Research article

Decreased alpha-adrenergic constriction of renal preglomerular arteries occurs with age and is gender-specific in the rat

Jeff C. Falcone*, Irving G. Joshua, & John C. Passmore

*Department of Physiology and Biophysics, Health Sciences Center, A-1115, University of Louisville, 500 South Preston St., Louisville, KY 40292, USA; *Author for correspondence (e-mail: jcfalc01@louisville.edu; fax: +1-502-852-6239)*

Received 22 October 2004; accepted in revised form 21 January 2005

Key words: aging, alpha adrenergic receptors, gender differences, rat, renal preglomerular arteries

Abstract

Age and/or gender appear to moderate alpha-adrenergic mediated constrictor mechanisms found in the interlobar arteries of the Munich Wistar rat. We have determined the extent of constriction to alpha-adrenergic receptor stimulation using norepinephrine, phenylephrine and A61603 (α_{1A} -adrenergic receptor agonist) as a function of age and gender. Norepinephrine produced less constriction in male-derived arteries at ages greater than eight months as compared to the younger adult male (four to six months). The arteries derived from females did not demonstrate altered constriction until greater than 15 months of age. Similarly, arteries derived from the male demonstrated weaker constrictions to phenylephrine (10^{-6} to 10^{-3} M) at ages greater than eight months while arteries from females showed differences at greater than 15 months. In contrast, the effective concentration of norepinephrine to cause a 50% maximal constriction (EC_{50}) was significantly less in the four to five-month-old male rats compared to the pooled data from older groups. Interestingly, four to five month old males had A61603 EC_{50} values similar to the 8- to 12-month and 15+ old females. These studies conclude that an age related loss of sympathetic α -adrenergic constriction of renal interlobar arteries is present in Munich Wistar rats. Furthermore, this loss, while similar along longitudinal aspects of age, is also different as a function of gender with the loss of α -adrenergic constrictor function delayed in the female when compared to the male.

Introduction

The present study was designed to determine if α -adrenergic-induced vasoconstriction of the renal resistance vasculature is impaired as a function of age and/or gender. It has been shown that human renal function begins to decline in healthy, active males after age 40 years at a rate of about 1% to 2% each year (Lindeman 1993). In addition, renal disease is much more prevalent in aging men than in aging women (Silbiger and Neugarten 1995; Wesson 1969). Similar to the human male degeneration of renal function, male rats also appear to suffer renal problems as a function of age (Baylis 1996).

Even more specifically, it has also been shown that female and castrated male Munich Wistar rats demonstrate less age-related glomerulosclerosis and proteinuria than does the intact male (Baylis 1996). The characteristics of, and the mechanisms for, impaired renal function as a function of age and possibly gender are why we embarked on these important studies centered on the α -adrenergic mechanisms of constriction.

There are examples that sympathetic adrenergic activation of renal blood vessels is impaired in aging. Aged rats have impaired baroreflex control of renal sympathetic nerve activity (Irigoyen et al. 2000). Mental stress induced renal vasoconstriction, in

humans, is associated with altered renal sympathetic nerve activity (Tidgren and Hjemdahl 1989). In elderly patients with systolic hypertension, induction of mental stress produced a passive increase in renal blood flow during increased blood pressure as opposed to the more normal response of renal vasoconstriction (Castellani et al. 1999). Yet another example of decreased renal vasoconstrictor effectiveness in aging is demonstrated when young men undergo an approximate reduction of about 45% in renal blood flow during exercise while healthy, elderly men undergo a significantly smaller decrease of only 12% to a similar exercise challenge (Kenny and Zappe 1994). Senescent Fischer 344 rats sustained shorter duration of elevated renal resistance and renal nerve activity compared to younger mature counterparts as a function of air-jet stress tests (Stauss et al. 1996). The literature paints an abundantly clear picture that aged humans and aged rats have similar impaired renal vasoconstriction to increases in the renal sympathetic nerve activity, which can occur related to activities such as stress and/or exercise. This reduced ability of renal sympathetic function to regulate the resistance of the preglomerular resistance arteries likely leaves the filtration unit of the kidney, the glomeruli, vulnerable to damage via elevated blood pressures, flow and circulatory dysfunction.

We have used isolated, cannulated renal resistance arteries to examine specifically the vascular smooth muscle responses to α -adrenergic agonists as a function of age and gender. We hypothesize that there is a decline in the response to α -adrenergic stimulation in the renal resistance arteries as a function of age and that females will show a lesser of a decline than the males.

Materials and methods

All experiments were approved by the University of Louisville Institutional Animal Care and Use Committee (IACUC). The Munich Wistar rat was chosen due to the strain having a relatively stable blood

pressure over the life span (Roth et al. 1993; Anderson et al. 1994). This aspect is important, again, to reduce the influence of other "disease type" influences—such as confounding aging with hypertension. The most scientifically sound approach to conducting live animal research as a function of age is to employ a longitudinal colony based study. A longitudinal study involves aging a colony of animals together and utilizing a random grouping at each age group desired. This type of study takes an enormous amount of time before any comparative data can be acquired due to the in-house aging aspect of the experimental animals. We have chosen to utilize three different age groups. Young adult animals will be considered as four to six months of age. Established, mature animals will be 8 to 13 months of age. Aged animals are considered to be at or beyond an age of 15 months. These age categories have been reported to correspond with the human age parameters of early 40 s, mid-50 s, and 65 or greater (Roth et al. 1993; Galbusera et al. 1988; Properzi et al. 1992; Scolnick et al. 1992; Sawaki et al. 1995). The table below provides a summarized comparison based on findings from the literature (Table 1).

The objective of this research was to examine and characterize the α -adrenergic sympathetic vasoconstrictor activity specific to the renal interlobar arteries, a preglomerular resistance vessel. Rats were obtained from Harlan Laboratories at 3.5-months and eight months of age (retired breeders). We then longitudinally aged the animals (all animals kept together and aged as a colony until experimental age was attained) in the Animal Care Facility at the University of Louisville Health Science Center. Rats were housed in an environmentally controlled facility. Food and water consumption (*ad libitum*) was monitored on a daily basis. Rats were anesthetized with a single injection of thiopental (100 mg/kg, i.p). A stable surgical plane of anesthesia was confirmed by a loss of response to auditory startle, toe pinch and corneal reflex. The experimental animals were handled gently with minimum strain and discomfort during both conscious and anesthesia conditions.

Table 1. Comparison of human with rat ages.

Functional age	Capable of reproducing	Mature adult	Start of aging	Mature aging	Senescence
Human	15 years	35 years	55 years	65 years	75 years
Rat	2.5 months	Four to five months	11–13 months	15–18 months	19–21 months

A midline abdominal incision was made and the distal portion of the abdominal aorta cannulated. Using this cannulation, the renal arteries and kidneys were rapidly flushed with 20 ml of an ice-cold phosphate buffered saline solution (PBS) containing: NaCl (120 mmol/L), KCl (2.7 mmol/L), phosphate buffer (10 mmol/L) without calcium and magnesium. Each kidney was then surgically excised and placed in a specialized temperature-regulated microdissecting well filled with cold (0 to 2 °C) MOPS buffered

(pH = 7.40 ± 0.03) physiological salt solution (MOPS-PSS) composed of NaCl (145 mmol/L), KCl (5.0 mmol/L), CaCl_2 (2.0 mmol/L), MgSO_4 (1.0 mmol/L), NaH_2PO_4 (1.0 mmol/L), dextrose (5.0 mmol/L), pyruvate (2.0 mmol/L), EDTA(2-Na; 0.02 mmol/L), and 3-(*N*-morpholino)propanesulfonic acid (MOPS; 3.0 mmol/L) (Kuo et al. 1988; Falcone et al. 1991, 1993a, b). The kidneys were then bisected and pinned to the flat, transparent bottom of a refrigerated microdissection chamber.

Figure 1. Isolated microvessel cannulation. *Upper panel:* Schematic of an isolated, cannulated arterial microvessel showing how the vessel is suspended between two glass pipettes and bathed by a temperature controlled physiological buffer solution. A water immersion lens was utilized to visualize, record and display images for quantitative analyses. *Lower panel:* Photo of an artery isolated from the Munich Wistar rat. The cannulated arterial system is pressurized to an approximate *in vivo* intraluminal pressure of 100 cmH₂O and bathed in a physiological salt solution buffered with MOPS to a pH of 7.38 (please see Materials and methods for detailed solution contents). Under these conditions this particular isolated vessel has an inner diameter of approximately 160 μm .

Resistance-sized interlobar arteries (100–250 μm , i.d.) were microsurgically dissected and mounted between two glass micropipette cannuli. The segment of the interlobar artery used was chosen based on a previous report describing that all levels of preglomerular blood vessels, from interlobar artery to afferent arteriole, contract similarly to catecholamine agonists (Casellas et al. 1985). In addition, it was possible to microsurgically excise arteries of adequate length so as to cannulate and confidently measure the vessel's unrestricted diameter (i.e., that portion not influenced by the tips of the micropipettes).

Isolated microvessel preparation

The isolation and cannulation procedures were modified from our previously published methods (Falcone et al. 1991, 1993a, b). Briefly, two micropipette cannuli, labeled primary and secondary, were prepared with tips and sizes designed on a microforge to match the individual size of each vessel lumen. These micropipettes were heat polished to limit any damage produced by forcing the cannula into the end portions of the vessel lumen. Both micropipettes were filled with suffusion solution and mounted in holders attached to a micromanipulator driven microscope stageplate. Cannulation involved sliding the vessel onto the primary pipette, securing it with 10–0 suture and flushing out the contents of the vessel by applying a slight positive pressure ($< 20 \text{ cmH}_2\text{O}$). The artery was then cannulated with the secondary pipette by a similar procedure.

The arteries were bathed at 37°C with the MOPS buffered physiological salt solution described above (MOPS-PSS). These suffusion conditions typically yielded a $p\text{O}_2$ of 45 to 60 mmHg, $p\text{CO}_2$ of 35 to 45 mmHg and a pH of 7.40 ± 0.03 (Falcone et al. 1991).

The length of the vessel was set to its approximate *in situ* length, as previously determined with an eyepiece micrometer during the initial vessel micro-

dissection, and then the entire apparatus was transferred to the stage of a modified Nikon-BMJ compound microscope. The resulting brightfield video image is displayed in Figure 1 (lower panel). Spontaneous (intrinsic) tone usually developed within 60 min after which the vessel was allowed to equilibrate for an additional 30 min.

Experimental protocol

Baseline interlobar artery diameter was measured at a constant intraluminal pressure of 100 cmH_2O in agonist free MOPS-PSS. Following this measurement the artery was subjected to randomized independent concentration–response protocols involving each of three topically applied α -adrenergic agonists. Topical applications of norepinephrine (non-selective α_1 - and α_2 -adrenergic agonist; 1×10^{-8} to $1 \times 10^{-3} \text{ M}$; Sigma, St. Louis), phenylephrine (selective α_1 -adrenergic agonist; 1×10^{-8} to $1 \times 10^{-3} \text{ M}$; Sigma, St. Louis) and A61603 (subtype specific and selective α_{1A} -adrenergic agonist; 1×10^{-10} to $1 \times 10^{-5} \text{ M}$; Tocris, Crookston) were all used in this study to differentiate both between and among alpha-receptors, arterial responses, age and gender.

Data handling and statistical methods

Statistical comparisons were performed on the younger age group *versus* the older age groups as a function of agonist response and gender. Where appropriate, simple comparisons of means and standard errors were performed using either a paired or unpaired, two-tailed, Student's *t*-test. For all experiments *n* is given as the number of vessels studied with each vessel representing a separate animal (i.e., one vessel per animal). When multiple comparisons were made, significance was determined using analysis of variance (ANOVA) in conjunction with Fishers protected least squares difference. Linear regression statistics were also utilized to separate out

Table 2. Weights of rats used in these studies as a function of gender and age group.

Gender	Age group		
	Four to six months	8 to 13 months	15 to 19 months
Male	$367 \pm 10 \text{ g}^*$	$405 \pm 7 \text{ g}^{*\dagger}$	$406 \pm 9 \text{ g}^{*\dagger}$
Female	$193 \pm 5 \text{ g}$	$227 \pm 6 \text{ g}^\dagger$	$238 \pm 5 \text{ g}^\dagger$

* $P < 0.05$ *versus* female. $^\dagger P < 0.05$ *versus* four months.

specific differences in the concentration–response curves with Fishers as the discriminator. Significance for all tests was defined with a probability less than 0.05 ($P < 0.05$).

Results

All rats remained healthy as determined by external appearance and observed behavior. Weight gain among gender groups grew somewhat exponentially as is consistent with that already reported in the literature (Roth et al. 1993; Anderson et al. 1994; Galbusera et al. 1988; Properzi et al. 1992; Scolnick et al. 1992; Sawaki et al. 1995; Baylis 1994). In addition, male weights were significantly greater at

all age groups compared to the female. A comparison of these weights as a function of age group and gender are presented in Table 2.

Norepinephrine at concentrations above 1×10^{-6} M produced significant constriction in the isolated interlobar arteries from both male and female rat as shown in Figure 2 panels A and B. The trend is evident that with increasing age the constriction lessens in both the male and the female derived arteries with the greatest difference between the four to six months age and the 15+ months age. These data begin to suggest that the males have lost a greater proportion of their total adrenergic constrictor ability in the early aged group of 8 to 13 months. The EC_{50} for this norepinephrine concentration–response relationship is not different between genders.

The concentration–response curves for phenylephrine application, an α_1 specific adrenergic agonist, at concentrations between 1×10^{-8} and 1×10^{-3} M on the isolated interlobar arteries as a function of age are presented in Figure 3. Specifically, Figure 3A depicts data from the male at ages of four to six months compared with 8 to 13 months or 15 to 22 months. The data clearly shows there is an overall loss of phenylephrine induced constriction at all concentrations beginning with 1×10^{-5} M and higher in the male derived resistance arteries at ages greater than eight months. In addition, both the 8 to 13 months and 15 to 22 months groups have a significantly lower maximum constriction ($93 \pm 10 \mu\text{m}$; $116 \pm 15 \mu\text{m}$, respectively) compared to the younger group ($51 \pm 6 \mu\text{m}$). The EC_{50} is also increased, shifting from 4.3×10^{-6} to 4.9×10^{-6} and 4.93×10^{-6} M when comparing the four to six months with 8 to 13 months and 15 to 22 months old male rats, respectively.

Similar phenylephrine concentration–response curves for interlobar arteries isolated from the female rat were also carried out and the data are presented as Figure 3B. In contrast to the male, the four to five-month-old female interlobar artery constriction did not become significantly different until the animals were 15 months or older. In addition, the arteries isolated from the female showed no change in maximal constriction until they were 15 months of age. Likewise, no change in the phenylephrine EC_{50} was noted in these arteries isolated from the female until the 15 months age.

Data based on age from the phenylephrine concentration–response curves between male and female interlobar arteries is presented in Figure 4, panels A

Figure 2. Norepinephrine concentration–response curve as a function of age for interlobar arteries isolated from the male (A) and female (B) Wistar rat kidney. Arterial inner diameter is expressed as a percent of the maximum passive diameter. * $P < 0.05$ for comparisons against the four to six months group.

and B. Figure 4A demonstrates that the arterial response to phenylephrine are similar between the male and female at the 4 to 6 month age. This similarity is based on maximum constriction and EC_{50} for phenylephrine. However, there is a striking difference between the genders at the 8 to 13 month age when challenged with phenylephrine. The arteries derived from the 8 to 13 month old female retain and even might somewhat improve their constrictor ability while those from the male have significantly lost a major portion of their constrictor function. Maximum constricted diameters are significantly different with the female attaining a diameter of $30 \pm 5 \mu\text{m}$ while the male is only at $93 \pm 10 \mu\text{m}$. Likewise, the EC_{50} to phenylephrine is also significantly different between female ($4.0 \times 10^{-6} \text{ M}$) and the male ($4.9 \times 10^{-6} \text{ M}$).

Figure 3. Phenylephrine concentration-response curve as a function of age for interlobar arteries isolated from the male (A) and female (B) kidney with the inner diameter expressed as a percent of the maximum under passive conditions. $*P < 0.05$ for comparisons against the 4-6 month group.

Figure 4. Concentration-response curve as a function of phenylephrine for vessels isolated from the male and female kidney at 4 to 6 months of age (A) and 8 to 13 months of age (B) depicting arterial diameter expressed as a percent of the maximum passive diameter. Panel B clearly indicates that the females appear to have a 'protected' α_1 -adrenergic constrictor function. $*P < 0.05$ for comparisons against the 4-6 month group.

Renal interlobar artery constriction to A61603, a specific α_{1A} -adrenergic receptor agonist, as a function of age and gender are presented as Figure 5. These data are qualitatively similar to those of phenylephrine and that maximum constricted diameter is not seen to differ between the two receptor agonists when compared within age groups and gender. A61603 induced maximum arterial constriction was significantly attenuated when comparing responses from those of the younger age group (four to six months; $37 \pm 2 \mu\text{m}$ for male and $47 \pm 11 \mu\text{m}$ for female) in both males (Figure 5A) and females (Figure 5B) but at differing age timepoints; 8 to 14 months of age for the male ($85 \pm 8 \mu\text{m}$) versus

Figure 5. A61603, an α_{1A} -specific adrenergic receptor agonist, concentration-response curve as a function of age depicting arterial diameter expressed as a percent of the maximum passive diameter for interlobar arteries isolated from the male (A) and female (B) kidney. * $P < 0.05$ for comparisons against the 4–6 month group.

14+ months for females ($85 \pm 13 \mu\text{m}$). Likewise, the EC_{50} values for A61603 were 1.8×10^{-8} and 9.3×10^{-9} M when comparing male ages of four to six months and 8 to 14 months, respectively. Similarly, the differences in EC_{50} values for A61603 in females were 1.8×10^{-8} M in the younger two groups (four to six and 8 to 13 month age) and 1.2×10^{-8} M for the 14+ months age group.

Discussion

Similar to humans, male Munich Wistar rats manifest renal pathological changes with age independent

of increases in blood pressure (Roth et al. 1993; Remuzzi et al. 1992). These reports in the literature depict that five of 15 rats tested at six months and 14 of 15 rats tested at 12 months had chronic renal nephropathy. By 13 to 18 months, 44 of 52 rats were found to have advanced renal failure. The cause of the sclerosis and glomerular loss does not appear to be immunologic in nature, as in many other forms of glomerulonephritis, but may be the result of tissue damage (Haley and Bulger 1983). Therefore, the rat appears to be a suitable model to investigate the mechanisms of altered renal vascular function with age.

The results of this study are based on a longitudinal model of aging animals. This scheme is where all rats were aged under similar conditions and randomly assigned into age usage groups. This methodology was employed to minimize environmental conditions that could lead to statistical error in comparisons. All animals utilized in these experiments appeared to be healthy as indicated by the daily assessment of general well-being, activity, coat, food and water intake.

Our results show that the preglomerular resistance arteries from the Munich Wistar rat have significantly impaired constrictor function to α -adrenergic challenges as a function of age. Furthermore we have demonstrated that this reduction in constrictor function can be attributed, at least in part, to the α_{1A} -adrenergic receptor. When coupled with the reported evidence that α -adrenergic receptors are the primary receptors that mediate changes in renal vascular resistance during sympathetic activation (Wolff et al. 1987; Blue et al. 1992), a loss of this type constrictor function could translate into lower preglomerular resistance resulting in higher glomerular pressures. Secondly, four to six months male and female Munich Wistar rats both reached maximum constriction at 1×10^{-3} M phenylephrine, and there was no gender difference at that time (Figure 4A). By eight months old, the male rats demonstrated a significant reduction in the amount of constriction which continued throughout the remaining age ranges studied (Figure 4B). On the other hand, female rats showed no change in maximum α_1 -adrenergic constriction until they were past the 15-month age. These studies reveal that there is a significant gender difference in the α -adrenergic constrictor function. This gender difference coincides with the concept that males undergo renal aging changes at an earlier age than do females.

Preglomerular arterial dysfunction has been described to contribute significantly to the renal

demise seen with age (Shanley 1996; Reckelhoff et al. 1992; Khraibi et al. 1993; Brenner and Anderson 1992; Anderson and Brenner 1986; Brenner et al. 1988; Anderson et al. 1988; Simons et al. 1994; Neuringer and Brenner 1992). This increased glomerular pressure can eventually lead to sclerosis and cell death (Khraibi et al. 1993; Anderson et al. 1988; Meyer et al. 1983). The literature is quite prevalent in describing the benefits realized by reducing blood pressure to the kidney, whether systemic or renovascular, in maintaining kidney function (Simons et al. 1994; Rennke 1988; Miller et al. 1990). Combined, these reports point to a significant vascular component in renal function with age. Our studies demonstrate that these cortical preglomerular vessels are compromised in their ability to constrict via α -receptor mediated mechanisms. Furthermore, we contend that this reduced ability to constrict then may translate into higher glomerular pressures and damage with age.

Even more specifically, A61603, an α_1 -adrenergic receptor agonist, demonstrated even a greater level of disparage within the gender groups and as a function of age (Figures 5A and B). These data point to a specific defect that occurs in the male at a much younger age than in the female. Both sets of curves depict significant changes in the EC_{50} when comparing the younger age group to the oldest age group examined with the alteration occurring at a much earlier time point in the male (eight months in the male *versus* 14 months in the female). Therefore, a major constrictor mechanism involving the α_1 -adrenergic receptor appears to be significantly impaired.

Only a few studies in tissue other than the kidney have correlated vasoconstrictor responses with aging. Miyauchi et al. (1989, 1992) showed a positive correlation between increases in plasma ET-1 and the age of hypertensive and normotensive human subjects. An increase in the plasma norepinephrine levels has been found in older humans; not related to an impairment of neuronal uptake (Lindeman 1993). However, elderly patients have less of a vasoconstriction to norepinephrine due to a reported down-regulation of adrenergic receptors in systemic skeletal muscle tissue (Wesson 1969).

The literature reports that in heart a norepinephrine spillover from the nerve endings to plasma (Ng et al. 1993) coupled with a reduction in re-uptake (Esler et al. 1995) suggest an augmentation in plasma norepinephrine with age (Ziegler et al. 1976; Young

et al. 1980). Renal sympathetic nerve activity also has been reported to increase, but there is impaired baroreflex control of both heart rate and blood pressure (Hajduczuk et al. 1991). In human males, a marked decline in baroreflex buffering of blood pressure is due to, at least in part, a marked reduction in α -adrenergic receptor function (Castellani et al. 1999; Jones et al. 2003). Speculation on how these findings could be reconciled might include: 1) a comparison of prazosin binding in the rat parotid cell indicating a naturally occurring post- α -adrenergic receptor defect in signal transduction (Ishikawa et al. 1989); 2) Age-related impairments in α -adrenergic responsiveness could be partially caused by alterations in the coupling of α -adrenergic receptors and G-proteins (Myamoto et al. 1992); 3) A decline in the G protein amplification of constriction (Robert et al. 1998) and 4) Competitive binding experiments (prazosin) revealed that maximal binding of the α -adrenergic receptor of the interlobar arteries is reduced 25% by 10 months of age and 50% by 18 months of age (Passmore et al. 2005). We speculate that the α -adrenergic receptor density or downstream signaling (specifically the G-protein cascade) events are altered as a function of age in the male rat; pointing to the possibility that the α -adrenergic receptors are down-regulated (Parekh et al. 2004). Future experiments will hope to clarify these issues as a function of aging and gender.

Therefore, there may be an overall loss of sensitivity to circulating constrictor agents, such as norepinephrine and endothelin with age. The results of our study supports the concept of a decreased function in the α_1 -adrenergic receptor mediated constrictor mechanism of the kidney preglomerular arteries with age. The decrease in constrictor function appears at an earlier age in males than in females. The overall decrease in constrictor mechanism function could then alter the hemodynamic profile exposing the glomeruli to unbuffered changes in renal afferent arteriole perfusion pressure leading to glomerular damage, decreased filtration capacity and increased glomerular resistance.

Acknowledgements

The work accomplished in this submission was supported in part by the American Federation for Aging Research (AFAR) Grant (JCF); American Heart

Association, Ohio Valley Affiliate Grant-In-Aid (JCF & JCP); and The University of Louisville.

The authors graciously acknowledge the outstanding technical support provided by Ms. Kathleen H. Hamilton.

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