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Reduced Alpha Adrenergic Mediated Contraction of Renal Preglomerular Blood Vessels as a Function of Gender and Aging

John C. Passmore,[1]* Irving G. Joshua,[1] Peter P. Rowell,[2] Suresh C. Tyagi,[1] and Jeff C. Falcone[1]

[1]Department of Physiology and Biophysics, School of Medicine, University of Louisville, Louisville, Kentucky 40292
[2]Department of Pharmacology and Toxicology, School of Medicine, University of Louisville, Louisville, Kentucky 40292

Abstract As human males age, a decline in baroreflex-mediated elevation of blood pressure occurs due, at least in part, to a reduction in alpha-1 adrenergic vasoconstrictor function. Alpha adrenergic constriction is mediated by guanosine triphosphate binding Protein (G Protein) coupled signaling pathways. Alpha-1 A/C, B, and D adrenergic receptor expressions, measured by GeneChip array, are not reduced during aging in renal blood vessels of male or female rats. Alpha-1 A GeneChip expression is greater, at all ages studied, in females than in males. Prazosin binding by alpha-1 adrenergic receptors is greater in young adult female rats than in young adult male rats; however, it is reduced with aging in both male and female rats. G alpha q GeneChip expression declines while expression of adrenergic receptor kinase (GRK2) and tyrosine phosphatases (TyrP) increase with aging in male rats. The declines in alpha-1 adrenergic receptor binding and G alpha q expression and also the increases in GRK2 and TyrP expression likely relate to the age-related decline of vasoconstriction in male rats. The information that the expression of alpha-1 A adrenergic receptors is greater in female rats and (GRK2) expression does not increase during aging could relate to the gender differences in vasoconstrictor function with aging. Gene therapy to ameliorate the age-related decline in renal function could possibly reduce the need for renal dialysis. Signaling pathways such as those reviewed herein may provide an outline of the molecular pathways needed to move toward successful renal gene therapy for aging individuals. J. Cell. Biochem. 96: 672–681, 2005.

Key words: kidney; stress; blood flow; male, female; micro-array, gene array

A decline in baroreflex buffering of blood pressure occurs as human males age and is due, at least in part, to a reduction in alpha-1 adrenergic receptor function [Jones et al., 2003]. Examples of decreased renal vasoconstrictor effectiveness in aging are demonstrated by the fact that young men undergo a reduction of approximately 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]. In addition, elderly subjects have a reduction in sympathetic neural control of blood pressure during tilting from supine to the upright posture [Barnett et al., 1999]. Similarly, senescent Fischer 344 rats have been reported to have sustained a shorter duration of elevated renal resistance compared to their younger male counterparts as a function of air-jet stress tests [Stauss et al., 1996]. Aged rats (24-months-old) also have impaired baroreflex control of renal sympathetic nerve activity [Irigoyen et al., 2000]. Renal sympathetic nerve activity increases but there is impaired arterial baroreflex control of heart rate and blood pressure, suggesting impaired constriction of renal blood

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*Correspondence to: John C. Passmore, PhD, Department of Physiology and Biophysics, School of Medicine, University of Louisville, Louisville, KY 40292.
E-mail: jcpass01@gwise.louisville.edu

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vessels during increased renal nerve activity [Hajduczok et al., 1991]. The information obtained from aging rats is consistent with reported findings from human studies ultimately describing a downregulation of the adrenergic control mechanisms of renal blood vessels during aging. Therefore, rats appear to provide a model, which can be used in studies to determine the role of the loss of renal vascular regulation in the altered circulatory and renal function of aging humans.

ETIOLOGY OF AGE-RELATED LOSS IN RENAL FUNCTION

It has been shown that human renal function declines by approximately 1–2% per year in essentially all males beginning around the age of 40 years [Lindeman, 1993]. The rat is described to have a similar etiology of renal decline as a function of age [Baylis, 1996], including the development of glomerular sclerosis [Parekh et al., 2004]. Tank et al. [1994] reported that renal plasma flow and GFR are increased in the aging rat. An increase in glomerular capillary pressure and plasma flow in partially nephrectomized rats is associated with glomerular sclerosis [Anderson and Brenner, 1986]. However, it has been demonstrated that glomerular capillary pressure is not increased in aging male rats at rest [Baylis, 1996]. Since there appears to be an age-related inability to reduce renal blood flow during stress [Stauss et al., 1996] and exercise [Kenny and Zappe, 1994], there remains the possibility that increased glomerular capillary blood flow in aging rats could occur in stressful situations due to reduced effectiveness of adrenergic-mediated vasoconstriction (Fig. 1). The concept that a decline in renal function appears in essentially all male humans and rats, leaves the impression that the decline is a "normal" part of aging. However, those "normal" changes, which appear to reduce renal function during aging, may be a prelude for more deleterious declines in renal and/or circulatory function in certain living conditions such as stress. The fact that a genetic change that may even be a "normal" part of aging may be associated with the onset of more serious declines in physiological function, reveals the importance of research related to the differentiation of the age- and gender-related effectiveness of preglomerular blood vessels to buffer the glomeruli from elevated blood pressure when stress-related vasoconstrictor agents are released into the circulation. Figure 1 provides an overall synopsis of a possible mechanism, which would convey the increase in adrenergic activity in stress through signal transduction mechanisms to cause an increase in blood pressure, which would not be buffered from causing elevated pressure to renal glomeruli.

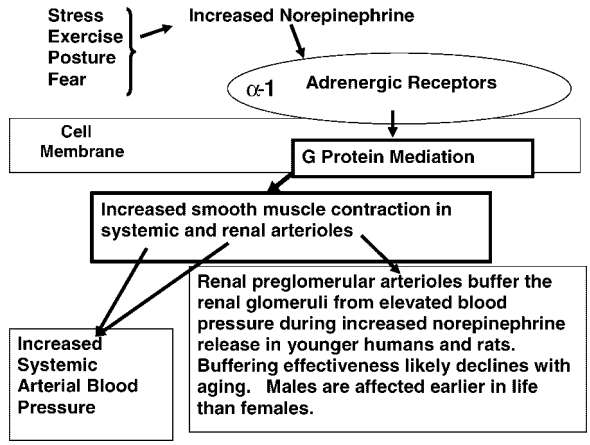

Fig. 1. Diagram to represent downregulation of renal preglomerular vasoconstrictor effectiveness in aging male rats.

SELECTION OF RAT AGE RANGES

With respect to the vasoconstriction studies, it appears that 4-month-old rats are mature adult animals. It has been shown that beta-1 and beta-2 adrenergic receptors that regulate glucose metabolism are mature in 2–3-month-old rats [VanErmen et al., 1992], and vascular distribution in the prostate gland is completed in 3-month-old rats [Skolnik et al., 1992]. Therefore, we consider 4 ± 0.5-month-old rats as young adult subjects, which have reached a mature stage of life. At the aging end of the life cycle, previous studies have shown that 14 of 15 male Wistar rats develop some chronic renal failure by 12 months of age [Roth et al., 1993]. The primary histological findings were chronic nephropathy, including interstitial fibrosis with lymphocyte infiltrates, tubular dilation, and cysts, which were large and in many cases, appearing to lead to hydronephrosis. Our laboratories have observed the same histological findings at 14 months of age [Parekh et al., 1999, 2004]. While renal vasoconstriction may or may not be related to the histological findings, 14 months of age was chosen as a starting point to analyze possible alterations in renal vascular

function. In the present study, the results of the vascular contraction experiments led to dividing the age ranges into three groups (3.5–4.5 months, 8–13 months, and 16–19 months of age), partially based on the relative constriction differences over age and gender. The 3.5–4.5-month-old age range is simplified by referring to it as 4 months old in this article.

ADRENERGIC CONTROL OF THE RENAL CIRCULATION

Affinity site studies, comparing the responsiveness of the renal circulation of rats treated with alpha l-adrenoreceptoyagonists to radioligand binding studies of cloned bovine alpha-1C adrenergic receptor and to that of the native type alpha-1 A adrenergic receptors of the rat, indicated equality between the two adrenergic receptors (which are termed alpha-1 A/C, herein). The alpha-1 A receptor is the predominant alpha-1 adrenergic receptor subtype, which mediates vasoconstrictor responses to exogenously administered norepinephrine in the perfused kidney of the adult rat [Blue et al., 1995; Passmore et al., 2005].

In this article, we summarize our findings related to the decline in alpha adrenergic receptor-mediated renal vasoconstrictor activity during aging in male rats compared to female rats as well as the possible role of currently recognized signal transduction activities, which occur as a result of stimulation of renal vascular alpha-1 adrenergic receptors. The studies summarized in Figure 2 reveal that interlobar arteries from 4 to 5-month-old male or female rats exposed to phenylephrine (alpha-1 A/C, B, and D agonist) or A61603 (alpha-1 A agonist) produced a maximal interlobar artery constriction, which reduced the diameter of the artery to approximately 25% of the original diameter. However, in the age range of 8–15 months the arteries from the male rats maximally constricted to approximately 50% of the original diameter to both agonists, while constriction of arteries from females at a similar age range were not distinguishable from those of females in the 4–5-month-old group [Falcone et al., 2005]. Female rats (17–19-month-old) demonstrated reduced constriction to both agonists similar to the reduction found in male rats over 8 months of age. Potassium-evoked vasoconstriction of interlobar arteries was not different among the groups, suggesting that loss of smooth muscle integrity is less likely to contribute to the downregulation of contraction than is loss of signal transduction integrity [Passmore et al., 2005].

Previous publications from our laboratories [Falcone et al., 2005; Passmore et al., 2005] reveal that both Wistar and Munich Wistar rat interlobar arteries show similar age- and gender-related changes in interlobar artery contraction. Figure 1 provides an overall synopsis of species, gender, and age concepts for interlobar artery contraction. It has been shown that all renal preglomerular arteries and arterioles in rats react similarly to adrenergic agonists so that interlobar artery studies likely represent the typical response found in all renal preglomerular arteries in these strains of rats [Casellas et al., 1985].

Summarizing the information to this point reveals that male rats undergo a significant reduction in preglomerular adrenergic constriction beginning by 8 months of age. Female rats appear to develop the same reduction by approximately 16 months of age. The information described above makes it clear that renal interlobar arterial constriction to alpha-1 adrenergic agonists in male rats is reduced approximately 8 months earlier in the life cycle than that of the female rats. Therefore, it is likely that constriction of the preglomerular renal blood vessels of male rats would exert less reduction of blood flow in the renal microcirculation during times of adrenergic-mediated stress responses at a much earlier age than those of female rats. The fact that there is reduced effectiveness to alpha-1 adrenergic stimulation in the preglomerular circulation of male rats over 8 months of age, but female rats are protected approximately twice as long, indicates the importance of investigating both the expression of and signaling pathways related to those receptors as a function of age and gender in rats to determine similarities between rat and human downregulation of renal vasoconstriction during aging.

GENETIC EXPRESSION OF ALPHA-1 ADRENERGIC RECEPTORS

Since genomic investigational techniques have made it possible to determine the potential effects of changes in gene expression on the effectiveness of cellular events, GeneChip expression studies were done to determine any

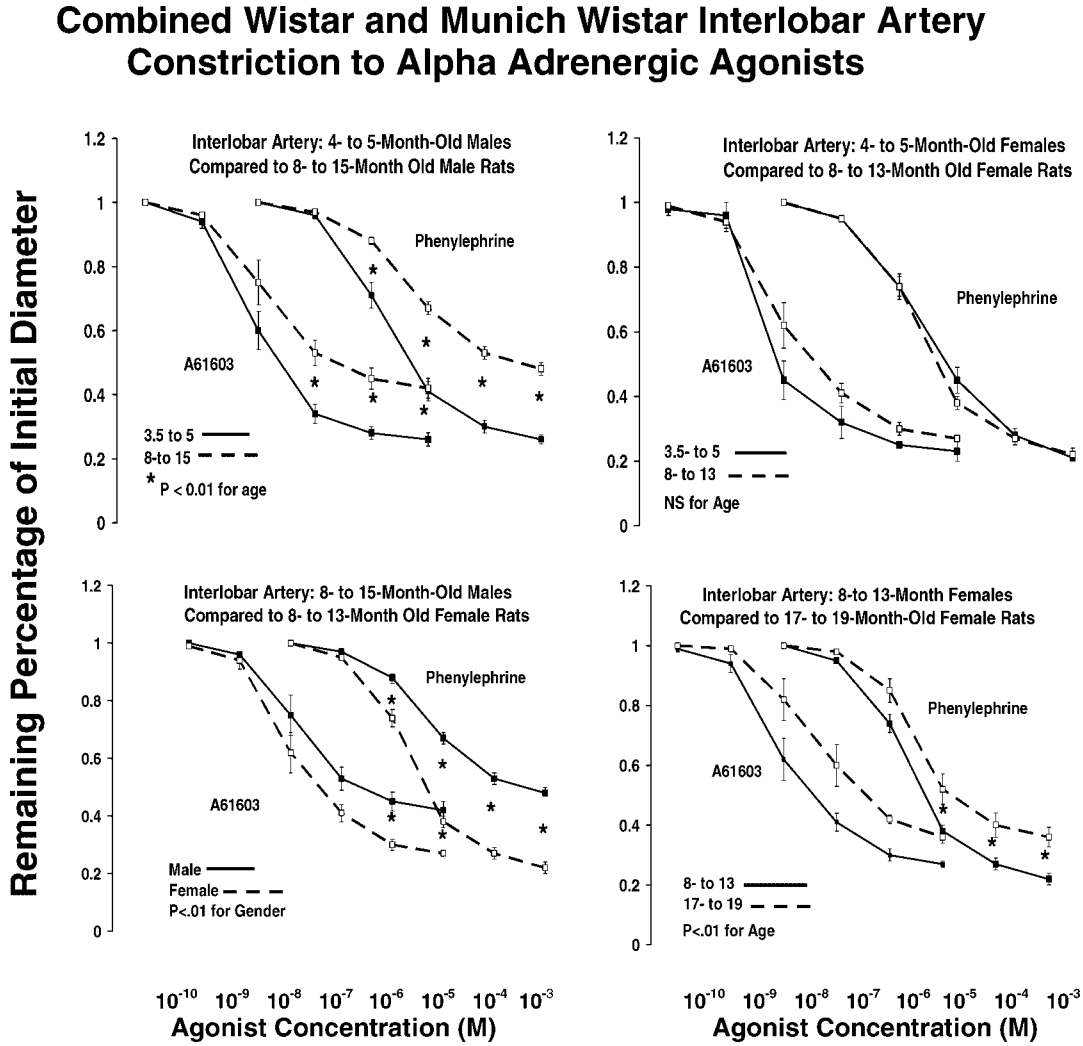

Fig. 2. A61603 (left) and phenylephrine concentration-response curve as a function of age for interlobar arteries isolated from male and female kidneys, with the inner diameter expressed as a fraction of the maximum diameter as measured under passive conditions. (n = 5–8 per group). All groups contain rats of both the Wistar and Munich Wistar species. Values shown are mean ± SE. *$P < 0.05$ for comparisons of the older group against the younger groups or male against female groups.

differences in expression of those genes that produce alpha receptors. For the GeneChip analyses, 4-month-old male Wistar rats were compared with 11-month-old male Wistar rats as the best ages to reflect changes related to downregulation of vascular constriction in males. The data from male rats are also compared to those found in female rats. Since female rats did not lose contractile effectiveness during the first 14 months of age, it seemed appropriate to choose an overall group that would still maintain maximum contractile effectiveness. Therefore, the GeneChip expressions were measured in females that were 4–11-month-old. These analyses indicated that gene expression was similar for younger and older male rats for all three adrenergic receptor types (A/C, B, D; [Passmore et al., 2005]). The information in Table I demonstrates that there are both age- and gender-related differences in gene expression. The gene analyses indicated no significant difference among young male, aging male and female Wistar rats for alpha-1B or alpha-1D adrenergic receptors. However, female rats in the 4–11 months age range demonstrated a more than twofold greater expression of alpha-1A/C adrenergic receptors than male rats at either 4 or 11 months of age (Table I). These studies indicate that the genetic production of alpha-1 adrenergic receptors

TABLE I. GeneChip Array Expression[a] of Alpha-1 Adrenergic Receptor Signaling Components in Young Adult Male, Various Aged Female, and in Aging Male Wistar Rats

Gene number and name	4-month-male	11-month-male	3.5–11-month female
gb:NM_016991.1 alpha-1B adrenergic receptor	152 ± 20	193 ± 4	170 ± 17
gb:U07126.1 alpha1C-adrenergic receptor	24 ± 10	24 ± 13	52 ± 7**,***
gb:NM_024483.1 alpha-1D-adrenergic receptor	22 ± 3	17 ± 2	24 ± 7
gb:NM_031036.1 GTP binding protein Gq, alpha	81 ± 2	43 ± 14*	53 ± 11**
gb:M12672.1 GTP binding protein G-i, alpha	275 ± 57	356 ± 46	325 ± 23
gb:BI277035 GTP binding protein G-s, alpha	3518 ± 248	3406 ± 370	3278 ± 379
gb:AI716801 adrenergic receptor kinase, beta 1	110 ± 10	173 ± 21*	112 ± 6***
gb:AI170771 growth hormone receptor	212 ± 11	167 ± 5*	133± 10**
gb:U05963 P tyrosine phosphatase, non-receptor	10 ± 1.5	34 ± 4*	34 ± 18**
gb: NM_012763 P tyrosine phosphatase, receptor type A	90 ± 4	143 ± 13*	214 ± 40**

[a]The signal intensity for each gene was calculated as the average intensity difference, as represented by [Σ(PM−MM)/(number of probe pairs], where PM and MM denote perfect match and mismatch probes.
*Signifies that the aging male group (11 months) is different ($P < 0.05$) from the young adult male group.
**Signifies that the female group (3.5 to 11 months) is different ($P < 0.05$) from the young adult male group (4-months-old).
***Signifies that the female group (3.5 to 11 months) is different ($P < 0.05$) from the aging male group (11 months).

is unchanged in the first 11 months of life in the male rat, while alpha adrenergic constriction is impaired by 8 months of age in male Wistar rats. On the other hand, female rats maintain an unchanged level of interlobar artery constriction during the first 13 months of life and also maintain a greater level of alpha-1 A/C receptor genetic expression during that time period. The increased level of alpha-1 A/C gene expression would likely contribute to the maintenance of renal vasoconstrictor activity in the female rats.

Additionally, reverse transcriptase polymerase chain reaction studies were performed on pieces of whole renal cortical tissue of both young adult and aging male Munich Wistar Rats. Alpha-1 A/C adrenergic receptor mRNA in renal cortex was also not significantly different between younger 4-month-old male rats and older 15-month-old male rats [Passmore et al., 2005].

ADRENERGIC RECEPTOR BINDING STUDIES

Binding studies showed a reduced alpha-1 adrenergic receptor binding activity to [^{3}H]-prazosin (to measure the maximum binding of alpha-1 A/C, B, D receptors) in renal arterial tissues from 9 to 10-month-old and 18 to 22-month-old male rats compared to that of 4-month-old male rats [Passmore et al., 2005]. Prazosin binding was significantly continuously reduced over both of the age ranges (4 vs. 9–10-month-old and 9–10-month-old vs. 18–22-month-old) studied in male rats. Arterial tissue obtained from female rats demonstrated significantly greater binding at both 4 and 9–10-months-old compared to those of male rats. When the values for 4 and 9–10-month-old female rats were combined and compared to the combined values for 4 and 9–10-month-old males, the results suggest that the females had greater prazosin binding throughout that 6-month period. Concurrently, the male rats had a decline in artery constriction while the females had no decline in artery constriction. By 18–22 months of age, male and female rats both demonstrated a reduced prazosin binding compared to 4-month-old rats, but no difference in prazosin binding between genders.

For the binding studies, our laboratories chose to measure the maximum binding (Bmax) data because a previous report indicated that the Bmax of prazosin (not the sensitivity, Km) was the alpha-1 adrenergic receptor factor, which changed with aging in prazosin binding studies of the rat renal cortical tissue

[Galbusera et al., 1988]. Also, the vasoconstriction factor that is changed with aging in male rats is the maximal contraction. The binding data could suggest that a greater Bmax for prazosin in the blood vessels from 4 to 10-month-old female rats, compared to the male rats at either age, is a reflection of the greater gene array expression of the alpha-1A/C receptors than that in similar aged male rats. Also the mechanism for the loss of vasoconstrictor effectiveness at an earlier age could relate to data indicating that alpha-1A/C receptor expression is greater in female rats than in male rats. However, the relative decline in binding over time in both male rats and female rats leaves the cause for the decline and even the gender differences unclear.

SIGNAL TRANSDUCTION RELATED TO ALPHA ADRENERGIC RECEPTORS

G Proteins

The activation of alpha adrenergic receptors results in the activation of heterotrimeric G proteins. It has been demonstrated that alpha adrenergic receptors are largely coupled to Gq/11 Gs and/or Gi types of G proteins (Fig. 3). The reduced gene expression for G alpha q in aging male rat renal arteries (Table I) could play a role in the renal vascular contraction deficit in male rats [Passmore et al., 2005]. However, this does not explain the difference between male and female rats, as the G alpha q Gene Chip expression for the female group (4–11-month-old) is not different from the aging male group (11-months-old). It is also known that alpha-1 adrenergic receptors can be coupled to other classes of G proteins [Garc'ia-S'ainz et al., 2000]. G alpha i and G alpha s gene expression appear similar in all groups. The idea that down-regulation of adrenergic receptor function affects downstream elements is illustrated by the report that epinephrine-stimulated $^{45}Ca^{++}$ efflux and inositol triphosphate production in parotid cells were reduced 31% and 36%, respectively, in old rats compared to young rats and the two events were directly correlated in both rat groups. The report also indicates that age-related impairments in alpha-1 adrenergic responsiveness were likely due to alterations in the coupling of alpha adrenergic receptors with G proteins [Myamoto et al., 1992].

Receptor Desensitization

A common functional feature of cellular responses to G protein coupled receptor stimulation by agonists is that their activity is rapidly attenuated by receptor desensitization, which is mediated by uncoupling of activated receptors from G proteins, and effectively terminates the signaling process [Grady et al., 1997]. Uncoupling of the activated receptor from its G proteins by receptor phosphorylation occurs within seconds to minutes of receptor activation. This receptor uncoupling is mediated by G protein receptor kinase (GRK; serine/threonine protein kinase). The concept of GRK activity in receptor desensitization is diagramed in Figure 3. GRK molecules, through their action to induce receptor phosphorylation and through uncoupling of the receptor from G proteins, terminate the receptor activity that occurs

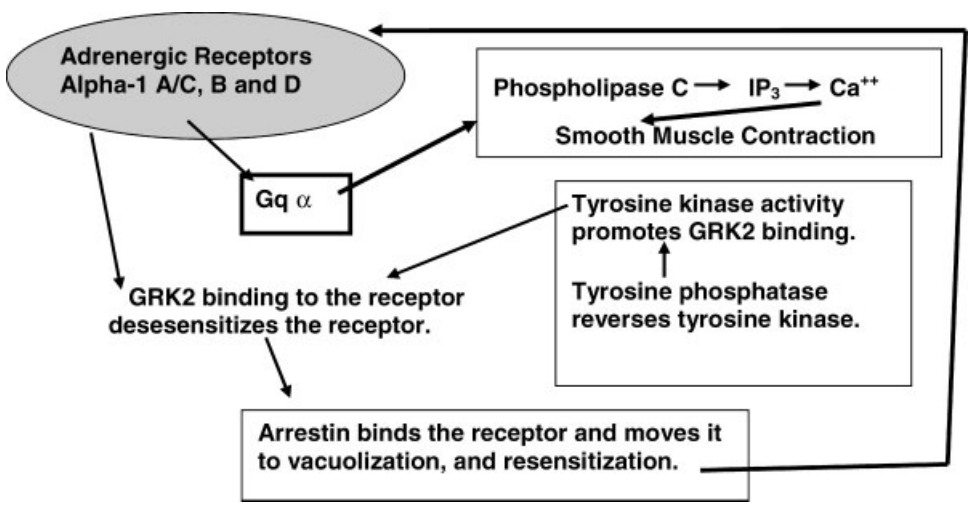

Fig. 3. Diagram to represent the possible signal transduction pathways described in the text.

following the stimulation of alpha-1A and alpha-1B subtypes. Additional proteins, known as arrestins, are involved in desensitization by initiating the process of internalization or vacuolization of the receptor protein. Receptor endocytosis reduces the number of receptors and further contributes to receptor desensitization and re-sensitization activity. GRKs are important modulators, which function in concert with arrestins and other kinases to regulate adrenergic receptor cycling and the interaction between the receptor and its respective heterotrimeric G protein. GRK2 and 3 are the kinases that have been reported to exhibit the most specific ability to desensitize alpha-1 adrenergic receptors [Carman and Benovic, 1998]. GeneChip array data in Table I reveals that the adrenergic G protein receptor kinase beta 1 (equivalent to GRK2) is increased in aging male Wistar rats compared to younger males and all females. Differences in the rate of receptor coupling or uncoupling activity could reduce the re-sensitization effectiveness of alpha-1 adrenergic receptors in aging male rats compared to the younger males and the chosen group of females. The lack of maximum binding capacity of alpha-1 adrenergic receptors in renal arterial tissues of aging rats could be related to a reduced effectiveness of functioning of the desensitization, internalization, and resensitization of the adrenergic receptors. Studies in human cadaver brains demonstrating that the immuno-blot densities of GRK2 and beta-arrestin-2 in human brains declined with aging (comparing 16–87 years of age) indicate the likely possibility that those components have reduced effectiveness in aging humans [Grange-Midroit et al., 2002]. Studies from our laboratories, which indicate reduced alpha adrenergic receptor effectiveness of renal vasoconstriction, along with the increase in adrenergic receptor kinase expression and the reduced expression of G alpha q type G proteins in aging male rats, support the concept that declining receptor effectiveness may be linked to the downstream signaling events in the declining renal vascular function during aging.

TYROSINE KINASES MODULATE G PROTEIN COUPLED RECEPTORS

Tyrosine Kinases (TyrK) are also known to be important factors in vascular smooth muscle contraction. Agonist activation of vasoactive receptors on smooth muscle membranes have been shown to induce tyrosine phosphorylation (TyrP) associated with vascular calcium release and smooth muscle contraction in rabbit ear arteries [Wijetunge et al., 1992; Srivastava and St. Louis, 1997]. Vanadate-induced smooth muscle contraction (ileum) involves decreased activity of TyrP [Swarup et al., 1982] suggesting that TyrP activity modulates increased or decreased contractile activity of smooth muscle [Saifeddine et al., 1994]. In experiments in which angiotensin II was used to constrict the blood perfused afferent and efferent arterioles of juxtamedullary nephrons in young adult rats, broad spectrum blockade of TyrK reduced the constriction of those arterioles by 34% and 52%, respectively, demonstrating that reduction in TyrK activity reduces renal vascular constriction [Carmines et al., 2001]. When a TyrK inhibitor (AG1478) that specifically blocks the epidermal growth factor receptor (EGFR) TyrK was administered, the constriction to Angiotensin II in afferent and efferent arterioles was reduced 52% and 51%, respectively, suggesting that renal afferent arteriolar constriction to angiotensin II is most affected by the EGFR form of TyrK. Afferent arteriolar calcium entry and release associated with afferent arteriolar constriction with angiotensin II [Che and Carmines, 2002] and norepinephrine [Salomonsson and Arendshorst, 2004] were also reduced by TyrK blockade. The L-type calcium channel blocker, nifendipine had no effect on calcium entry in the TyrK-blocker-treated arterioles suggesting that TyrK plays a major role in calcium entry during norepinephrine contraction [Salomonsson and Arendshorst, 2004]. It is clear that there is an interaction between vasoconstrictor agonists and TyrK activity, particularly the TyrK of the EGF receptor.

The information that TyrP plays a role in mediation of vascular tone, which is opposite to that of TyrK [Saifeddine et al., 1994; Che and Carmines, 2002], suggests that the role of TyrK in vascular smooth muscle contraction would be reduced in vascular tissue containing elevated levels of TyrP. Results from the GeneChip array experiments demonstrate that both receptor type and non-receptor type TyrP are increased in aging male rats and that the TyrP GeneChip array data from the female rat group were not different from that in the aging males (Table I). Our laboratories reported a marked reduction

in TyrK activity in whole renal cortical tissues (not specifically blood vessels) of aging male rats [Parekh et al., 1999].

GRK2 phosphorylation on its tyrosine residues promotes an increased activity of GRK2 toward its substrates, such as G protein-mediated receptors, which suggests that GRK2 phosphorylation by c-Src is inherent to G protein coupled receptor activation [Sarnago et al., 1999]. Treatment with a Src inhibitor abolishes TyrK phosphorylation of GRK2 and abolishes desensitization of the GRK2 associated receptor [Fan et al., 2001]. Loss of receptor desensitization by GRK2 would prevent the completion of the desensitization/re-sensitization cycle. An increase in GRK2 expression during aging is suggested by the increased expression of adrenergic receptor kinase shown in Table I. However, the increases in expression of both receptor and non-receptor TyrP (Table I) would indicate a possible mechanism for the reduction of the effect of TyrK activity to activate the GRK2 and would lead to the postulation of an age-related loss of effectiveness to complete adrenergic receptor desensitization/re-sensitization cycling in male rats. The increase in intracellular Ca^{++} to induce contraction of smooth muscle cells following GPCR stimulation is prevented by c-Src inhibition with Lavendustin A [Seki et al., 1999]. The linking of EGFR effectiveness to c-Src and the linking of c-Src to vascular smooth muscle contraction provide a logical format to explain dysfunctional arterial contraction in the aging male rats. The concept that the TyrK, c-Src, appears to play a role related to GRK2 in renal vascular contraction to GPCR is diagramed in Figure 3. Interestingly, female rats over the whole 4–10-month-old age range demonstrate elevated receptor type TyrP expression suggesting the possibility that the role for TyrK activity in constriction of interlobar arteries from female rats differs from that in those from male rats.

OVERALL SUMMARY

In summary, reduced alpha adrenergic receptor effectiveness for renal vasoconstriction, in the context of increased GRK2 expression and reduced expression of G alpha q type G proteins in aging male rats supports the concept of the involvement of signaling events in declining renal vascular function during aging. The activating and deactivating of signal transduction molecules among adrenergic receptors, G proteins, GRK2, TyrK, TyrP, and arrestins appears to be altered in a manner that is both age and gender specific. The early onset of reduced renal interlobar arterial constriction in male rats compared to female rats coincides with the gender specific downregulation of renal vasoconstrictor ability and renal function in humans. The relative complexity of information regarding the relationship between the signal transduction mechanisms and renal arterial constriction in aging male and female rats makes this important area of research difficult yet essential to the understanding of renal aging. Prospectively, the development in the understanding of receptor signaling mechanisms and relating the effectiveness of those mechanisms to the effectiveness of the downstream pathways to induce vasoconstriction is a fertile research area. The results of such studies will undoubtedly yield the critical information for future gene transfection experiments to improve renal vascular function in aging male rats and ultimately improve renal healthiness in aging humans.

Currently, patients in the over 65 years or older age range (especially men) make up approximately 50% of all patients on dialysis for end-stage renal disease related to diabetes, hypertension, vascular diseases, and glomerulonephritis [Lien and Lai, 2002]. Gene transfer studies in experimental animals have had varying degrees of success. Gene therapy strategy involves identification of a genomic region likely to contain the disease gene and then locating the disease gene [Patel, 1993]. The therapy entails introduction of the cloned gene into the affected organ. When a specific receptor (D2R) associated with a change in physiological function was identified and the vector injected into the specific area of tissue, an upregulation of the gene and a change in physiological function was observed under limited conditions [Ingram et al., 1998]. While gene therapy for kidney disease in aging individuals is still some distance in the future, integrative physiological, biochemical, and molecular biology studies of specific genes and their related physiological functions of the type reviewed herein and those completed in our laboratories are likely to improve the identification of the specific disease genes related to downregulation of renal vascular control in aging.

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