Influence of Endothelin-1 on Age-related Changes in Renal Function in Male Rats

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ABSTRACT

The kidney is one of the organs that are highly susceptible to age-related tissue damage. Several human and animal studies show decline in renal function with age. We examined the effect of endothelin-1 on age-related changes on renal function and whether this effect is mediated by ET-1 receptor types A or B. Also, we investigated the hemodynamic response to ET-1 and ET-1 receptor antagonist. Two age groups of male rats were used: young (4–5 months) and old (19–20 months). Each group was subdivided into four subgroups in which hemodynamic and renal function data were measured after administration of saline (control group), acute intravenous injection of endothelin-1 (ET-1 group), administration of BQ-123, ET_A receptor antagonist, 20 minutes before ET-1 (ET_A antagonist group) and administration of BQ-788, ET_B receptor antagonist, 20 minutes before ET-1(ET_B antagonist group). We found that aging is associated with elevated mean arterial blood pressure and reduced renal function data. ET-1 injection resulted in more pressor response in old rats and more reduction of renal function data in young rats. Pretreatment with BQ-123 improved renal function with more augmentation in old rats while BQ-788 pretreatment has no effect on renal function. These results indicated that ET-1 and $ET\text{-}1_A$ receptor play a crucial role in age-related change in renal function.

INTRODUCTION

Aging is a planned biological process controlled by genes successively toggled on or off signals to the nervous, endocrine and immune systems. In most species aging is associated with defective adaptive and homeostatic mechanisms that make the individual vulnerable to environmental or internal stress followed by increasing disease and death rates[1,2,3]. Aging resulted in significant changes in renal anatomy and function, both in animal models and in humans[4,5]. Aging is coupled with progressive declines in glomerular filtration rate (GFR) and renal blood flow (RBF)[3,6], distorted creatinine tubular handling, reduced sodium reabsorption and potassium secretion and diminished renal reserve[7]. The mechanisms of these renal functional and structural changes with aging are under investigation.

Several mechanisms have been identified for injury in the aging kidney. Changes in the activity and/or responsiveness to vasoactive substances plays a part, with a tendency toward increased sensitivity to vasoconstrictor stimuli and decreased vasodilatory capacity[6].

Most importantly changes in the activity of the renin-angiotensin and nitric oxide systems[3,6]. These renal physiological changes resulted in diverse abnormalities in fluid and electrolytes homeostasis[8]; enhance the risk of volume depletion and prerenal acute renal failure[9], in addition to progressive chronic renal disease[3,6]. The resultant decline in renal function confines general health and life expectancy and in sequence may implicate on cardiovascular and metabolic disorders [10].

Endothelin-1 (ET-1), an endothelial derived 21-amino acid peptide, is the most predominant isoform of the endothelin peptide family, which also includes endothelin-2 and endothelin-3[11,12]. ET-1 is produced by the majority cell types in the kidney, including glomerular endothelial cells, mesangial cells and epithelial cells[13]. ET-1 mediates its effect via two receptors, A (ET_A) and B (ET_B). ET_B receptors protect the kidney against ET_A receptor dependent vasoconstriction, cell proliferation, matrix accumulation and inflammation[14]. ET_B receptors have a principal role in clearance of circulating ET-1, which occurs mostly in the lungs and the kidneys[15]. ET-1 has a crucial role in regulation of renal function; it reduces RBF and GFR[16]. Moreover, it has a vital role in the pathogenesis of diabetic renal injury and arterial hypertension. Blocking of endothelin receptor seems to be efficient in renal therapy [11]. Aging is associated with increased ET-1 levels in plasma (mRNA and protein) together with changed ET_A to ET_B ratio [17].

The present study hypothesized that ET-1 may contribute to renal aging and this is mediated by alteration of receptor response. We examined the effect of endothelin-1 on renal function during physiological aging process in male rat and whether this effect is mediated by ET_A or ET_B receptors. Also, we investigate the hemodynamic response to ET-1 before and after administration of ET_A and ET_B receptor antagonist.

Materials and methods:

Animals:

In this study 48 White Albino male rats were used. The rats were obtained from animal house of Faculty of Medicine, Assiut University, Egypt. They were maintained under normal conditions at room temperature and natural photoperiod, adequately fed and provided with sufficient fresh water available all the time by stainless steel nipples.

All experimental protocols followed the guidelines of the Animal Committee of the Faculty of Medicine of Assiut University and were in accordance with the recommendations in the ARRIVE guidelines in the care and use of experimental animals. The researchers concerned in this study have paid particular efforts to minimize the number of animals used and their suffering.

The rats are divided into the following groups: group I: young rats (age 4–5 months, n: 24) and group II: old rats (age 19–20 months, n: 24). Each group was subdivided into the following subgroups:

- **Subgroup a (Control group):** in which hemodynamic and renal function data [GFR, RPF and urinary sodium ($U_{Na+}V$) and

potassium ($U_{K+}V$) were measured in the rats after administration of saline.

- **Subgroup b (ET-1 group):** in which hemodynamic and renal function data were measured in the rats after acute intravenous (i.v.) injection of endothelin-1 (1 nmol/kg body weight) dissolved in normal saline [18].
- **Subgroup c (ET$_A$ antagonist group):** in which BQ-123, an ET$_A$ receptor antagonist, dissolved in distilled water and administrated intravenously in a dose of 0.25 mg/kg body weight 20 minutes before administration of ET -1[19]. Then, hemodynamic and renal function data were measured.
- **Subgroup d (ET$_B$ antagonist):** in which BQ-788, an ET$_B$ receptor antagonist, dissolved in distilled water and administrated intravenously in a dose of 1 mg/kg body weight 20 minutes before administration of ET-1[19]. Then, hemodynamic and renal function data were measured.

Before the experiment, rats were starved for at least 12 h, but water was given ad libitum. Rats were anesthetized by an intraperitoneal injection of urethane (600 mg/kg, Sigma-Aldrich, Inc., St Louis, MO, USA) and were kept under anesthesia through the experimental period. The trachea was exposed and intubated with a short cannula to facilitate ventilation. Left common carotid artery was exposed over a midline incision and a dissection was made between the sternocleidomastoid and the sternohyoid muscles, parallel to the trachea. Catheter filled with heparin-saline solution (100 U/ml)

was placed into the left common carotid artery for mean arterial blood pressure (MABP) measurement and periodic sampling of blood. The right jugular vein was cannulated for infusion. Throughout the study, blood pressure and heart rate were monitored via an arterial catheter connected to a blood pressure transducer (Harvard App LTD) and attached to universal oscillograph.

A catheter was placed in the urinary bladder to collect urine samples. A ventral suprapubic incision was made. The abdominal muscles were carefully separated using blunt forceps and cotton swabs. The bladder was exteriorized and a small incision was made into the dome of the bladder. Then, the end of the catheter was carefully placed into the urinary bladder. A 4-O suture was placed around the catheter and the bladder to secure the catheter into the bladder. A 4-O suture was used to close the abdominal muscle and skin around the catheter. After placement of the bladder catheter, the end of the catheter extrudes from the lower abdomen. This end is closed with artery forceps. This allows the rat to normal urinate until the time that the artery forceps is removed.

Measurement of the renal hemodynamic:

The best and most common parameter for evaluating the renal function is measurement of glomerular filtration rate and renal plasma flow[20] and they are traditionally measured by inulin and p-aminohippuric acid (PHA) clearance, respectively. The procedure follows that of Gabel et al.[18]. Briefly, each rat was given an intravenous

(i.v.) bolus (2 ml/kg) of the inulin/PAH solution, followed by an i.v. infusion (25 µl/min) of the inulin/PAH solution via an infusion pump. The inulin/PAH solution contained 3% inulin and 2% PAH in saline. Inulin (1.5 g) and PAH (5 ml of 20% solution) were added to 45 ml of saline to get the final infusion concentrations. The infusion was maintained for 1 h prior to the start of the baseline clearance periods. ET-l was prepared at a concentration of 1 nmol/ml in saline and given as an i.v. bolus at 1 nmol/kg for a dose volume of 1 ml/kg. Vehicle-treated rats were given an i.v. bolus of saline at a volume of l ml/kg.

Analytical methods:
Inulin assay:

Measurement of inulin in urine and plasma was determined by the method of Gabel et al.[18]. This method is based on hydrolysis of inulin to fructose by inulinase. Then, fructose by sorbitol dehydrogenase (SDH) was converted to sorbitol with utilization of nicotinamide adenine dinucleotide (NADH). The amount of NADH utilized was proportional to the amount of inulin initially present in the sample. The amount of NADH utilized was measured before and after incubation with SDH by spectrophotometer.

The urine samples were pre-diluted 1:200 with saline and heparinized plasma samples were used without dilution. Plasma and urine samples (15 µl each) were mixed with 260 µl of inulinase reagent (0.11 U/ml). The samples were then incubated at 37 °C for 10 min. Following incubation, 400 µl of the SDH/NADH reagent was added to

each sample. The samples were then incubated again at 37 °C for 20 min. Following incubation, the absorption of each sample was determined at 340 nm.

Assay calibration was done by using 20 mg/dl of inulin in 60 g/l bovine serum albumin (BSA) for plasma samples and in normal saline for urine. The value for the endogenous fructose was then subtracted from each plasma sample value.

PAH assay:

PAH was determined by a calorimetric reaction with dimethylaminocinnamaldehyde (DACA) solution in low pH by the method of Gabel et al.[18]. The intensity of color generated was proportional to the amount of PAH present in the sample which is measured by spectrophotometer. Briefly, rat urine samples were diluted 1:40, and heparinized plasma samples were used without dilution. Determination of PAH was done by a calorimetric reaction between PAH and 2 mg/dl DACA in 2 mol/dl hydrochloric acid (HCL). The intensity of the color was measured at 546 nm after 5 min of incubation at 37°C.

Assay calibration was done by using 5 mg/dl of PAH solution in 60 g/l BSA for plasma samples and 100 mg/dl of PAH solution in saline for urine samples.

Urinary sodium and potassium concentrations were determined by flame photometer.

Chemicals and reagents:

Inulin (from Dahlia tubers) and PAH were purchased from Acros Organics (New Jersey, USA) as powder form (CAS: 9005-80-5, Lot:

A0245624 and CAS: 200-518-9, Lot: A0235503, respectively). Inulinase (Novozym) was purchased from Sigma Chemical Co. (St. Louis, MO) as aqueous glycerol solution (CAS: 9025-67-6, Lot: 019M2195V). The stock solution was diluted 1:100 with 10 mmol/l sodium phosphate (pH 5.0) for use in the assay. SDH was purchased from Sigma Chemical Co. (St. Louis, MO) as lyophilized form (CAS: 9028-21-1, Lot: 091K1047V). SDH reagent was prepared by dissolving 10 mg of SDH in 10 ml of deionized water (40 U/ml). NADH was purchased from Sigma Chemical Co. (St. Louis, MO) as solution (CAS: 104809-32-7, Lot: 192M7523V). NADH solution was prepared by dissolving 5 mg of NADH in 10 ml of phosphate buffered saline pH 7.6 (0.5 mg/ml). After the SDH and NADH solutions were prepared, they were mixed in equal amounts and used as one reagent.

Endothelin-1 was purchased from Sigma Chemical Co. (St. Louis, MO) as powder form (CAS: 117399-94-7, Lot: 129K4851). BQ-123 was purchased from Sigma Chemical Co. (St. Louis, MO) as lyophilized powder form (CAS: 136553-81-6, Lot: 355M132V). BQ-788 was purchased from Sigma Chemical Co. (St. Louis, MO) as powder form (CAS: 156161-89-6, Lot: 021M1442V).

Calculations:

The clearances of PAH and inulin were calculated by using standard formulas; C_{IN} and C_{PAH} were used to approximate GFR and RPF, respectively. These formulas were as follows: C_{IN} (ml/min) = U_{IN} x V/P_{IN}, C_{PAH} (ml/min) = U_{PAH} x V/P_{PAH}, where U_{IN}, P_{IN}, U_{PAH}, and P_{PAH} are the concentration of inulin and PAH in urine and plasma, respectively, and V is the urine volume.

Statistical analysis:

All values are expressed as means ± standard error of the mean (SE) for n observations. The difference among groups was analyzed by using a Mann-Whitney test. Differences were considered significant at $P < 0.05$.

RESULTS

Basal hemodynamic and renal function data in the control anesthetized young and old rats:

Basal MABP was significantly higher in old rats than that of young rat (137 ± 4 mmHg versus 114 ± 4 mmHg, $p < 0.001$). While, basal HR did not show significant difference between young and old rats (367 ± 9 beat/min versus 386 ± 14 beat/min, respectively). Fig. 1. showed basal GFR, RPF and $U_{K+}V$ were significantly higher in young than old rats (1.01 ± 0.07 ml/min versus 0.52 ± 0.05 ml/min, $p < 0.01$, 4.03 ± 0.15 ml/min versus 1.45 ± 0.06 ml/min, $p < 0.01$ and 27.14 ± 0.72 µEq/min versus 14.77 ± 0.60 µEq/min, $p < 0.01$, respectively). While, basal $U_{Na+}V$ was significantly lower in young than old rats (1.29 ± 0.07 µEq/min versus 3.12 ± 0.16 µEq/min, $p < 0.01$).
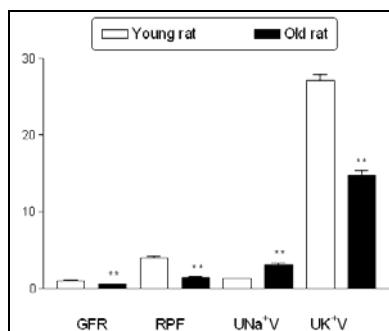
Figure 1. Basal renal function data [glomerular filtration rate (GFR), renal plasma flow (RPF), urinary potassium excretion ($U_{K+}V$)) and urinary sodium excretion (UNa_+V)] in the control anesthetized young and old rats. Bars represent mean $\pm$ SE, ** $p < 0.01$.

Effect of acute intravenous administration of ET-1 on hemodynamic and renal function data in the anesthetized young and old rats:

Acute intravenous administration of ET-1 produced a biphasic response characterized by a transient depressor response followed by a sustained pressor phase in both young and old rat. The depressor response was not significantly different between young and old rat (26 ± 4 mm Hg versus 21 ± 2 mmHg). However, the pressor response was significantly higher in old rat compared to young rat (45 ± 3 mm Hg versus 30 ± 2 mmHg, $p<0.001$) (Fig. 2A, B). Acute intravenous administration of ET-1 reduced GFR, RPF, $U_{Na+}V$ and $U_{K+}V$ in both young and old rat compared to the control

level, however, the reduction was more in young than in old rats (Fig. 3A,3B and Table 1).
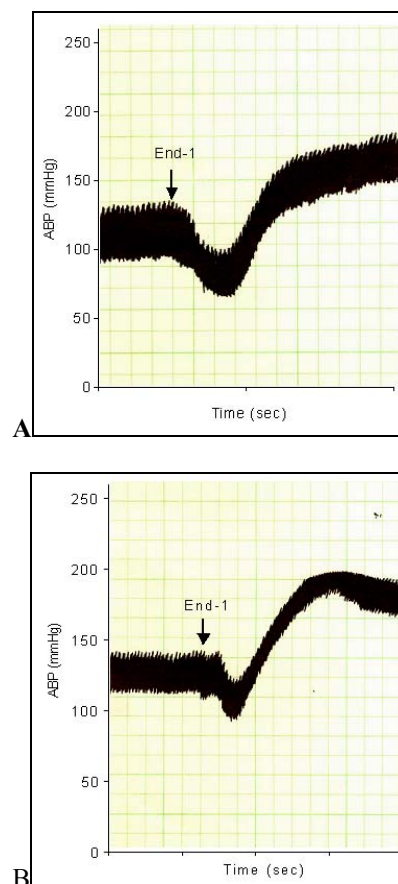

Figure 2. Representative recording of the effect of acute intravenous administration of endothelin-1 (ET-1) on arterial blood pressure (ABP) in anesthetized young (A) and old (B) rats. Arrow referred to administration of ET-1.
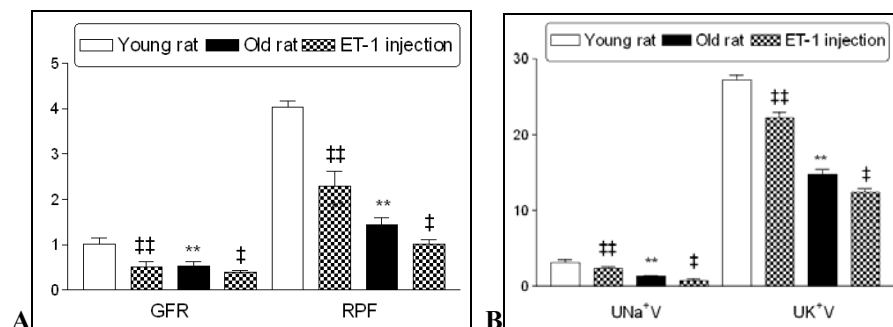
Figure 3. Effect of acute intravenous administration of endothelin-1 (ET-1) on glomerular filtration rate (GFR), renal plasma flow (RPF) (A) and urinary potassium excretion ($U_{K+}V$)) and urinary sodium excretion ($U_{Na+}V$) (B) in the anesthetized young and old rats. Bars represent mean ± SE, **: $p < 0.01$ compared to the young rat, ‡: $p < 0.05$ and ‡‡: $p < 0.01$ compared to the basal level.

Table 1. Effect of endothelin-1 and endothelin-1 receptor antagonist on renal hemodynamic in young and old anesthetized rat

Age	Group	GFR (ml/min)	RPF (ml/min)	$U_{Na}+V$ (µEq/min)	U_K+V(µEq/min)
Young rat	Control	1.01 ± 0.07	4.03 ± 0.15	1.29 ± 0.07	27.14 ± 0.72
	ET-1	0.51 ± 0.05‡‡	2.30 ± 0.32‡‡	0.78 ± 0.07‡‡	22.18 ± 0.74‡‡
	BQ-123 pretreatment	0.79 ± 0.08†	3.27 ± 0.28†	1.10 ± 0.13†	24.51 ± 0.43†
	BQ-788 pretreatment	0.57 ± 0.04	2.34 ± 0.33	2.12 ± 0.24	22.66 ± 0.99
Old rat	Control	0.52 ± 0.05**	1.45 ± 0.06 **	3.12 ± 0.16**	14.77 ± 0.60**
	ET-1	0.40 ± 0.01‡	1.01 ± 0.10‡	2.39 ± 0.20‡	12.40 ± 0.40‡
	BQ-123 pretreatment	0.52 ± 0.03††	1.39 ± 0.04†	0.98 ± 0.02††	14.07 ± 0.44††
	BQ-788 pretreatment	0.07 ± 0.06	0.79 ± 0.07	0.71 ± 0.06	11.25 ± 0.47

All data were presented as mean ± SE (standard error). ET-1: endothelin-1, BQ-123: ET-1 receptor A antagonist, BQ-788: ET-1 receptor B antagonist, GFR: glomerular filtration rate, RPF: renal plasma flow, $U_{Na}+V$: urinary sodium excretion, U_K+V: urinary potassium excretion. **: $p<0.01$ compared to young rats, ‡: $p < 0.05$, ‡‡: $p<0.01$ compared to the control level, †: $p < 0.05$, ††: $p < 0.01$ compared to the effect of endothelin-1 administration.

Effect of BQ-123 pretreatment on hemodynamic and renal function data in the anesthetized young and old rats:

Pretreatment with the selective ET_A receptor antagonist (BQ-123), 20 minutes before ET-1 administration, did not affect the ET-1–induced depressor response but significantly reduced its pressor effect in young rats (from 30 ± 2 to 15 ± 2 mm Hg, $p < 0.001$). In old rats pretreatment with the BQ-123 produced more prolonged significant depressor response and abolished the pressor response (Fig. 4A, 4B). Pretreatment with the BQ-123 produced significant increased GFR, RPF and $U_{K+}V$ in young and old rats in comparison with ET-1 administration with more increase in old rats. While, $U_{Na+}V$ significantly reduced (Fig. 5A, 5B and Table 1).
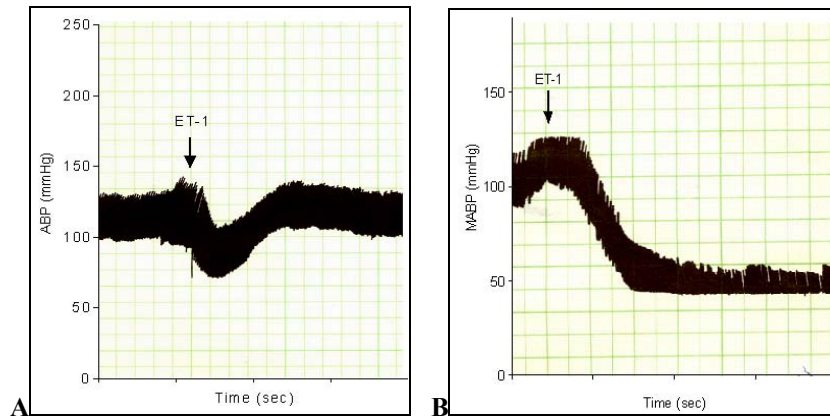

Figure 4. Representative recording of the effect of BQ-123 pretreatment on arterial blood pressure (ABP) in anesthetized young (A) and old (B) rats. Arrow referred to administration of ET-1.
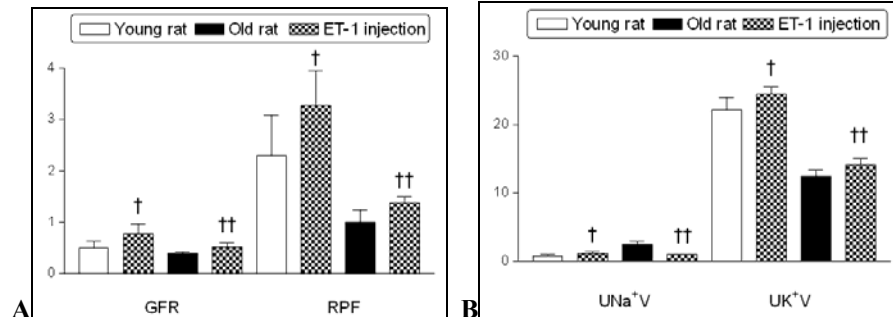

Figure 5. Effect of BQ-123 pretreatment on glomerular filtration rate (GFR), renal plasma flow (RPF) (A) and urinary potassium excretion ($U_{K+}V$)) and urinary sodium excretion ($U_{Na+}V$) (B) in the anesthetized young and old rats. Bars represent mean $\pm$ SE, †: $p < 0.05$ and ††: $p < 0.01$ compared to the endothelin-1 (ET-1) injection.

Effect of BQ-788 pretreatment on hemodynamic and renal function data in the anesthetized young and old rats:

Pretreatment with the selective ET_B receptor antagonist (BQ-788), 20 minutes before ET-1 administration, abolished the initial depressor response of ET-1 and the pressor response was not reduced significantly from 30 ± 2 mmHg to 22 ± 3 mmHg

in young rat. While, in old rats the pressor response was potentiated by pretreatment with BQ-788 from 45 ± 3 mm Hg to 60 ± 5, p< 0.01 (Fig.6A, 6B). Pretreatment with the BQ-788 produced no significant change in GFR, RPF, $U_{Na+}V$ and $U_{K+}V$ in young and old rats in comparison with ET-1 administration (Fig. 7A, 7B and Table 1).
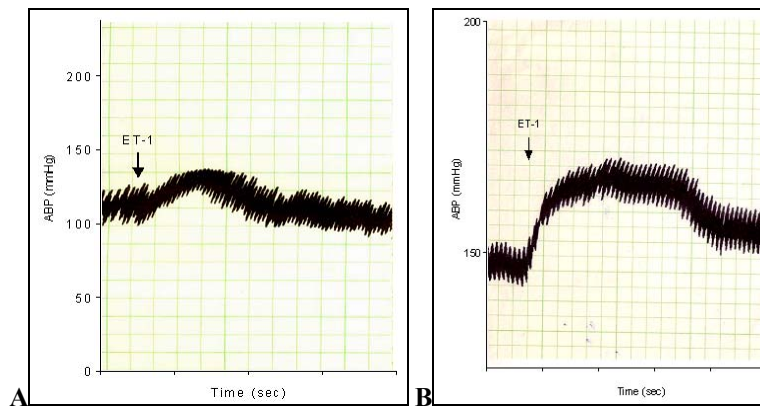

Figure 6. Representative recording of the effect of BQ-788 pretreatment on arterial blood pressure (ABP) in anesthetized young (A) and old (B) rats. Arrow referred to administration of ET-1.
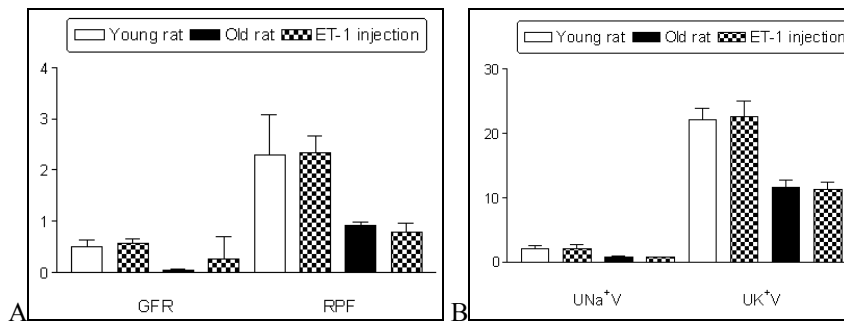

Figure 7. Effect of BQ-788 pretreatment on glomerular filtration rate (GFR), renal plasma flow (RPF) (A) and urinary potassium excretion ($U_{K+}V$)) and urinary sodium excretion (UNa+V) (B) in the anesthetized young and old rats. Bars represent mean ± SE.

DISCUSSION

Several studies demonstrated an age-related increase in the circulating levels of ET-1[21,22] and enhanced ET-1 vasoconstrictor tone[23]. Recently, **Goel et al.**[24] reported an increased exocytotic release of ET-1 by aged endothelium. However, the pathophysiological consequence of this elevated level on renal function is unclear. The current study highlighted the contribution of ET-1 in reduction of renal function with aging. The most direct evidence was that ET_A receptor inhibition with BQ-123 restored the age-related impairment in renal function.

The present study revealed that MABP was elevated in old rats than young rats. This result coincided with the result of **Greenfeld et al.**[25]. Other studies reported that old rats develop isolated systolic hypertension with advancing age[10,26]. Contrary to our result, other studies reported no difference in blood pressure with aging[27,28,29]. The mechanisms of this age-associated effect are beyond the scope of the current study.

The kidney is highly susceptible to the age-related damage and this affects general health and life expectancy[10,29,30]. Our result demonstrated that advancing age resulted in reduction in renal function data, as expressed by remarkable decrease in GFR, RPF and $U_{K+}V$. Whereas, $U_{Na+}V$ was higher in old rats. These results are concomitant with those of **Baynes and Murray**[31] and Starr and Deary[32] who reported progressive decline of renal function with aging. Earlier studies showed an increase in the rates of impairment of GFR in old healthy individuals[33,34,35]. **Greenfeld et al.**[25] reported that the middle-aged rats had significantly higher GFR and RPF relative to the old group. **Musso and Oreopoulos**[7] demonstrated increased urinary Na^+ output and reduced urinary K^+ excretion in old people. They claimed this result to reduced sodium reabsorption and decreased basal plasma concentrations of renin and aldosterone, and the response to their stimuli in old age. Contrary to our result, **Silva et al.**[30] found that aging had no effect on urinary Na^+ excretion while urinary K^+ excretion was increased.

The current study showed that acute intravenous administration of ET-1 resulted in biphasic response of MABP with initial depressor response followed by pressor response in both young and old rat. The pressor response was significantly higher in old rat compared to young rat. This result is concomitant with those of Matsuura et al.[36] and Aleksandra et al.[37] who revealed that injection of ET-1 into anaesthetized rats resulted in an initial transient hypotensive response, followed by a sustained hypertensive response. This response explained by **Stauffer et al.**[38] who claimed that ET-1 exerts two opposite effects on blood vessel by two ET receptor subtypes (ET_A and ET_B receptors). ET_B receptors are located on both vascular smooth muscle and endothelial cells and its activation results in NO-mediated vasodilatation. While, ET_A receptors are located only on vascular smooth muscle cells and

its activation causes contraction and subsequent vasoconstriction.

Injection of ET-1 reduced GFR, RPF, $U_{Na+}V$ and $U_{K+}V$ in both young and old rat compared to the control level, however, the reduction was more in young than in old rats. In accordance with our results, it was reported that ET-1 administration resulted in decreased GFR, RBF and urinary sodium excretion [25].

Pretreatment with BQ-123 did not affect the ET-1–induced depressor response but significantly reduced its pressor effect in young rats. While, in old rats it produced more prolonged significant depressor response and abolished the pressor response. Pretreatment with BQ-788 abolished the initial depressor response of ET-1 and the pressor response was not changed in young rat. While, in old rats the pressor response was potentiated by pretreatment with BQ-788.

The mechanism of hypertensive response of BQ-788 was explained by **Boulanger and Luscher**[39] who reported that BQ-788 interfered with ET_B-dependent release of endothelial derived relaxing factor by endogenous ET-1 and resulted in an increase of endothelial production or release of ET-1. Also, **Fukuroda et al.**[40] and Dupuis et al.[41] claimed that BQ-788 displaced endogenous ET-1 from its ET_B clearance receptor. Therefore, blockage of this receptor increase plasma ET-1 levels, which may produce more ET_A receptor activation and marked vasoconstriction.

Bird et al.[42] reported abolished pressor effects of ET-1 during administration of ET_A receptor blocker and ET-1. Matsuura et al.[36]

showed that injection of BQ-788 completely abolished the depressive effect of ET-1.

Previous studies in rat demonstrated that ET_A receptor plays a central role in age-related increase in vascular tone in skeletal muscle[43] and coronary vessels[44,45]. Also, Van Guilder et al.[23] support the role of the ET_A receptors in the age-related elevated vascular tone in humans.

Pretreatment with the BQ-123 significantly increased renal function data in young and old rats with more increase in old rats. While, pretreatment with the BQ-788 produced no change in renal function data.

In accordance with our results, it was reported that blockage of ET_A slowed the progression of renal injury and preserved the renal function in experimental renovascular disease[46]. **Rubanyi and Polokof** [47] reported that BQ-123 administration decreased sodium excretion because of the reduction in filtered load. Bird et al.[42] reported that administration of ET_A blocker produced no significant change in GFR, whereas, it partially reduced the marked change in renal blood flow induced by ET-1 administration. Eileen et al.[48] found that administration of ET_A blocker to anesthetized male rats decreased renal blood flow but no effect on glomerular filtration rate.

Contrary to our results, **Greenfeld et al.**[25] demonstrated that acute inhibition of ET-1 did not change GFR or RPF neither in young nor in old rat however UNa^+V was increased in all age groups.

In conclusion, the findings of our study highlighted into the role of ET-1

and its ET-1$_A$ receptor in the age-related change in the renal function. These findings may prove relevant for development of novel therapeutic approaches that rely on these mechanisms. Yet, additional studies are required to explore this issue.

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أثر الاندوثلين-١ على التغيرات المرتبطة بالعمر في وظيفة الكلى في ذكور الفئران

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مقدمة: الكلى من الأجهزة المعرضة للتلف مع التقدم فى العمر وتبين ذلك من العديد من الدراسات على الإنسان الحيوانات.

الهدف من الدراسة: درسنا تأثير الاندوثلين-١ على التغيرات المرتبطة بالعمر على وظيفة الكلى وما إذا كان هذا التأثير بواسطة مستقبلات الاندوثلين-١ A أو B. وأيضا درسنا استجابة الدورة الدموية للاندوثلين-١ ومستقبلاتة.

المواد والأساليب : استخدمنا فئتين عمريتين من ذكور الفئران: فئة الشباب (٤-٥ أشهر) وفئة المتقدمين فى العمر (١٩-٢٠ شهرا). تم تقسيم كل مجموعة إلى أربع تجارب تم فى كل منها قياس وظيفة الدورة الدموية وظائف الكلى بعد إعطاء محلول الملح (مجموعة المراقبة)، بعد الحقن الحاد للاندوثلين-١ في الوريد (مجموعة الاندوثلين-١)، بعد حقن بى كيو-١٢٣ (المضاد لمستقبلات الاندوثلين-١ اية) ٢٠ دقيقة قبل حقن الاندوثلين-١ (مجموعة مضاد مستقبلات الاندوثلين-١ اية) ، ١ بعد حقن بى كيو-٧٨٨ (المضاد لمستقبلات الاندوثلين-١ بى) ٢٠ دقيقة قبل حقن الاندوثلين-١ (مجموعة مضاد مستقبلات الاندوثلين-١ بى).

النتائج: يرتبط مع الشيخوخة ارتفاع ضغط الدم وانخفاض وظائف الكلى. و حقن الاندوثلين-١ أدى الى ارتفاع ضغط الدم والحد من وظائف الكلى فى صغار الفئران والفئران المتقدمة فى العمر. مع المعالجة ببى كيو-١٢٣ حدث تحسن فى وظيفة الكلى مع التحسن الأكثر في الفئران المتقدمة فى العمر بينما المعالجة ببى كيو-٧٨٨ ليس لها أي تأثير على وظائف الكلى.

الاستنتاج: وبذلك نستنتج من هذه الدراسة ان الاندوثلين-١ ومستقبلاتة نوع اية تلعب دورا هاما في التغيير المرتبطة بالعمر في وظائف الكلى.