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(Pro)renin/renin receptor expression during normal and preeclamptic pregnancy in rats

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ABSTRACT

Aims: Pregnancy is a physiological stage with profound cardiovascular changes leading to hypotension. Preeclampsia (PE) reverts these normal changes inducing hypertension. Renin-angiotensin system (RAS) has been related in PE genesis. It has been reported a novel receptor in the system, the Prorenin/Renin receptor (PRR), with several roles in renal and cardiovascular illnesses. It is not known, however, if PRR changes its expression or is activated during normal or PE-complicated pregnancy on tissues intimately related to hypertension. So, the aim of this work was to describe PRR expression during normal and hypertensive pregnancy in rats.

Methods: We used a subrenal aortic coarctation (SRAC) model in rats. Atria, septum and ventricular heart tissue, aorta and renal tissue samples were homogenized and immunoblotted using anti-PRR and anti-PLZF antibodies. We also measured gene expression by RT-PCR.

Key findings: Hypertension and proteinuria were observed in SRAC-pregnant rats. In pregnant, non-SRAC rats, PRR showed a higher expression of both, gene and protein compared to non-pregnant rats in heart, aorta and kidney tissues. PE induces a very high expression of PRR in cardiac tissues and, on the contrary, decreases PRR expression in both, aorta and kidney. PLZF, a marker of PRR function, was augmented only in aorta and kidney in non-SRAC pregnant rats. In SRAC-pregnant rats, PLZF increment disappeared.

Significance: These findings indicate that PRR expression changes differently during pregnancy and PE in tissues related to cardiovascular functions and suggest a probable participation of the receptor during normal and preeclamptic pregnancy in the rat.

1. Introduction

Pregnancy is a physiological stage associated to increased cardiac output, circulating blood volume and serum concentrations of renin and angiotensin II [1]. These effects are accompanied, interestingly, of unchanged or even low blood pressure during normal pregnancy in humans and animals [2,3]. Previously, it has been shown that vascular resistance and sensitivity to diverse circulating pressor and vasoconstrictor agents are blunted in this stage. These physiological changes have been mainly attributed to the characteristic hormonal environment that, in turn, gives rise to increased synthesis of endothelium derived relaxing factors. Also, changes in vasoactive receptor expression seem to participate in this homeostatic adjustment [4]. In the other hand, in preeclampsia, these normal vasodilator events are altered or absent or constrictor stimuli are increased. Several theories have been proposed to explain this pathology, involving a wide variety of systems, pathways and pathophysiological mechanisms. Renin-angiotensin-aldosterone system (RAAS) has been related to these theories [5,6]. Indeed, changes in production of angiotensinogen, ACE expression and receptor activity have been involved in preeclampsia. Role of AT1 and AT2 receptors seems to be relevant. AT1R has a vasoconstrictor, prohypertrophic role, while AT2R seems to have opposite effects. We have previously shown that relative expression of both receptors during normal pregnancy favors AT2R upon AT1R, indicating that this last has a possible participation on preeclampsia development [4], however, low or no modification of this receptor has been found.

RAAS has become a complex system. The finding of prorrenin/renin (PRR) receptor has introduced new insights in its physiology. The concept of renin and its precursor, prorrenin, as ligands with their own receptor it is very interesting. Since its first description [8], PRR has

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shown to have a putative role in different diabetes- and hypertension-related pathologies. For instance, PRR has been implicated in the inflammation and albuminuria-associated development of nephropathy in streptozotocin-diabetic rats [9]. The inhibition of PRR action using a peptide derived from the renin prosegment as shown to reduce serum creatinine, left ventricular mass, and cardiac fibrosis and improved cardiac function without affecting blood pressure in spontaneously-hypertensive rats [10]. Shan et al. have described that PRR may have a role as a system regulator, specifically, modifying the neural control of cardiovascular functions at the supraoptic nucleus in rats, suggesting that PRR may participate on superior blood pressure control systems [11]. Li et al. showed that knocking down this receptor attenuates angiotensin II-dependent hypertension in mice [12]. This body of evidence suggests that PRR may accomplish AT1R-like activities, making it attractive to explore.

Although no definitive transductional pathways have been described for this receptor, several seem to be activated [13]. Interaction of PRR with prorrenin and renin may activate MAPK as p42/p44 and p38, activating TGF-β production and Hsp-27, respectively. PRR has also been described as a component of Wnt transductional pathway, and it has been proposed to participate in cardiac hypertrophy and remodelation [13]. Also, modification of PLZF, a transductional factor protein, has been considered an activation marker for this receptor. In this regard, PLZF participation is interesting, due to previous reports indicating that PRR-activated PLZF may promote DNA synthesis and proliferation in VSMC, cardiomyocytes and endothelial cells, all of them considered crucial components in hypertension remodelation and diabetes-induced vasculopathy [14].

In this context, the possible participation of this receptor during pregnancy is not known. Although it has been described on human myometrium, decidual and amniotic membranes and the modification of its expression due to parturition [15], PRR expression on tissues intimately related to hypertension, such as heart, aorta and kidney during normal pregnancy is not known, neither is known if this presence might be modified by normal pregnancy, or preeclampsia [16]. Thus, the aim of this work was to describe PRR expression during normal and hypertensive pregnancy in rats.

2. Methods

2.1. Animals

All procedures described here were approved by the Animal Care Committee in our institution, according to the Mexican Official Norm (NOM-062-ZOO-1999), SAGARPA; and National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised 1978,USA).

We used female Wistar rats weighing 250 ± 20 g with free access to tap water and a standard pellet diet (Lab Diet 5001, Purina). Animals were divided randomly in non-pregnant and pregnant groups. Subrenal aortic coarctation (SRAC), a model that resembles several human disease features, based upon indirect placental ischemia, was performed as previously described [4,7,17–19]. Pregnancy was accomplished two weeks later by coupling sets of 3 female rats with a competent male per set during 48 h; first day of pregnancy was determined when spermatozoa were observed in a vaginal smear. The pregnant group (n = 6–8) comprised animals at the end of the third week of pregnancy; this stage was further confirmed by the observation of pups in utero during tissue removal. All animals were kept in similar dark-light conditions and used at the end of the 3rd week of pregnancy (days 20–21).

2.2. Pregnancy-induced hypertension model indicators

Blood pressure was measured by a tail cuff method using a pressure transducer coupled to a LETICA system (Panlab, Barcelona, Spain). Animals were placed in metabolic cages to measure proteinuria in 24 h urine samples. This parameter was expressed as g/L. Pups weights were obtained and recorded after mothers were euthanized.

Immunoblot assays. PRR expression was assayed by immunoblot. Experiments were performed on tissues from pregnant and non-pregnant rats with subrenal aortic coarctation. At the end of the 3rd week, pregnant animals (and corresponding time-control animals), were sacrificed with pentobarbital (65 mg/Kg), to obtain heart, aorta and kidney. All tissues were dissected and homogenized with Tris 100 mM, pH 7.4 using a cocktail of protease inhibitors (Complete Mini, EDTA-free, Roche Diagnostics, Germany), centrifuged and protein concentration was measured in the supernatant using Bradford's method. 100 μg of protein of each sample were loaded in 10% SDS-PAGE under reducing conditions. Afterwards, proteins in the gel were transferred to PDVF membranes using a semi-dry electroblotting system (BIORAD, Hercules, CA, USA). Membranes were incubated with rabbit polyclonal specific antibodies against PRR (Anti-PRR, Abcam, UK), or PLZF (Santa Cruz Biotechnology, CA, USA). Secondary antibodies conjugated with horseradish peroxidase were used and bands were identified by chemoluminescence (Amersham International, Arlington Heights, IL, USA). Membranes were photographed and the image digitalized to carry out densitometric analysis using Quantity One software (Biorad, Hercules, CA, USA). The relative presence of each protein was normalized with β-actin as housekeeping protein.

2.3. Analysis by end-point reverse transcription-polymerase chain reaction of PRR

Animals were sacrificed as previously described, and aorta, heart and kidney were isolated (n = 4 per group). Total RNA was extracted from aorta artery using TRIzol (GIBCO Life Technologies). Reverse transcription was conducted in a reaction volume of 20 μl containing 1 μg RNA, 1 μl dNTP mixture (10 mM), 2 μl PCR buffer (10×), 1 μl Oligo(dT)12–18 (0.5 μg/μl), 2 μl $MgCl_2$ (25 mM), 2 μl dithiothreitol (0.1 M), 1 μl (200 units) of SuperScript II RT (Invitrogen), at 42 °C for 50 min. The reaction was inactivated at 70 °C for 15 min. After first-strand synthesis of RNA, 2 μl cDNA were then amplified using specific primers. The primers used in the experiment to amplify the target gene have been reported previously: Renin/prorrenin, forward primer: 5′-CATAAGCATCTCGCCAAGG-3′; reverse primer: ACCAGGGATGTGT CGAATGA-3′ (GenBank Accession AB188298) [20]. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) cDNA was amplified as control gene and was used to normalize amplification products [21]. The sense primer was 5′-ACC ACA GTC CAT GCC ATC AC-3′ (extending from base 562 through base 581) and the antisense primer was 5′-TCC ACC ACC CTG TTG CTG TA-3′ (complement of nucleotides 1013–1032). PCR was conducted using a PCR kit (Invitrogen Technologies), and a Bio-Rad Thermal Cycler (Gene Cycler; BIO RAD, USA). The amplification profile involved denaturation at 94 °C for 1 min, annealing at 60 °C (PRR) or 58 °C (GAPDH) for 1 min, and extension at 72 °C for 1 min for 45 cycles. After amplification, PCR products were electrophoresed on a 2% agarose gel for 1 h at 100 V. Bands corresponding to PRR (120 bp long), and GAPDH (452 bp long), were visualized with ethidium bromide by UV light after agarose gel electrophoresis, and digitalized with a Gel Doc EZ system (BIO RAD,CA, USA). Their intensities were measured by densitometry using Quantity One 1-D Image Analysis Software (BIO RAD, CA, USA).

All results are expressed as mean ± SD of at least 4–6 different animals. ANOVA followed by Bonferroni's test were used to compare groups using Graph Pad Prism 5 software. Differences were considered significant when $p < 0.05$.

3. Results

Characterization of preeclampsia model is resumed in Table 1. The model resembles functional changes similar to human disease. As previously described [4], normal pregnancy induces hypotension. A mild

Table 1
Pregnancy-induced hypertension model indicators.

	NP	P	PE
Systolic blood pressure	110.5 ± 1.80	73.5 ± 1.57*	142.5 ± 2.5*,#
Proteinuria	4.28 ± 0.41	5.01 ± 0.6	7.80 ± 0.17*,#
Pup weight	–	6.4 ± 0.24	3.9 ± 0.17#
Pup length	–	4.3 ± 0.09	3.6 ± 0.2#

NP: Non-SRAC, non-pregnant rats. P: Non-SRAC, 3rd week pregnant rats. PE: SRAC, 3rd week pregnant rats. Groups were set with at least 6–8 rats. Systolic blood pressure is expressed in mmHg; Proteinuria is expressed in mg/mL; Pup weight and length is expressed in g and cm, respectively. Median number of pup: 6–8 for both groups.

* $p < 0.05$ compared to NP group.

# $p < 0.05$ compared to P group.

proteinuria is normal in rats. Normal pregnancy shows no significant changes in this parameter, compared to control animals. Preeclampsia, in the other hand, rises systolic blood pressure and proteinuria in these animals. Besides, intra-uterine development is impaired, as shown by the lower weight and length in offspring.

PRR has been previously described in several tissues [8]. We were able to detect PRR both, protein and mRNA, in the heart, aorta and kidney, tissues intimately related to hypertensive disorders, and in the three groups considered in this work: non-pregnant, pregnant and preeclamptic animals. There is a modest, basal expression of this receptor in left (Fig. 1) and right atria (Fig. 2), as well as in septum (Fig. 3) and left ventricle (Fig. 4) in control animals. During pregnancy, adaptation to cardiovascular changes implies temporal modifications at every component of cardiovascular system. In this regard, we found that PRR expression is modified by pregnancy. Cardiac tissue showed a moderate elevation of PRR protein in left atrium (Fig. 1), a sustained increase in right atria (Fig. 2) and septum (Fig. 3) and a marked increase in left ventricle (Fig. 4). Interestingly, preeclampsia increases PRR expression even to higher levels that normal pregnancy in all

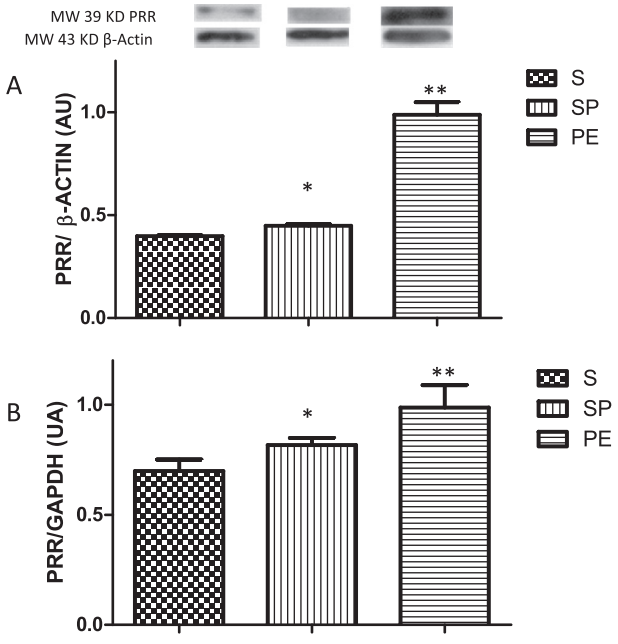

Fig. 1. PRR expression in pregnant rats. PRR was detected by immunoblot (A) and RT-PCR (B) in left atria from sham non-pregnant (S), sham-pregnant (SP) and preeclamptic (PE) rats. Each bar represents media ± SD of 4 experiments. Immunoblots were normalized using β-actin as housekeeping protein and PCR experiments were normalized using GAPDH. Both graphs are expressed as arbitrary units. At the top of A, a typical experiment is shown. *$p < 0.05$ vs. S, #$p < 0.05$ vs. SP.

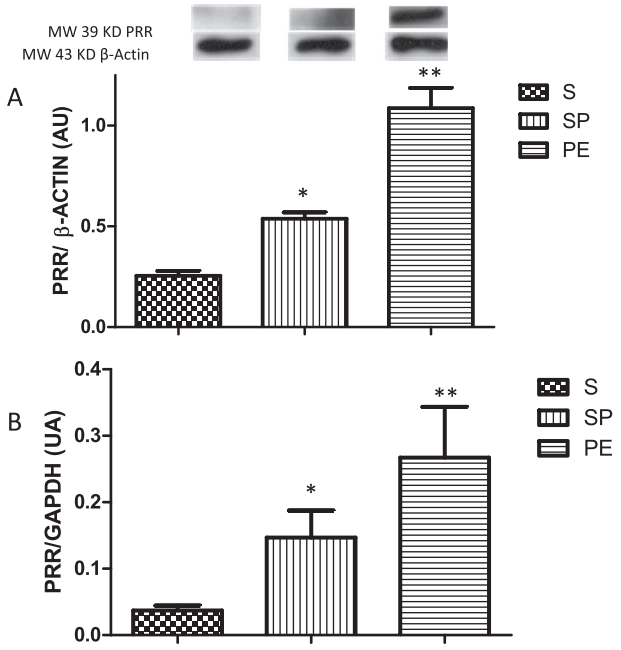

Fig. 2. PRR expression in pregnant rats. PRR was detected by immunoblot (A) and RT-PCR (B) in right atria from sham non-pregnant (S), sham-pregnant (SP) and preeclamptic (PE) rats. Each bar represents media ± SD of 4 experiments. Immunoblots were normalized using β-actin as housekeeping protein and PCR experiments were normalized using GAPDH. Both graphs are expressed as arbitrary units. At the top of A, a typical experiment is shown. *$p < 0.05$ vs. S, #$p < 0.05$ vs. SP.

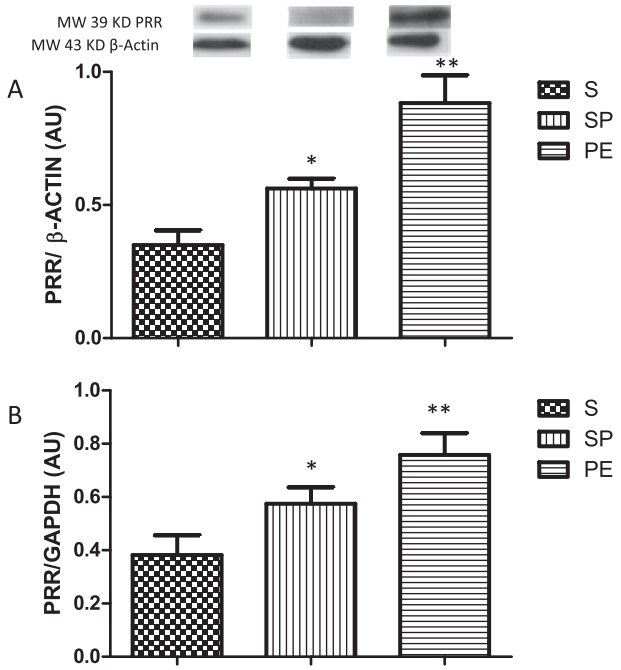

Fig. 3. PRR expression in pregnant rats. PRR was detected by immunoblot (A) and RT-PCR (B) in septum from sham non-pregnant (S), sham-pregnant (SP) and preeclamptic (PE) rats. Each bar represents media ± SD of 4 experiments. Immunoblots were normalized using β-actin as housekeeping protein and PCR experiments were normalized using GAPDH. Both graphs are expressed as arbitrary units. At the top of A, a typical experiment is shown. *$p < 0.05$ vs. S, #$p < 0.05$ vs. SP.

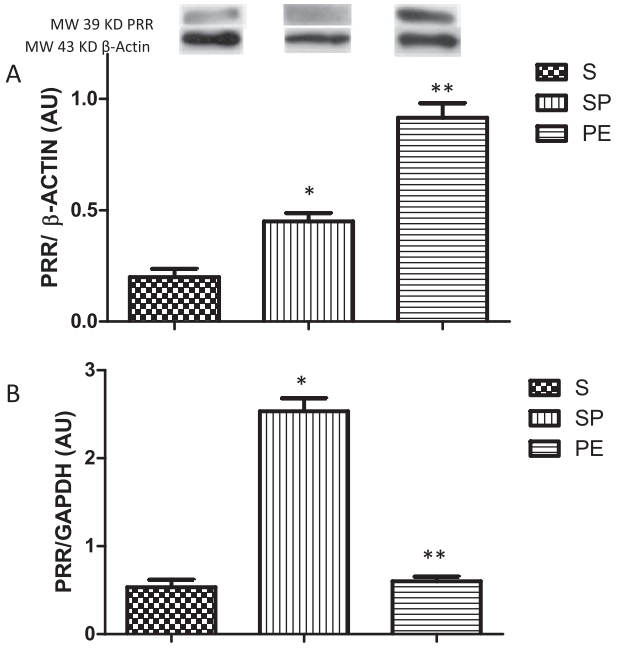

Fig. 4. PRR expression in pregnant rats. PRR was detected by immunoblot (A) and RT-PCR (B) in left ventricle from sham non-pregnant (S), sham-pregnant (SP) and preeclamptic (PE) rats. Each bar represents media ± SD of 4 experiments. Immunoblots were normalized using β-actin as housekeeping protein and PCR experiments were normalized using GAPDH. Both graphs are expressed as arbitrary units. At the top of A, a typical experiment is shown. $^{*}p < 0.05$ vs. S, $\#p < 0.05$ vs. SP.

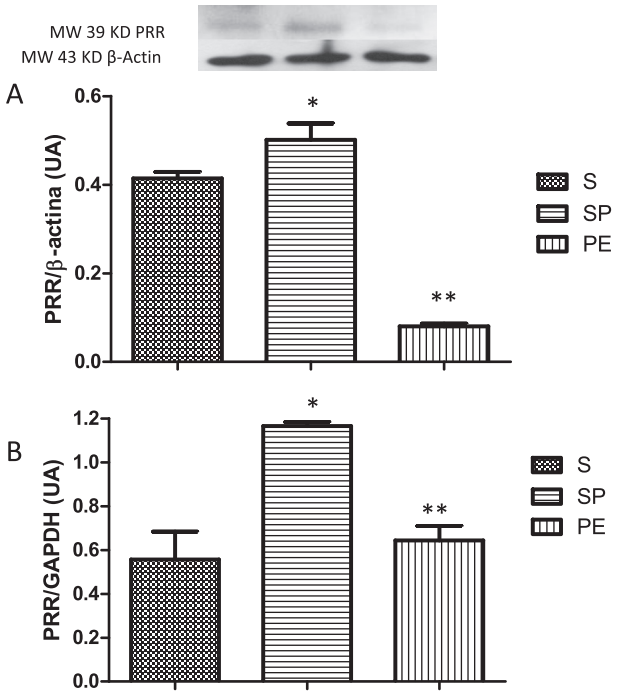

Fig. 5. PRR expression in pregnant rats. PRR was detected by immunoblot (A) and RT-PCR (B) in thoracic aorta from sham non-pregnant (S), sham-pregnant (SP) and preeclamptic (PE) rats. Each bar represents media ± SD of 4 experiments. Immunoblots were normalized using β-actin as housekeeping protein and PCR experiments were normalized using GAPDH. Both graphs are expressed as arbitrary units. At the top of A, a typical experiment is shown. $^{*}p < 0.05$ vs. S, $\#p < 0.05$ vs. SP.

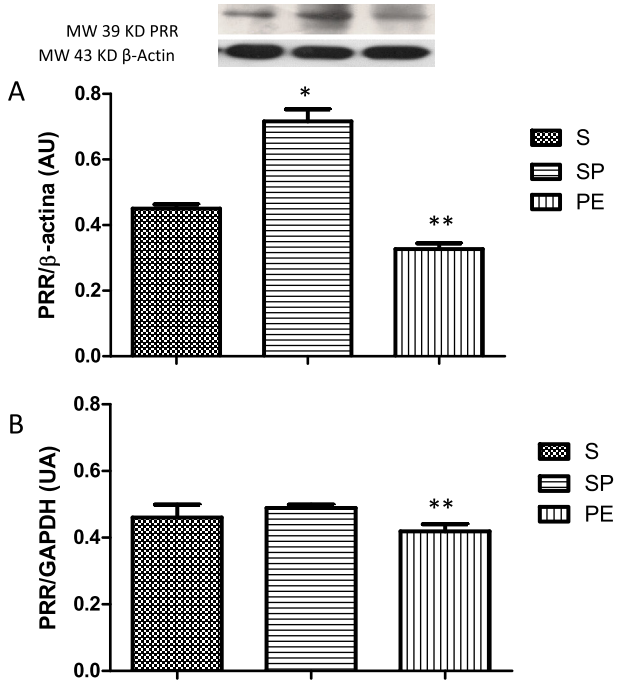

Fig. 6. PRR expression in pregnant rats. PRR was detected by immunoblot (A) and RT-PCR (B) in abdominal aorta from sham non-pregnant (S), sham-pregnant (SP) and preeclamptic (PE) rats. Each bar represents media ± SD of 4 experiments. Immunoblots were normalized using β-actin as housekeeping protein and PCR experiments were normalized using GAPDH. Both graphs are expressed as arbitrary units. At the top of A, a typical experiment is shown. $^{*}p < 0.05$ vs. S, $\#p < 0.05$ vs. SP.

cardiac tissues studied.

We found that aorta also expresses PRR protein and RNA in both segments, thoracic and abdominal, and in non-pregnant, pregnant and preeclamptic rats. Similarly to heart, this vessel also increases PRR expression due to pregnancy, both protein and RNA, however, inter-segment differences were not evident. Opposed to what happened in cardiac tissue, hypertensive disorder induces a fall in PRR expression in both segments, thoracic (Fig. 5) and abdominal (Fig. 6).

Renal tissue also expresses PRR in cortex (Fig. 7) and medulla (Fig. 8). Changes induced by pregnancy are in consonance with the findings in aortic tissue: protein and RNA are increased during pregnancy and preeclampsia seems to revert these changes.

Finally, it is described that PRR activation induces PLZF, a protein that, among other actions, acts like a negative feedback regulator of PRR. This interaction is considered an indicator of PRR activation. As a first approach to study possible PRR activation, we measured PLZF in heart, aorta and renal cortex. Fig. 9 shows these results. We found that normal pregnancy did not modify PLZF expression in the heart, contrary to what we found in PRR expression. This might suggest that PRR could not be necessarily active in this tissue although is being high-expressed however, more specific assays must be done to confirm this finding. In aorta and renal cortex, normal pregnancy augmented PLZF expression in both tissues; whereas, preeclampsia reverted these increasing. These data are important because suggest that PRR could be activated in these tissues and this activity is modified by normal pregnancy and the hypertensive process as well.

4. Discussion

In this work, we describe for the first time, that PRR is expressed, measured as mRNA and protein levels, in relevant cardiovascular tissues during pregnancy, and that this receptor alters its expression in preeclampsia. We also found that in aorta and kidney, this receptor

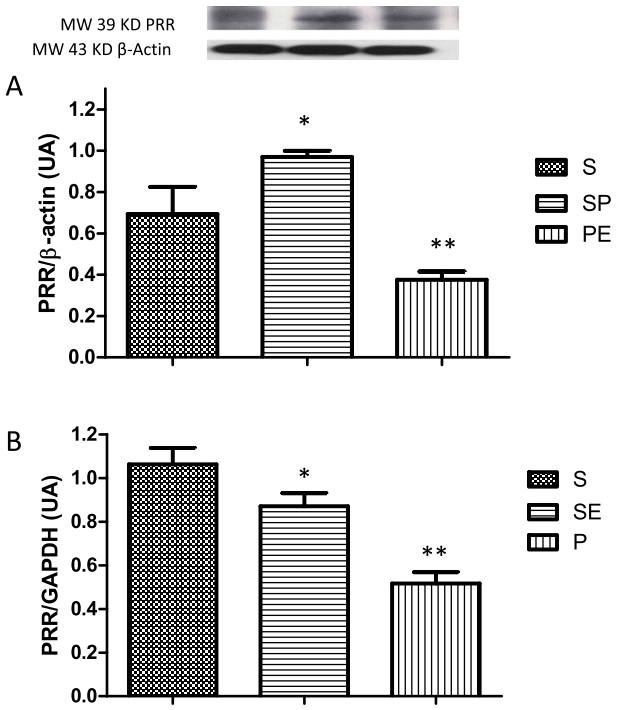

Fig. 7. PRR expression in pregnant rats. PRR was detected by immunoblot (A) and RT-PCR (B) in renal cortex from sham non-pregnant (S), sham-pregnant (SP) and preeclamptic (PE) rats. Each bar represents media ± SD of 4 experiments. Immunoblots were normalized using β-actin as housekeeping protein and PCR experiments were normalized using GAPDH. Both graphs are expressed as arbitrary units. At the top of A, a typical experiment is shown. $^{*}p < 0.05$ vs. S, $\#p < 0.05$ vs. SP.

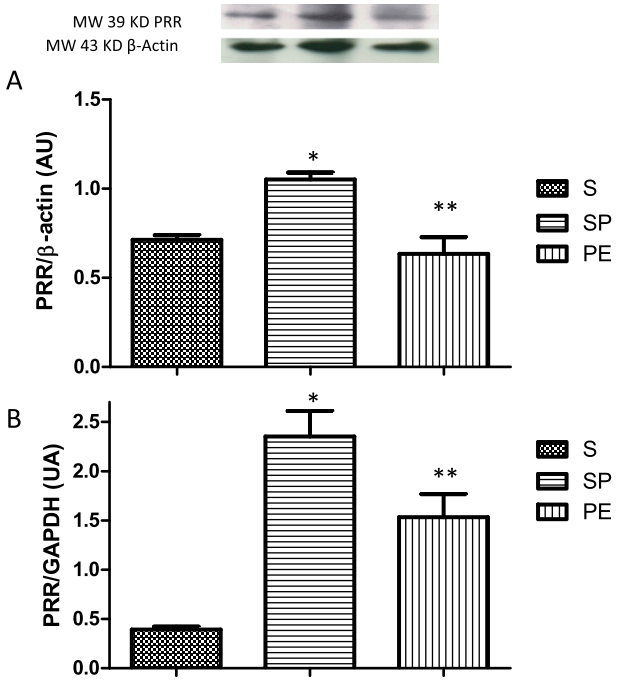

Fig. 8. PRR expression in pregnant rats. PRR was detected by immunoblot (A) and RT-PCR (B) in renal medulla from sham non-pregnant (S), sham-pregnant (SP) and preeclamptic (PE) rats. Each bar represents media ± SD of 4 experiments. Immunoblots were normalized using β-actin as housekeeping protein and PCR experiments were normalized using GAPDH. Both graphs are expressed as arbitrary units. At the top of A, a typical experiment is shown. $^{*}p < 0.05$ vs. S, $\#p < 0.05$ vs. SP.

seems to be activated, suggesting a probable role in both, physiological and pathological stages.

Finding of PRR has given a new impulse for the study of RAAS as an important factor in the pathogenesis of several diseases, such as diabetes, hypertension, glomerulopathic disorders, and others. Among hypertensive disorders, preeclampsia is relevant because a defined or responsible system has not been clearly found; instead, the idea of a multifactorial etiology has become more relevant [22].

The relationship between preeclampsia and RAAS has been settled previously in literature. The action of AT1R seems to have a relevant role, however, low or no modification of this receptor has been found [4], so the possibility of PRR participation arises, due to its similarity of action with AT1 receptor. Description of PRR as a novel receptor in the system, binding renin and prorrenin, gives relevance to the molecule and introduces new paths to be explored. PRR has been related to several diseases as a possible pathogenic factor. Siragy et al. [23,24] have proposed a role for PRR in developing and evolution of diabetic nephropathy, showing its relationship with AT1R and NADPH Oxidase over-expression in diabetic rats. It has also been proposed that PRR may contribute to initial damage in cardiac tissue in a congestive heart failure model in animals, suggesting an important participation in the remodeling phenomena boosted by lesion [25]. No information, however, has been offered regarding its role during normal or altered pregnancy.

Pregnancy is a peculiar stage where normal changes are induced in order to support maternal and fetal needs. Many cardiovascular adaptations are made in order to manage an increased circulating volume, to augment heart output and renal function without producing high blood pressure [26].

In heart, we were able to show that PRR shows a modest increment during normal pregnancy, and this phenomenon is amplified significantly by preeclampsia. There is evidence suggesting that PRR participating in local RAAS systems develops local, intrinsic modifications in tissues expressing them [27]. Heart possess local Ang II-generating systems where PRR may contribute to classical Ang II-AT1R effects such as adaptive hypertrophy, tachycardia, vasoconstriction, via an angiotensin-II dependent pathway. In this work we could not find activation of PRR measured as PLZF expression in heart, however, the possibility of PRR-dependent Ang II generation as part of a local RAAS seems plausible. In the other hand, PRR may activate at least two different pathways: one activating ERK1/ERK2 and p38 MAPK pathways, or the Wnt-Frizzled receptor pathways. In both cases, relationships with cellular regulation, anti-apoptotic signals and morphological changes are fully described. If PRR activates in pregnancy or preeclampsia these pathways specifically in heart, remains to be studied.

In aorta we found that PRR expression increases significantly along with PLZF expression. These results suggest that PRR is activated during normal pregnancy. It is accepted since a long time ago that RAAS plays an important role in maintaining blood pressure during normal pregnancy [28]. Among other circulatory changes, vessels are modified to manage pregnancy-induced volume increasing. PRR seems to participate in these changes. Zhang et al. demonstrated in a diabetes model, that aorta expresses PRR and that activation of this receptor by circulating prorrenin, induces both Ang II-dependent and Ang-II independent responses that alter vascular function [29]. So, the possibility arises that PRR could be partially responsible of vascular changes induced by pregnancy in order to adapt to this physiological stage. Moreover, we found that preeclampsia inhibits PRR expression in aorta. Interestingly, PLZF seems to diminish along with it. If PRR, as we proposed here, is participating during vascular adaptations, this seems to suggest that, in a hypertensive disorder, where blood pressure is already high, PRR function is blunted. Anyhow, more experiments need to be done to confirm this.

Finally, we were able to detect PRR in kidney cortex and medulla, and in both cases, PRR seems to be active. During normal pregnancy, kidney is one of the most affected organs in order to manage volume

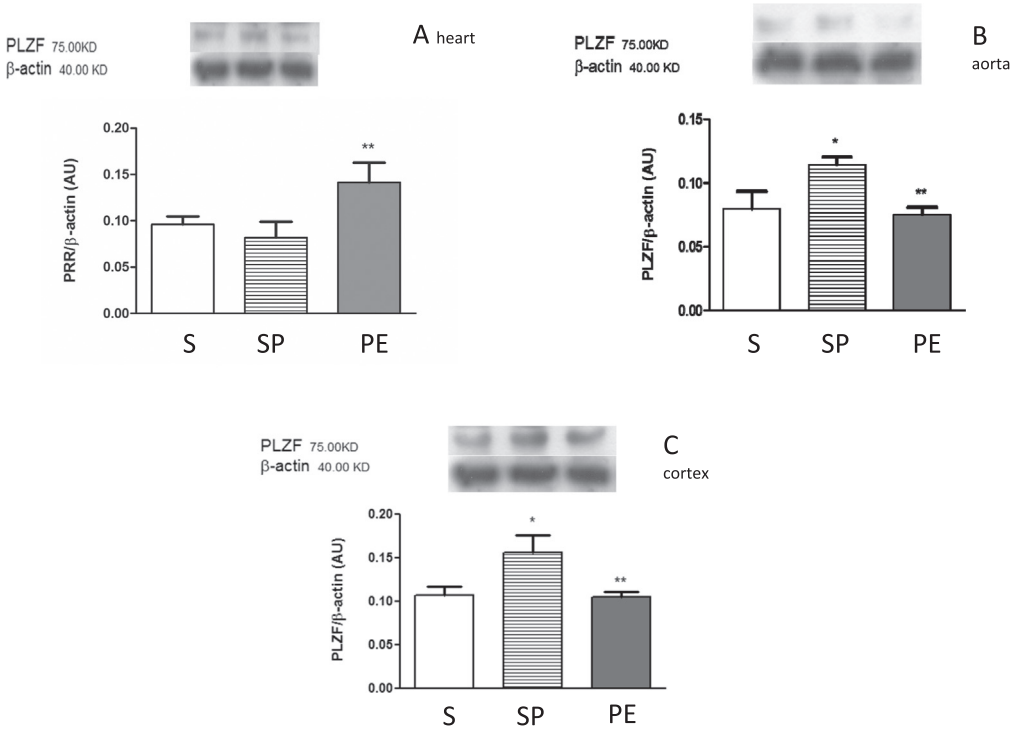

Fig. 9. PLZF expression in pregnant rats. PLZF was detected by immunoblot in left ventricle (A), aorta (B) and renal cortex (C) from sham non-pregnant (S), sham-pregnant (SP) and preeclamptic (PE) rats. Each bar represents media ± SD of 4 experiments. Immunoblots were normalized using β-actin as housekeeping protein. All graphs are expressed as arbitrary units. A typical experiment is shown at the top of each graph. $*p < 0.05$ vs. S, $**p < 0.05$ vs. SP.

expansion, sodium handling and waste disposal [16]. There is no information regarding PRR role in kidney during pregnancy, however, several works have shown PRR participation upon alterations induced by diverse pathologies in animals and humans. Of special interest is the capacity of PRR to induce sodium retention upon medullar tubules, which in turn results in a volume expansion; and the close interaction between PRR, Ang II and high prostaglandins production in inner medulla during hypertension induced by Ang II injection, to buffer development of high blood pressure [30]. In concordance with this, our findings of PRR in medulla and cortex suggest that this receptor could be participating in volume expansion due to sodium retention on normal pregnancy. In contrast, during preeclampsia, this function might be blocked, as we found in our results, where PRR and PLZF expression are abolished significantly. More experiments, however, need to be done to confirm this.

5. Conclusion

We described in this work, for the first time, how PRR expression changes differently during pregnancy and preeclampsia in tissues intimately related to cardiovascular functions, suggesting a probable participation of this receptor during normal and preeclamptic pregnancy in the rat.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Acknowledgments

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References

[1] H. Gao, U. Yallampalli, C. Yallampalli, Protein restriction to pregnant rats increases the plasma levels of angiotensin II and expression of angiotensin II receptors in uterine arteries, Biol. Reprod. 86 (3) (2011) 1–8. Article 68.
[2] J.J. Duvekot, L.L. Peeters, Maternal cardiovascular hemodynamic adaptation to pregnancy, Obstet. Gynecol. Surv. 49 (12 Suppl) (1994) S1–14.
[3] G.J. Gilson, M.D. Mosher, K.P. Conrad, Systemic hemodynamics and oxygen transport during pregnancy in chronically instrumented, conscious rats, Am. J. Phys. 263 (6 Pt 2) (1992) H1911–H1918.
[4] L. Anguiano-Robledo, et al., Renal angiotensin-II receptors expression changes in a model of preeclampsia, Hypertens. Pregnancy 26 (2) (2007) 151–161.
[5] K. Kanasaki, R. Kalluri, The biology of preeclampsia, Kidney Int. 76 (8) (2009) 831–837.
[6] K. Verdonk, et al., The renin-angiotensin-aldosterone system in pre-eclampsia: the delicate balance between good and bad, Clin. Sci. (Lond.) 126 (8) (2014) 537–544.
[7] E. Podjarny, G. Losonczy, C. Baylis, Animal models of preeclampsia, Semin. Nephrol. 24 (6) (2004) 596–606.
[8] G. Nguyen, et al., Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin, J. Clin. Invest. 109 (11) (2002) 1417–1427.
[9] P. Balakumar, G. Jagadeesh, Cardiovascular and renal pathologic implications of prorenin, renin, and the (pro)renin receptor: promising young players from the old renin-angiotensin-aldosterone system, J. Cardiovasc. Pharmacol. 56 (5) (2010) 570–579.
[10] T.L. Reudelhuber, Prorenin, renin, and their receptor: moving targets, Hypertension 55 (5) (2010) 1071–1074.
[11] Z. Shan, et al., Involvement of the brain (pro)renin receptor in cardiovascular homeostasis, Circ. Res. 107 (7) (2010) 934–938.
[12] W. Li, et al., Brain-targeted (pro)renin receptor knockdown attenuates angiotensin II-dependent hypertension, Hypertension 59 (6) (2012) 1188–1194.
[13] H. Funke-Kaiser, et al., Signal transduction of the (pro)renin receptor as a novel therapeutic target for preventing end-organ damage, Hypertens. Res. 33 (2) (2010) 98–104.
[14] S. Kirsch, et al., The (pro)renin receptor mediates constitutive PLZF-independent pro-proliferative effects which are inhibited by bafilomycin but not genistein, Int. J. Mol. Med. 33 (4) (2014) 795–808.
[15] K.G. Pringle, et al., Molecular evidence of a (pro)renin/(pro)renin receptor system in human intrauterine tissues in pregnancy and its association with PGHS-2, J. Renin-Angiotensin-Aldosterone Syst. 12 (3) (2011) 304–310.
[16] C.A. West, J.M. Sasser, C. Baylis, The enigma of continual plasma volume expansion in pregnancy: critical role of the renin-angiotensin-aldosterone system, Am. J. Physiol. Ren. Physiol. 311 (6) (2016) F1125–F1134.
[17] M.M. Abitbol, Simplified technique to produce toxemia in the rat: considerations on cause of toxemia, Clin. Exp. Hypertens. B 1 (1) (1982) 93–103.
[18] J. Li, B. Lamarca, J.F. Reckelhoff, A model of preeclampsia in rats: the reduced uterine perfusion pressure (RUPP) model, Am. J. Physiol. Heart Circ. Physiol. 303 (1) (2012) H1–H8.
[19] P. Javadian, et al., Effect of morphine on the reduced uteroplacental perfusion model of pre-eclampsia in rats, Eur. J. Obstet. Gynecol. Reprod. Biol. 168 (2) (2013) 161–166.
[20] M. He, et al., Inhibition of renin/prorenin receptor attenuated mesangial cell proliferation and reduced associated fibrotic factor release, Eur. J. Pharmacol. 606 (1–3) (2009) 155–161.

[21] G. Chen, et al., Regulation of cyclo-oxygenase gene expression in rat smooth muscle cells by catalase, Biochem. Pharmacol. 55 (10) (1998) 1621–1631.
[22] N. Melamed, et al., Gestational hypertension and preeclampsia: are they the same disease? J. Obstet. Gynaecol. Can. 36 (7) (2014) 642–647.
[23] C. Li, H.M. Siragy, High glucose induces podocyte injury via enhanced (pro)renin receptor-Wnt-beta-catenin-snail signaling pathway, PLoS One 9 (2) (2014) e89233.
[24] H.M. Siragy, J. Huang, Renal (pro)renin receptor upregulation in diabetic rats through enhanced angiotensin AT1 receptor and NADPH oxidase activity, Exp. Physiol. 93 (5) (2008) 709–714.
[25] T. Hirose, et al., Gene expression of (pro)renin receptor is upregulated in hearts and kidneys of rats with congestive heart failure, Peptides 30 (12) (2009) 2316–2322.
[26] P.M. Bosio, et al., Maternal central hemodynamics in hypertensive disorders of pregnancy, Obstet. Gynecol. 94 (6) (1999) 978–984.
[27] A. Ichihara, Pro)renin receptor and vacuolar H(+)-ATPase, Keio J. Med. 61 (3) (2012) 73–78.
[28] N.F. Gant, et al., A study of angiotensin II pressor response throughout primigravid pregnancy, J. Clin. Invest. 52 (11) (1973) 2682–2689.
[29] J. Zhang, et al., Receptor-dependent prorenin activation and induction of PAI-1 expression in vascular smooth muscle cells, Am. J. Physiol. Endocrinol. Metab. 295 (4) (2008) E810–E819.
[30] M. Hennrikus, A.A. Gonzalez, M.C. Prieto, The prorenin receptor in the cardio-vascular system and beyond, Am. J. Phys. Heart Circ. Phys. 314 (2) (2018) H139–H145.