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PII S0024-3205(99)00621-9

Life Sciences, Vol. 66, No. 6, pp. 511–520, 2000

0024-3205/00/$--see front matter

# G-PROTEINS IN KIDNEYS OF SPONTANEOUSLY HYPERTENSIVE RATS

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(Received in final form September 14, 1999)

## Summary

$G_{s\alpha}$-, total $G_{i\alpha}$- and $G_{q/11\alpha}$-protein concentrations were investigated by quantitative immunoblotting in membranes of total kidney, renal cortex and medulla as well as in cortical tubules and glomeruli of Spontaneously Hypertensive Rats (SHR) and normotensive Wistar Kyoto rats (WKY), aged 5 weeks, 3 or 8 months. We found that total kidney of 5 week old SHR possess less $G_{s\alpha}$-, $G_{i\alpha}$- and $G_{q/11\alpha}$-proteins than controls. For $G_{s\alpha}$-proteins, differences found in total kidney were mirrored both in cortex (tubules and glomeruli) and in medulla. Decreased $G_{i\alpha}$-concentrations were accompanied by lower tubular but higher glomerular levels, while medullar levels were also increased. Decreased $G_{q/11\alpha}$-concentrations were reflected in decreased glomerular and medullary concentrations. Kidneys of 3 month old SHR and WKY possessed similar concentrations of all $G_{\alpha}$-species. In 8 month old SHR similar $G_{i\alpha}$-, but decreased $G_{s\alpha}$-and $G_{q/11\alpha}$-concentrations were observed. The $G_{s\alpha}$-decrease was reflected in cortex and medulla, the $G_{q/11\alpha}$-decrease in the medulla. We conclude that the main strain-related differences in $G_{\alpha}$-concentrations are seen in prehypertensive SHR.

*Key Words:* spontaneously hypertensive rats, G-proteins, hypertension, kidney, renal, rat, medulla, cortex, tubules, glomeruli

G-proteins are cell membrane proteins that link cell surface receptors to intracellular effector systems, such as adenylyl cyclase (AC) and phospholipase C (PLC), leading to the formation of second messengers such as cyclic AMP (cAMP) and inositol phosphates. The generation of cAMP is under dual control of stimulatory ($G_s$) and inhibitory ($G_i$) G-proteins, while generation of diacylglycerol and inositol-1,4,5-trisphosphate is mediated by $G_q$-proteins (1). In renal tissue, two compartments with clear different physiological function are distinguished. In the tubular compartment, reabsorption processes are regulated through the activity of the $Na^+/H^+$-exchanger

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(NHE) and the $Na^+/K^+$-pump in tubular apical and basolateral membranes respectively, and the regulatory control of these exchanger proteins depends on both AC and PLC pathways (2,3). In the vascular compartment, vascular tone is regulated through vasodilator agents which stimulate the activity of AC (4-7) and through vasocontractile agents which inhibit the activity of AC (8,9) and stimulate the activity of PLC (8,10). It is well known that both transduction systems are crucially implicated in the initiation of hypertension, by enhancing the $Na^+$-resorption and the vascular tone in the tubular, respectively the vascular compartments (11,12).

In the Spontaneously Hypertensive Rat (SHR), numerous abnormalities in the AC and PLC signal transduction have been found both in tubular and vascular renal compartments. In particular, altered dopamine (DA ; 2,13), adrenergic (14,15) and angiotensine II (ang II ; 16,17) reactivity has been reported. Alterations in receptor density have been reported before (18-21) but results were far from consistent over the whole life span of the SHR and especially not consistently present at the time of initiation and development of the hypertensive syndrome (19,22,23). Defective signal transduction might also be caused by downstream transduction partners, like G-proteins. It is known that G-proteins play a pivotal and catalytic role in the signal transduction chain implying that their relative abundance's are crucial to normal signal transduction (1). In SHR kidney in particular, evidence points to alterations of the $G_s$- and $G_i$-mediated pathways (24) and of the AC- (25,26) and PLC-pathways (27) which are distal from the receptor and proximal to the G-protein (23,26,28,29).

G-proteins and their tissue expression have been studied in kidneys from SHR and WKY, either in total kidney at different ages (30) or in one specific renal compartment at a particular stage of the hypertensive syndrome, most often the young adult stage (31-33). However, since the interpretation of results obtained either in total kidney or at an isolated stage of hypertension as to the etiology of the syndrome is difficult, we measured G-proteins both in vascular and tubular renal compartments at three different stages : the prehypertensive stage and the established hypertensive stage in young and older adult rats. In addition, a number of technical drawbacks, like blotting efficiency (34), have repeatedly hampered conclusive $G_\alpha$-protein measurements with Western immunostaining techniques. In a recent paper, however, we have shown that inclusion of an internal standard protein yields reliable data for comparative G-protein measurements (35). Taking these considerations into account, we decided to investigate $G_{s\alpha}$-, $G_{i\alpha}$- and $G_{q/11\alpha}$-proteins in membranes of different kidney fractions, including cortex, medulla and total kidney as well as cortical tubules and glomeruli, in SHR and WKY at the ages of 5 weeks, 3 months and 8 months.

## Methods

Male Okamoto-Aoki SHR, aged either 5 weeks, 3 or 8 months, and sex- and age-matched normotensive WKY were obtained from Harlan (Zeist, the Netherlands). They had free access to food (normal rat chow) and tap water. Systolic arterial blood pressure was assayed in triplicate on at least 2 different occasions by a tail-cuff-method (36) ; the last measurement was performed the day preceding the tissue preparation. Animal experiments were performed in accordance with the actual Belgian law on animal experimentation. Rat characteristics are summarized in Table 1.

Animals were killed by decapitation, kidneys were removed, freed from connective tissue and placed in ice cold homogenization buffer (50 mmol/L Tris-HCl, 2 mmol/L EDTA, 0.5 mmol/L phenylmethylsulfonylfluoride, 0.001 mmol/L leupeptine, pH 7.4). Cortex and medulla were dissected under a low magnification microscope. Total kidney, cortical and medullary membranes were prepared by homogenization and centrifugation as described before (35). The resulting membrane pellet was extracted in Laemmli sodiumdodecylsulphate (SDS)-buffer (62.5 mmol/L Tris-HCl, 5 % ß-mercaptoethanol, 2 % SDS, 10 % glycerol, 0.001 % bromophenolblue, pH 6.8;

37) in order to release the G-proteins from the lipophylic membrane domain. Protein concentration was determined by the method of Lowry (38) as modified by Chang (39), allowing determination of proteins in SDS-containing buffers.

For the isolation of glomeruli and tubules, cortices from 4 rats, aged 5 weeks or from 2 rats, aged 3 or 8 months were pooled for one determination. The procedure described by Sundaresan and Kelvie (40) was followed in all details. Briefly, glomeruli and tubules were isolated by successive sieving of a minced, sieved, centrifuged and washed cortical paste; tubules were retained by a 125 μm sieve (Retsch, Haan, Germany) and glomeruli by a 63 μm sieve. The purity of the fractions was evaluated by light microscopy after 0.1 % toluidine blue staining and amounted to 89.1 ± 1.1 % and 82.2 ± 2.4 % ($n$=60) for tubules and glomeruli respectively. Isolated glomeruli were generally without Bowman's capsule (a non-vascular structure continuous with the tubule) and the structure was fairly well preserved. The fractions were prepared for electrophoresis by ultrasonic homogenization in lysis buffer (10 mmol/L Tris-HCl, 10 mmol/L $MgCl_2$, 2 mmol/L EDTA, 0.001 mmol/L leupeptine, 0.2 mmol/L phenylmethylsulfonylfluoride with 0.0001 % aprotinine and 0.0025 % DNase); this homogenate was extracted and protein concentration was determined as described above.

Antibodies against $G_{s\alpha}$- and $G_{i\alpha}$-proteins were raised in white albino rabbits according to standard methods (41). The selected amino acid sequences were "TPEPGEDPRVTRAKY" (amino acids 325-329) for $G_{s\alpha}$ and "SKFEDLNKRKDT" (amino acids 306-317) for $G_{i\alpha}$ (42). Reactivity of the antisera was tested using an ELISA method, in which immunoplates were coated with the synthetic peptides and was found to be specific for the corresponding antigens; moreover, when tested in two-dimensional gelelectrophoresis experiments, the antisera proved to label all splice variants of the $G_{s\alpha}$ and all $G_{i\alpha}$-protein species respectively (results not shown), as was obtained previously with antisera against these peptides (42,43). Rabbit-anti-elastase and rabbit-anti-$G_{q/11\alpha}$-antisera were purchased from Rockland Laboratories (SanverTECH, Boechout, Belgium).

TABLE

| | | AGE | | |
|---|---|---|---|---|
| | | 5 weeks | 3 months | 8 months |
| BP | SHR | 129 ± 3[a] | 207 ± 5[b,c] | 224 ± 6[b] |
| | WKY | 136 ± 4 | 146 ± 4 | 141 ± 3 |
| BW | SHR | 128 ± 4[a] | 295 ± 6[c] | 384 ± 6 |
| | WKY | 137 ± 3 | 279 ± 3[c] | 388 ± 9 |
| KW | SHR | 544 ± 21[a] | 925 ± 20[c] | 1150 ± 30 |
| | WKY | 582 ± 19[a] | 895 ± 15[c] | 1135 ± 30 |
| RK | SHR | 4.24 ± 0.14[a] | 3.15 ± 0.05[d] | 2.98 ± 0.06 |
| | WKY | 4.26 ± 0.10[a] | 3.25 ± 0.04[c] | 2.93 ± 0.05 |

BP, systolic blood pressure in mm Hg; BW, body weight in g; KW, kidney weight in mg; RK, relative kidney weight (kidney weight:body weight ratio) in mg/g. Values are means ± SEM; $n$=25.
[a] $p < .001$ vs WKY;
[b] $p < .005$ vs 3 month old and vs 8 month old rats of the same strain;
[c], [d] $p < .005$ resp .05 vs 8 month old rats of the same strain.

All methods for blotting and immunostaining have been described in detail before (44). Conditions for obtaining optimal linear dose/response curves were determined in preliminary experiments. Stained blots were scanned with the 'Image master DTS' scanner (Pharmacia, LKB) and staining intensity was integrated (PDI-software, Pharmacia, LKB). These figures were corrected for the protein concentration of the applied sample and for the internal protein standard. The results, given in arbitrary units per mg protein, were used as estimates for the concentration of $G_\alpha$-proteins. When the antibody against $G_{s\alpha}$ is used, two clearly discernible bands with molecular weights of 52 kD ($G_{s\alpha long}$; $G_{s\alpha l}$) and 45 kD ($G_{s\alpha short}$; $G_{s\alpha s}$) are seen. $G_{i\alpha}$- and $G_{q/11\alpha}$-proteins are recognized as a single band at a molecular weight of 41 to 42 kD.

All values are given as means ± S.E.M.. For each $G_\alpha$-protein species and at each age, all data were initially compared in a two-way ANOVA with interaction of both parameters "strain" and "fraction". Upon significance, the influence of the hypertensive status was calculated separately for each fraction by means of an unpaired two tailed Student's *t*-test. *t*-values were adjusted according to the Bonferonni correction for multiple comparisons; $p<0.05$ was considered statistically significant.

## Results

Average values for the $G_{s\alpha}$-, $G_{i\alpha}$- and $G_{q/11\alpha}$-assays in kidney fractions are shown in figure 1A to figure 1I ; representative examples of immunoblot determination of $G_{s\alpha}$-, $G_{i\alpha}$- and $G_{q/11\alpha}$-proteins in kidney fractions of SHR and WKY are depicted in Figures 2A to 2D.

*$G_{s\alpha}$-protein concentrations.* In 5 week old rats, the cortical $G_{s\alpha l}$- and $G_{s\alpha s}$-concentrations in SHR amount to roughly half the concentrations in WKY. This seems at least partially to be due to decreased concentrations (by 40 % in average) of both isoforms in SHR tubules. There is no difference however in $G_{s\alpha}$-concentration in glomeruli of SHR and WKY. The medullary fraction of the 5 week old SHR also contains about 30 % less of both isoforms when compared to WKY, but only the decrease in the large isoform is significant. In keeping with these results, about 35 % less of both $G_{s\alpha}$-isoforms is found in total kidney membranes of the SHR. In 3 month old rats, no significant differences are found between SHR and WKY in any of the fractions. In 8 month old rats, the cortical $G_{s\alpha l}$-and $G_{s\alpha s}$-concentrations are decreased (about 25 %) in SHR when compared to WKY. Neither tubular, nor glomerular concentrations of these SHR are however altered. The medullary $G_{s\alpha}$-protein isoforms are also decreased in SHR (by about 25 %). In keeping with these results, ca. 30 % less of both $G_{s\alpha}$-isoforms is observed in total kidney membranes of SHR.

*$G_{i\alpha}$-protein concentrations.* In 5 week old rats, the cortical $G_{i\alpha}$-concentration in SHR amounts to roughly half the concentration in WKY. This might be due, in part, to a decreased (by ca. 30 %) concentration of tubular $G_{i\alpha}$-proteins. In contrast, the glomerular $G_{i\alpha}$-concentration, is increased in SHR (by about 40 %). The medullary $G_{i\alpha}$-concentration is also about 20 % higher in SHR than in age-matched WKY. As a result, total renal membranes of SHR are found to possess a (ca. 20 %) smaller $G_{i\alpha}$-protein concentration than controls. In established hypertensive rats, aged 3 or 8 months, no significant differences are found between SHR and WKY.

*$G_{q/11\alpha}$-protein concentrations.* In 5 week old rats, the cortical $G_{q/11\alpha}$-concentration in SHR amounts to roughly half the concentration in WKY. The tubular $G_{q/11\alpha}$-concentration is unchanged, but the glomerular $G_{q/11\alpha}$-concentration is significantly decreased in SHR (by about 25 %). The medullary $G_{q/11\alpha}$-concentration is also about 30 % smaller in SHR when compared to age-matched controls.

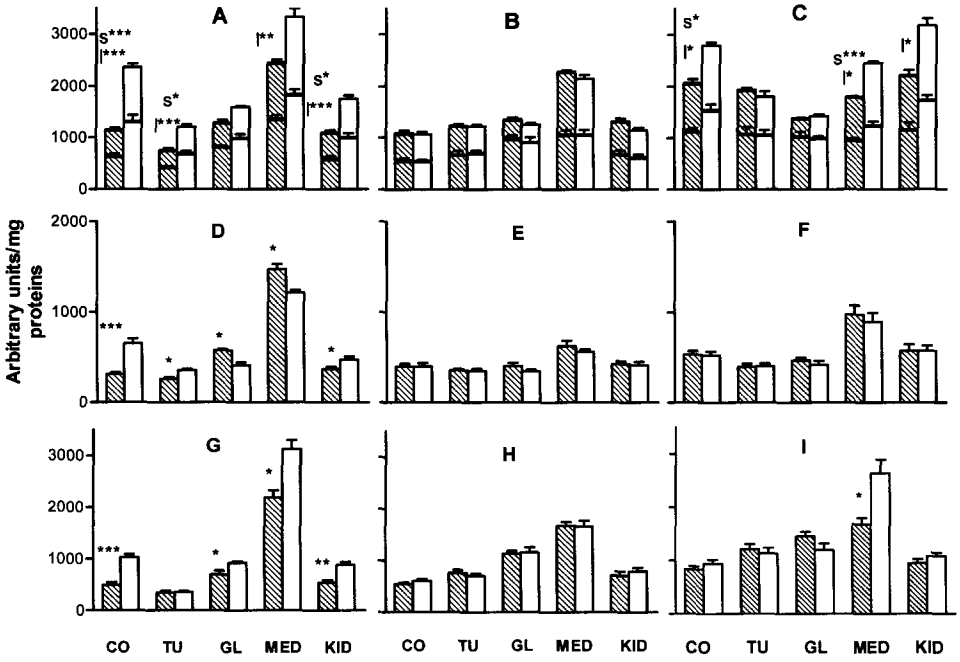
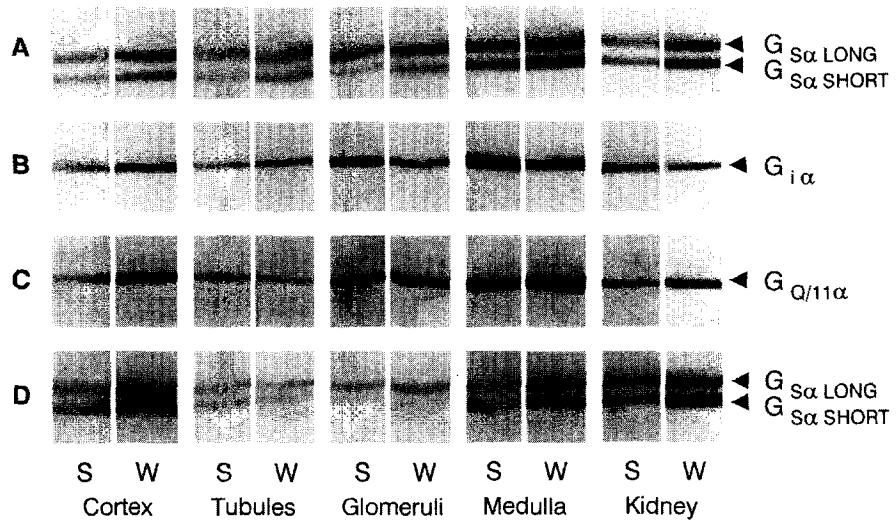



Fig. 1

$G_\alpha$-protein concentrations in arbitrary units/mg protein in kidney fractions, including cortex (CO), cortical tubules (TU) and glomeruli (GL), medulla (MED) and total kidney (KID) of Spontaneously Hypertensive Rats (hatched) and Wistar Kyoto rats (blank), aged 5 weeks (A, D, G), 3 months (B, E, H) and 8 months (C, F, I). A, B and C : $G_{s\alpha l}$ (lower part)- and $G_{s\alpha s}$ (upper part) concentrations ; D, E and F : $G_{i\alpha}$-concentrations and G, H and I : $G_{q/11\alpha}$-concentrations ; means ± SEM; $n$=5 ; *, **, *** p<.05, .01 resp. .005 vs normotensive controls ; " | " = $G_{s\alpha l}$ ; "S" = $G_{s\alpha s}$.

In keeping with these results, about 40 % less of $G_{q/11\alpha}$-proteins is found in total kidney membranes of SHR. In 3 month old rats, no significant differences are found between SHR and WKY. In 8 month old rats, the $G_{q/11\alpha}$-concentration is similar in total cortical membranes of both SHR and WKY; cortical tubules and glomeruli of both SHR and WKY possess similar $G_{q/11\alpha}$-concentrations. $G_{q/11\alpha}$-proteins are found to be decreased (by about 35 %) in SHR medulla. Total renal membranes of SHR are found to possess slightly, but not significantly, decreased $G_{q/11\alpha}$-concentration, as compared to age-matched controls.

The $G_{s\alpha l}/G_{s\alpha s}$-ratios were calculated for all fractions in all age groups of both strains (results not shown). Since we are dealing with ratio data, age- next to strain- and fraction-comparisons are possible. In general, the $G_{s\alpha l}/G_{s\alpha s}$-ratio is near to 1 or slightly higher (average: 1.19 ± 0.03; range 0.86-1.34; $n$=24), remains constant during aging and is not significantly different between rats of




Representative examples of a $G_{s\alpha}$(A)-, $G_{i\alpha}$(B)- and $G_{q/11\alpha}$(C)-immunoblot experiment in kidney fractions, including cortex, medulla and total kidney as well as in cortical tubules and glomeruli of 5 week old Spontaneously Hypertensive Rats (S) and Wistar Kyoto controls (W); representative example of a $G_{s\alpha}$(D)-immunoblot experiment in kidney fractions of 8 month old Spontaneously Hypertensive Rats and Wistar Kyoto controls.

both strains. In glomeruli, however, the $G_{s\alpha l}/G_{s\alpha s}$-ratio is significantly higher than this average in 5 week old rats (1.79 ± 0.14 and 1.64 ± 0.08), is further increased in 3 month old rats (2.66 ± 0.16 and 2.76 ± 0.07) and not significantly altered in 8 month old rats (2.60 ± 0.11 and 2.33 ± 0.17) ($n$=5 for each result; data are given for SHR and WKY respectively).

## Discussion

In this paper, the results of a detailed study on the $G_{s\alpha}$-, total $G_{i\alpha}$- and $G_{q/11\alpha}$-protein concentrations in renal membranes prepared from total kidney and in different kidney fractions, including cortical and medullary membranes as well as cortical tubules and glomeruli, at three different stages of the hypertensive syndrome in SHR are reported. $G_{q/11\alpha}$-proteins are found to be decreased (by about 35 %) in SHR medulla. Total renal membranes

Our findings in total renal membranes are compatible with literature data obtained in total renal membranes of about 6 week and 28 week old SHR and in cortical membranes of 11 week old SHR and WKY (30,45). In kidney fractions, similar $G_{s\alpha}$-concentrations in renal proximal tubules of young adult SHR and WKY were reported (31,33) which is in keeping with our observations.

However, White and Sidhu (31) find that the $G_{q/11\alpha}$-concentration is slightly depressed and that $G_{i\alpha 2}$- and $G_{i\alpha 3}$-protein concentrations are higher in SHR. Although this represents conflicting data, it has to be kept in mind that the proximal tubules used by White and Sidhu originate from the outer cortex only, while our tubule preparation, originating from the whole cortex, probably consists of proximal tubules as well as of cortical ascending limbs and cortical collecting ducts. Our results should therefore be compared with those of McLellan et al (45). These authors report similar concentrations of immunoreactive $G_{i\alpha}$ protein species in plasma membranes of the total cortex of 11 week old SHR and WKY. Furthermore, in renal microvessels of 11 week old animals, Mokkapatti et al. (32) found similar steady state levels of $G_{s\alpha}$, $G_{i\alpha}$ and $G_q$ in both SHR and WKY, which is in full agreement with our observations in glomeruli of the same age group.

In cortical tubules of 5 week old SHR we find both lower $G_{s\alpha}$- and $G_{i\alpha}$-concentrations. This could help to explain a number of physiological observations. It has been reported that the activity of both the apical NHE (46) and the basolateral $Na^+/K^+$-pump (47) were increased in prehypertensive SHR, resulting in greater retention of salt. Both exchanger molecules are inhibited by AC activated cAMP production (2,3). Although a number of $G_s$- or $G_i$ -coupled signal systems can influence their activity, it is known that in particular the potent natriuretic agent dopamine displays reduced inhibitory effects upon these exchangers as well as reduced AC activated cAMP production in SHR (22,24,46). These impairments, however, do not seem to be due to altered receptor densities in prehypertensive SHR (23,48). Our results in 5 week old SHR suggest a defective $G_s$-stimulatory AC pathway. This is compatible with the findings that the effects of DA on both exchanger molecules (13,24,25) and of some other AC-activating hormones, like parathyroid hormone on the NHE (13), are reduced in prehypertensive SHR. Interestingly, in cortical tubules as well as in the medulla of prehypertensive SHR there is a predominant loss in the large molecular form of the $G_{s\alpha}$-protein, $G_{s\alpha l}$. Seifert et al. demonstrated before that, in membranes of insect Sf9 cells transfected with the appropriate recombinant baculovirus, the ß-adrenergic signal transduction system, the transduction and coupling efficiency for the $G_{s\alpha l}$ -coupled system was significantly higher than for the small molecular weight form ($G_{s\alpha s}$-) coupled system (49). Hence, it is possible that the altered ratio $G_{s\alpha l}$ / $G_{s\alpha s}$ could play a similar role in the present system.

We also describe a modest loss of the $G_{i\alpha}$ -proteins in cortical tubules of prehypertensive SHR which could actually counterbalance in part the loss of $G_{s\alpha}$. According to Bertorello and Aperia (50), however, the DA-mediated inhibition of the $Na^+/K^+$-pump in proximal tubules requires the activation of both DA1-like and DA2-like receptors. Moreover, these same authors (51) also demonstrated the implication of pertussis toxin sensitive G-protein ($G_i/G_0$ family) in this inhibition (next to $G_{s\alpha}$). A parallel decrease of both $G_{s\alpha}$ and $G_{i\alpha}$, as we observe, could therefore lead to a clear diminished inhibition of the $Na^+/K^+$-pump by DA, as observed in young SHR.

Cortical glomeruli of 5 week old SHR exhibit similar $G_{s\alpha}$- concentrations, while $G_{i\alpha}$- concentrations are significantly increased. Glomeruli are vascular element and changes observed in these structures might possibly reflect general vascular alterations. It is well known that the vascular reactivity of young SHR is exaggerated when compared to normotensive controls ; in particular, the sensitivity of the renal microvasculature to Ang II is increased (16,17). This does not seem to be due to an altered number or subtype distribution of vascular Ang II receptors, since these are similar in both strains (22). The Ang II receptor is associated both with $G_i$- and $G_q$- proteins. Ang II acts through a $G_i$-protein to inhibit the production of cAMP (52). This can oppose the effect of vasodilator agents that act via $G_s$ such as DA (26), prostaglandine E2 (PGE2, 53) and $ß_2$-adrenergic agonists (54). Ang II also acts through $G_q$ to activate PLC (22) thereby activating a biochemical cascade leading to smooth muscle contraction and therefore active vasoconstriction. However, it seems to be the $G_i$-component of the Ang II transduction which is altered in SHR, since both pretreatment with

pertussis toxin (29), which inactivates $G_{i\alpha}$, and treatment with direct activators of either $G_{s\alpha}$ or AC (26) normalize enhanced renovascular responses to Ang II in prehypertensive SHR. Therefore, these results correlate well with the increased glomerular $G_{i\alpha}$-proteins levels as described here.

We also find decreased $G_{q/11\alpha}$-concentrations in total kidney, total cortex and cortical glomeruli but not in cortical tubuli of prehypertensive SHR. Remarkably, both renal $\alpha_1$-(18,55) and Ang II (21,56,57) receptor densities are increased on cortical tubular structures of prehypertensive SHR while their stimulatory input on the NHE was reported to be unchanged (13). This fits well with the described decrease in cortical $G_{q/11\alpha}$-levels, shown to be implicated in the transduction mechanism of both molecules. The fact that this decrease was not found in our sample of total cortical tubules might suggest that the alteration is limited to proximal tubules only. For the adrenergic signal transduction, reduced $G_{q/11\alpha}$-levels also correspond to a reduction in norepinephrine-stimulated inositol phosphate accumulation, as was found in total cortical slices from 4 week old SHR (14) and in renal membranes from 6 week old SHR (15). However, this reduction of inositol phosphate accumulation was not attributed to a specific renal compartment. Therefore, it remains enigmatic to reconcile decreased glomerular $G_{q/11\alpha}$-levels and increased vasocontractile sensitivity to a number of $G_q$-coupled signal molecules, like norepinephrine (58). Clearly, further experiments are needed to elucidate this issue.

Medullary membranes of 5 week old SHR exhibit lower $G_{s\alpha}$- and $G_{q/11\alpha}$-concentrations while $G_{i\alpha}$-concentrations were higher. Like cortical tissue, medullary tissue consists of vascular and tubular elements. In the tubular compartments, it was shown that the medullary $Na^+/K^+$-pump is also inhibited by activation of AC (59) ; a sharply decreased $G_{s\alpha}/G_{i\alpha}$-ratio therefore could significantly contribute to the enhanced activity of this pump, as seen in prehypertensive SHR (47). In the vascular compartments, decreased $G_{s\alpha}$- together with the increased $G_{i\alpha}$-levels could significantly contribute to a diminished vasodilatory function of AC-stimulating signal molecules like PGE2 and arginin vasopressin (60), contributing thereby to the increased vascular resistence of these 5 week old SHR.

$G_\alpha$-protein concentrations are not altered in 3 month old SHR. In 8 month old SHR, renal cortical membranes exhibit lower $G_{s\alpha}$-concentrations, while medullary membranes exhibit both lower $G_{s\alpha}$- and $G_{q/11\alpha}$-concentrations. None of these alterations are reflected in cortical tubular or glomerular G-protein alterations.

In summary, using a thoroughly optimized quantitative immunoblotting method, this report firmly establishes differences in $G_{s\alpha}$-, $G_{i\alpha}$- and $G_{q/11\alpha}$-protein concentrations between SHR and normotensive WKY. The most important alterations are seen in prehypertensive SHR, which do not yet exhibit hypertensive symptoms, while no differences are found once the hypertension is settled. In older SHR, finally, it can be speculated that the $G_\alpha$-protein alterations are secondary to the syndrome. The differences seen in the young SHR tend to point in the same direction : a reduction of the (AC- and PLC-) stimulatory $G_\alpha$-proteins and an increase (at least in cortical glomeruli and in the medulla) of the inhibitory $G_\alpha$-proteins. These alterations help to explain repeatedly reported signal transduction defects, implicated in enhanced sodium retention in tubular elements and in increased myogenic tone of both cortex and medulla of prehypertensive SHR.

## Acknowledgements

The authors are grateful to Prof. Dr. W. De Potter for the use of the 'Image master DTS' scanner

and to Erwin Schaerlaeken for his helpful assistance in using the PDI-software. The technical expertise of Marianne Bailleul for help with blotting experiments and of Erik Vandevelde for the camera work is acknowledged. The authors wish to thank Prof. Dr. R. Lefebvre for critical reading of the text.

The financial support of the Belgian F.W.O. (grants 3.9006.87 and 7.0080.91) is acknowledged. A. Bazan was supported with a specialization grant of the 'Flemish Institute for the Promotion of Scientific-Technological Research in Industry (IWT)'.

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