Urinary Prostaglandins in the Lyon Strains of Hypertensive, Normotensive, and Low Blood Pressure Rats

DANIEL BENZONI, PHARM.D., MADELEINE VINCENT, PHARM.D., PH.D., AND JEAN SASSARD, PHARM.D., M.D.

SUMMARY A longitudinal study of the urinary excretion of prostaglandins (PGs) E and Fα was performed in simultaneously selected hypertensive (LH), normotensive (LN), and low blood pressure (LL) female rats of the Lyon strains aged from 5 to 45 weeks. The urinary excretion of PGE did not significantly differ between LL and LN rats whereas in LH rats it was found to be significantly lower than that of LN or LL rats starting at the age of 32 weeks. The urinary excretion of PGFα was significantly reduced in both LL and LH rats; however, this decrease was more marked in LH than in LL animals and, from 9 weeks of age, the urinary PGFα were significantly lower in LH than in age-matched LL rats. In addition, both PGE and PGFα were found to be significantly and negatively related to the systolic blood pressure level in LH rats (r = -0.56, n = 58, p < 0.001 for PGE; and r = -0.78, n = 58, p < 0.001 for PGFα) but not in LN or LL animals. In conclusion, it seems unlikely that renal PGs could play a primary role in the spontaneous hypertension observed in the Lyon strain of rats. (Hypertension 4: 325-328, 1982)

KEY WORDS • prostaglandins • kidney • spontaneous hypertension • rats

It is generally accepted that the kidney could play a critical role in the control of blood pressure and therefore in the pathogenesis of various forms of hypertension. Among the different ways in which the kidney might influence blood pressure, its ability to secrete prostaglandins (PGs) has aroused recent interest.

Previous studies concerning the metabolic enzymes and the secretion of renal PGs in spontaneously hypertensive rats of the New-Zealand (GH rats) or Japanese (SHR) strains have suggested that there could be an increased renal content in PGs.1-4,10 Since, in contrast to man and most other species, PGs seem to induce a renal vasoconstriction in the rat,7,8 such an increase could play a pathogenetic role in this form of experimental hypertension. However, the authors disagreed whether increased synthesis1-4,9 or decreased metabolism5,6,9,10 was the principal factor responsible for increased renal content of PGs.

Since most of these experiments were conducted in vitro, it appeared interesting to study, under physiological conditions, the renal secretion of PGs during the development of spontaneous hypertension as Baer and Cagen11 recently did in GH rats. Consequently, the aim of the present work was to measure, at different ages, the urinary excretion of PGs used as an index of their renal production12-15 in genetically hypertensive, normotensive, and low blood pressure rats of the Lyon strains.14-10

Material and Methods

Groups of 12 females belonging to the 18th generation of the simultaneously selected Lyon hypertensive (LH), normotensive (LN), and low blood pressure (LL) rats were used. They were housed under constant conditions of temperature (21°C ± 1°C), lighting (8 am to 8 pm), and humidity (60% ± 10%) and received a standard diet (UAR entretien) and tap water ad libitum.

At the ages of 5, 9, 21, 32, and 45 weeks, the same rats were placed into individual metabolic cages. After 72 hours of adaptation, urines were collected in a flask maintained at 4°C for two consecutive 24-hour periods. At the end of each period, urine volume was measured, and then centrifuged to eliminate cells and kept at -20°C until the assay.
The urine content in PGE and PGFₐ was obtained by using our previously described radioimmunoassay technique after extraction and chromatographic separation on silicic acid columns. Since the antibodies that we raised in rabbits, although highly specific toward other PGs and metabolites, could not distinguish between PGs of the series 1 or 2, the results were expressed without specification of the series.

Systolic blood pressure (SBP) was recorded in the prewarmed (37°C, 10 min) unrestrained conscious rat using a tail cuff plethysmographic technique (Plethysmograph NARCO DM P4B and Physiograph recorder). SBP and body weight (BW) were measured the day before and the day after the urine collection period. At each age, each individual value of SBP, BW, and urinary PGE and PGFₐ is the mean of the two consecutive measurements. Results are expressed as mean ± SEM, and further statistical analysis used the Student's t test for unpaired data.

Results

Systolic Blood Pressure and Body Weight

As shown in figure 1 (upper graph), SBP was, at every age tested, significantly higher in LH than in age-matched LN female rats. LL rats exhibited a slight (6 mm Hg) reduction in SBP up to the age of 32 weeks, which almost disappeared in 45-week-old animals.

The BW of LH rats, shown in figure 1 (lower graph), was markedly higher than that of LN rats starting at the age of 9 weeks. The BW of LL rats did not differ from that of age-matched LN rats.

Urinary Excretion of Prostaglandins E and Fₐ

The urinary excretion of PGE (ng/24 hr/100 g BW) did not significantly differ between LL and LN rats. In LH rats, the urinary elimination of PGE was slightly depressed in young animals and became significantly lower than that of LN and LL rats at the age of 32 weeks. At every age, the urinary excretion of PGFₐ was significantly reduced in both LL and LH rats compared to LN controls. However, this reduction was more marked in LH animals and, starting at the age of 9 weeks, the urinary PGFₐ was significantly lower in LH than in age-matched LL rats (fig. 2).

In addition, the urinary excretion of PGE and PGFₐ observed between 5 and 45 weeks of age was inversely related to SBP in LH rats (r = −0.56, n = 58, p < 0.001 for PGE; and r = −0.78, n = 58, p < 0.001 for PGFₐ) but not in LN and LL animals.

Due to the sharp decrease observed in urinary PGs between the ages of 5 and 9 weeks, the relationship was also calculated after eliminating the values observed in 5-week-old rats. It remained significant for PGFₐ (r = −0.45, n = 46, p < 0.01) but not for PGE (r = 0.24, NS). Finally, urinary PGE but not PGFₐ was found to be inversely related to age in the three strains.

Discussion

In the present study, rats from the three simultaneously selected Lyon strains were used, since they were derived from the same original group of unselected rats and offered opportunities for comparison among the strains. As we failed to obtain truly hypotensive rats, the LL strain, whose SBP is only slightly different from that of the LN strain, might be considered as a second control strain for LH animals. However, the use of LL rats might be useful in helping
to distinguish among the differences existing between LH and LN rats, namely, those that could be related to the genetically determined SBP level from those that could not be.

The determination of the urinary excretion of PGs allowed us to maintain these rats in physiological conditions and to follow each of them at different stages of their development. Under these conditions, we demonstrated that, in LH rats compared to either LN or LL controls, there was a significant decrease in the urinary PGE and PGFα. This decrease progressively developed with age and appeared sooner and more markedly for PGFα than for PGE. Such a result is in accord with those obtained by Sirois and Gagnon in SHR. Interestingly, Baer and Cagen recently reported a decreased urinary PGE and PGFα excretion in 18-week-old female GH rats. This decrease was not observed in male GH rats and could not be attributed to an alteration of the 15-hydroxy PG dehydrogenase activity in the kidney.

On the contrary, Ahnfelt-Röning and Arrigon-Martelli found an elevated urinary excretion of PGFα and Tobian and O'Donnell an increased renal content of PGFα but not of PGE at various ages in SHR. Other investigators, using in vitro assays, found either an increased renal PG synthetase activity in SHR with established hypertension, or a decreased 15-hydroxy PG dehydrogenase activity in SHR and in GH rats. These findings allowed them to conclude that, as a result of an enhanced synthesis or of a decreased degradation, there might be an elevated renal content in PGs during the course of spontaneous hypertension. Since PGE and, to a lesser extent, PGFα, have been shown to exhibit renal vasoconstrictor properties in the rat, most of these authors concluded that the observed alterations in PG metabolism could play a causal role in the pathogenesis of genetic hypertension.

However several points should be discussed: 1) an increased PG synthetase activity observed in vitro is not necessarily associated with an increased in vivo content in PGs; 2) the enzymatic defects found in SHR and in GH rats were generally more pronounced in rats with established hypertension than in young prehypertensive animals, a time course evolution that does not favor the hypothesis of an early causal alteration; and 3) a progressive increase in renal PGE synthetase activity has also been reported in rats made hypertensive by clipping a renal artery, i.e., in a secondary form of experimental hypertension.

If one assumes that, in the rat, PGs are vasoconstrictor for the kidney — a point that has recently been questioned — the activity reported here could be considered as an adaptative mechanism for genetically determined hypertension in LH animals. Such a hypothesis is supported by the inverse relationship found between the urinary PGs and SBP in LH animals. The demonstration of this relationship was favored by the wider SBP values observed in LH rats than in the other two control animals. However, it remained significant after the sharp changes in both urinary PGs and SBP found between the ages of 5 and 9 weeks were eliminated, and could not be explained solely by the age factor.

In conclusion, the present work demonstrates that LH female rats exhibit a decreased urinary excretion of PGE and PGFα when compared to two simultaneously selected control strains of rats. The progressive development with age of this alteration does not favor the hypothesis of a genetic defect in PG synthesis that could play a primary role in the spontaneous hypertension observed in the Lyon strain of rats.
Acknowledgments

We thank Dr. J.E. Pike (Upjohn Company) for his generous gift of prostaglandins and metabolites, Dr. D. Trepo for help in these experiments, and Mrs. N. Gallo-Bona, J. Sacquet and F. Seon for their technical assistance.

References

Urinary prostaglandins in the Lyon strains of hypertensive, normotensive, and low blood pressure rats.
D Benzoni, M Vincent and J Sassard

Hypertension. 1982;4:325-328
doi: 10.1161/01.HYP.4.2.325

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/4/2/325

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at: http://hyper.ahajournals.org//subscriptions/