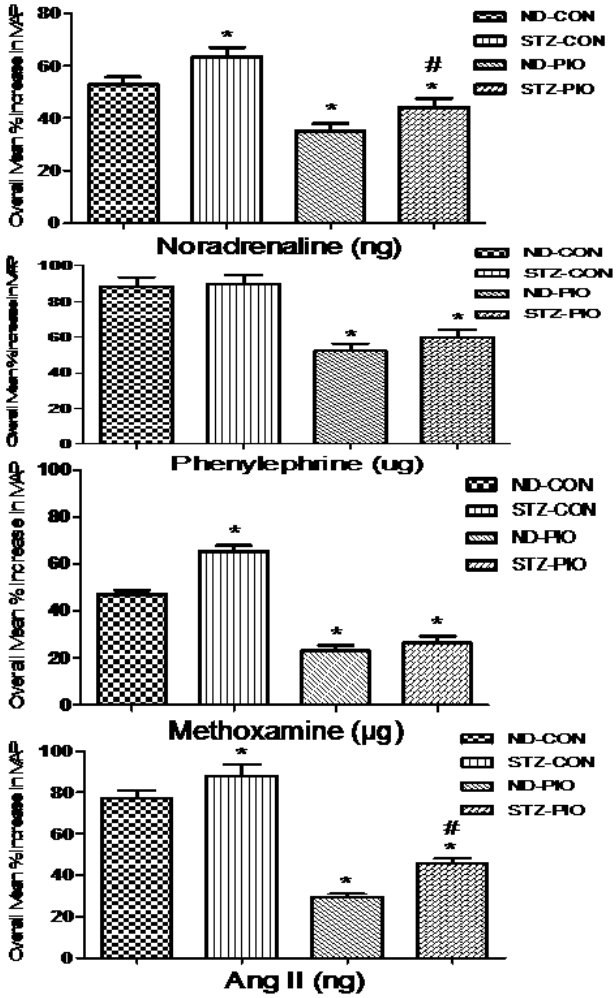

Fig. 3: The overall vasopressor response to adrenergic agonists and Ang II. Bar graph shows the overall vasopressor response to NA, PE, ME, ANG II in the systemic vasculature of control ND-CON, STZ-CON, ND-PIO, STZ-PIO, Values are mean ±SEM of n = 6 rats in each group. *p<0.05 vs. ND-CON, #p<0.05 between ND-PIO and STZ-PIO

DISCUSSION

PPAR-γ agonist, pioglitazone, attenuated the development of hypertension and reduced the vascular reactivity of blood vessels to alpha adrenoceptors and angiotensin II administration, in the diabetic model of SHR. Adiponectin contributes to the antihypertensive activity of pioglitazone as the activation of PPAR-γ agonist has the potential for the treatment of endothelial dysfunction related to diabetes. Therefore, current study reveals that an interaction/cross talk exists between PPAR-γ agonist, pioglitazone, postsynaptic alpha adrenoceptor subtypes and ANG II in systemic vasculature of non-diabetic and diabetic model of SHR.

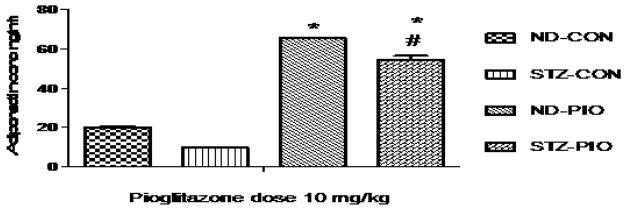

Fig. 4: Adiponectin concentration expressed as ng/ml values mean±SEM (n=6) rats with (p<0.05) = significant, data analyzed by one-way ANOVA followed by Bonferroni post hoc test. * P ≤0.05, compared to ND-CON, # compared to STZ-CON & ND-CON.

Effect of pioglitazone on body weight and blood glucose levels

Blood glucose levels were significantly elevated with STZ administration but pioglitazone treatment had no effect on the magnitude of increase in either the diabetic or non-diabetic groups. This is most likely because the STZ-induced diabetic animals were insulin deficient rather than insulin-resistant. The effect of pioglitazone treatment is mediated via adiponectin and has the ability to influence body weight due to its action at the level of adipose tissue although this was not evident in the experiment. There was a moderate increase in body weight of ND-CON and STZ-CON groups. However, the body weight of ND-PIO and STZ-PIO were not significantly different as compared to their respective controls. This finding is in consistent that of Kong (Kong, Ma *et al.,* 2013)

Effects of pioglitazone on blood pressure

The MAP of 4-week STZ-CON SHRs was considerably higher as compared to ND-CON while three weeks treatment with pioglitazone caused MAP to be significantly lower in the ND-PIO and STZ-PIO SHRs; however the extent of reduction of MAP in the STZ-PIO was less compared to ND-PIO. These results are in similar to those of previous studies using pioglitazone in STZ-induced diabetic SD rats (Majithiya, Paramar *et al.,* 2005) and fructose-overloaded SD rats (Peredo, Mayer *et al.,* 2008). It is important to note that regulation of MAP and vascular tone depends upon nitric oxide (NO), which acts as endothelium derived molecule (Kong, Ma *et al.,* 2013). Secretion of rennin from kidneys mediates the production of angiotensin II from angiotensinogen, whereas ANGII inhibits adiponectin production thereby offsetting the dilator action of NO reflecting an important interaction with the RAAS in the regulation of blood pressure through the production of NO (Wang and Scherer 2008), and thus impacts on blood pressure control. In this study the antihypertensive effect of pioglitazone is linked with an increase in circulating

plasma adiponectin levels which stimulates the production of nitric oxide in blood vessels, and thushas the potential as a treatment for endothelial dysfunction related to diabetes and atherosclerosis.

Vasopressor responses effects of pioglitazone

In our experiment, daily oral administration of pioglitazone (10mg/kg) for 21 days blunted the vasopressor responses to alpha adrenergic agonists and ANGII control and diabetic SHR treated with pioglitazone, independently of any change in insulin sensitivity. This could be due to the effect of pioglitazone on SNS, which results in decrease in vascular tone of blood vessels. As hyperinsulinemia is a known stimulus of SNS, lower insulin levels with pioglitazone may be associated with a reduced sympathetic drive (Anderson, Hoffman *et al.,* 1991). One of the important findings in the current study was the blunted vasopressor responses of the systemic vasculature to adrenergic agonists in the diabetic pioglitazone treated SHRs. It was evident that diabetic SHRs exhibited significant increase in pressor responses to exogenously applied NA and Me, and these responses are mediated by postsynaptic a1-adrenoceptors, and there is evidence that the PPAR- γ agonist, (pioglitazone) improves vascular control exerted by adrenergic nerves in hyperinsulinaemic states (Takatori, Zamami *et al.,* 2008). The tone of underlying vascular smooth muscle cells is impacted upon by the endothelium through the production of vasodilator mediators, whereas diabetes lead to dysfunction in vascular smooth muscle cells and endothelium as patho-physiological manifestations (Creager, Lüscher *et al.,* 2003). Impaired endothelium-dependent vasodilatation has been recognized in various vascular beds of animal models with diabetes (De Vriese, Verbeuren *et al.,* 2000). The Ppar-γ agonists, glitazones, including pioglitazone, are known to counteract the characteristics of diabetes, i.e., they improve insulin sensitivity, lipid metabolism and reduce blood pressure (Gao, Fall *et al.,* 2013), secondly they decrease in endothelin-1expression (Iglarz, Touyz *et al.,* 2003), thirdly they improve endothelial function in diabetic mouse models, and finally activating via the production of ADN which is a critical mediator moderating oxidative stress through activation of signalling cascades, such as cAMP-PKA and AMPK-eNOS component (Wong, Tian *et al.,* 2011). In addition to these mechanisms, the ability of TZDs to interfere with the rennin-Ang II system plays a significant role (Zanchi, Perregaux *et al.,* 2006). In the present study, pioglitazone reduced the blood pressure and improved endothelial function in the diabetic SHR by reducing the vasopressor responses to exogenously administered alpha adrenergic agonists and Ang II probably via the increased plasma adiponectin levels through production of nitric oxide.

The vascular contractility in present studies was pronounced in the STZ-diabetic rats, which could possibly be due to increased oxidative stress and poor endothelial activity. Administration of pioglitazone for 3 weeks decreased markedly contractility to NA and ME, and which may be one reason for reduced blood pressure.

It is interesting to note that angiotensin II (Ang II) and its endothelial signalling pathways play vital roles in modulation of blood pressure. Apart from insulin sensitizing action of pioglitazone, the antihypertensive effect may also result from its action to the attenuation of the heightened responsiveness to Ang II in diabetes via an improvement in endothelial function (El-Mas, El-Gowelli *et al.,* 2011), however in this study, pioglitazone treatment also decreased the responsiveness to ANG II in ND-PIO, although the size of the decrease response was less in STZ-PIO versus ND-PIO. Earlier studies also revealed that TZDs decreased the production of angiotensin I and II from human subcutaneous adipose tissue (Harte, McTernan *et al.,* 2005), whereas in other studies PPAR-γ (TZDs) agonists have been reported to down regulate the expression of angiotensin AT1 receptor mRNA in vascular smooth muscle cells (Sugawara, Takeuchi *et al.,* 2001). In diabetes, Ang II (AT1) receptor expression is up regulated whereas the Ang II (AT2) receptor is down-regulated (Giacchetti, Sechi *et al.,*2005). These findings demonstrate that PPAR-γ agonists (TZDs) also have interactions with RAAS at multiple levels although the exact level of interaction may vary across both diabetic and hypertensive states.

Pioglitazone and plasma adiponectin

It was notable that, treatment of SHRs with pioglitazone for 3 weeks significantly increased ADN levels and in the diabetic SHR mildly reduced the severity of hyperglycaemia while plasma ADN levels were elevated compared to the non-diabetic SHR. Diabetes induced by high-dose STZ is similar to human type 1 diabetic model (Havel, Hahn *et al.,* 2000). The results from the present study revealed that plasma ADN levels were reduced after the streptozotocin induction of diabetes. As adiponectin is an insulin sensitizing agent (Hirose, Kawai *et al.,* 2002), the reduction of its plasma concentration in the diabetic SHRs would contribute to the diabetic condition. In contrast to our findings, it has been reported that plasma ADN levels were elevated in type 1 diabetic subjects (Hadjadj, Aubert *et al.,* 2005). The difference could be related to the immune system which if defective could lead to β-cell damage and absolute insulin deficiency in STZ-induced diabetic SHRs (Imagawa, Funahashi *et al.,* 2002).

CONCLUSION

The current study revealed that a 21-day treatment with pioglitazone restored the vasopressor responses. In addition, dependence of the vascular responses to vasoactive agonists in this study indicates an important

interaction between PPAR-γ and postsynaptic α1-adrenoceptors at and is dependent on an intact RAAS in the diabetic normotensive and spontaneously hypertensive rats. In a nut shell, this study highlighted the following:

First, PPAR-γ has a considerable function in the control of systemic haemodynamics in diabetic SHR rats. Second, an interactive/cross-talk relationship exists between PPAR-γ and adrenergic neurotransmission in the peripheral vasculature of diabetic and non-diabetic SHRs.

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