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Possible involvement of orphan receptors GPR88 and GPR124 in the development of hypertension in spontaneously hypertensive rat

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ABSTRACT

Hypertension (HBP) is a chronic disease characterized by increased blood pressure, which despite several treatments maintains a high morbi-mortality, which suggests that there are other mechanisms involved in this pathology, within which the orphan receptors could be candidates for the treatment of the HBP; these receptors are called orphan receptors because their ligand is unknown. These receptors have been suggested to participate in some pathologies because they are associated with various systems such as GPR88, which has been linked to the dopaminergic system, and GPR124 with angiogenesis, suggesting that these receptors could take part in HBP. Hence, the aim of this work was to study the expression of orphan receptors GPR88 and GPR124 in various tissues of normotensive and hypertensive rats. We used Wistar Kyoto (WKY) and spontaneously hypertensive rat (SHR) of 6–8 and 10–12 weeks of age and we determined systolic blood pressure (SBP), heart rate, as well as mRNA of GPR88 and GPR124 receptors by reverse transcription polymerase chain reaction (RT-PCR) in the aorta, heart, kidney, and brain. Our results showed that GPR88 and GPR124 were expressed in all analyzed tissues, but their expression is dependent on the age and development of HBP because their expression tends to be modified as HBP is established. Therefore, we conclude that GPR88 and GPR124 receptors may be involved in the development or maintenance of high blood pressure.

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Introduction

Hypertension (HBP) is classified as a blood pressure greater than or equal to 140/90 mm Hg systolic blood pressure (SBP) and diastolic blood pressure (DBP) (1). This pathology is considered one of the main risk factors for coronary heart disease, stroke, heart failure, and renal insufficiency (2), making it one of the main causes of mortality worldwide; the prevalence of HBP is approximately 1 billion people and causes approximately 7.5 million deaths per year (3). Interestingly, there are several treatments for this pathology; however, high morbidity and mortality still exist, which suggests that other mechanisms are involved in the development of this pathology.

Recently, a new class of receptors has been discovered, which are called orphan receptors, because their endogenous ligand has not been found (4). These receptors have been classified depending on their structure and location in seven-domain receptors (GPR) and nuclear. On the other hand, within the GPR receptors, these have been subclassified mainly in three families such as classes A, B, and C, with class A being the largest family having as a characteristic that they have homology with the receptors of rhodopsin (5), whereas class B receptors with secretin homology and some of their non-orphaned receptors have been found to have peptide-type ligands (6), and finally we have class C receptors, which have homology to the metabotropic receptors of glutamate (7).

These receptors have been associated with various pathologies such as diabetes, anxiety, depression, cancer, etc. (8–11), where changes in their expression have been observed to both increase and decrease and these changes have been associated not only with development but also with establishing these pathologies. Among the receptors that have been associated with various pathologies, we have the GPR88, as well as the GPR124 (12,13).

The orphan receptor GPR88 has been reported to be expressed basally in the brains of mice; interestingly, the deletion of the gene from this receptor is associated with increased psychiatric disorders. These disorders have been associated with alterations in the dopaminergic system (12), so we do not rule out that these alterations can modify the cardiovascular system because dopamine is a neurotransmitter that has been associated in the pathogenesis of HBP (14). This receptor belongs to class A of seven-domain receptors and has been reported in humans in the chromosomal region

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1p21.3, as well as in rats in the 2q41 position; both receptors have a homology of 86% among them and have an open reading frame of 384 amino acids (15). On the other hand, GPR124 has been reported to belong to class B, and has been reported to be expressed in several human tissues. Although it tends to overexpress itself in the blood vessels of tumors, several functions have been ascribed to this receptor within which is included angiogenesis (13), which has been associated with the development of HBP (16). This receptor in humans is found at chromosomal location 8p11.22, whereas in rats it is located in the 16q12.4 region, exhibits 84% homology in its amino acid sequence among them, and codes for a protein of 1331 amino acids (17). Therefore, because it has been described that GPR88 takes part in the regulation of the dopaminergic system and GPR124 in neovascularization and both mechanisms have been associated with the development of HBP, the objective of this work was to evaluate whether orphan receptors GPR88 and GPR124 were involved in the development or establishment of HBP.

Materials and methods

Animals

Male Wistar Kyoto (WKY) rats and spontaneously hypertensive rats (SHR) between 6–8 and 10–12 weeks of age were kept in light-dark cycles of 12 hours with food and water *ad libitum*. All procedures described here were approved by the Postgraduate Bioethics Committee of our institution and the Mexican Official Norm (NOM-062-ZOO-1969) regarding technical specifications for production, care, and use of laboratory.

Physiological parameters

Body weight was measured with a conventional balance individually for each rat and in triplicate using a precision balance (Ohaus Scout Pro CS200). SBP was measured by the tail-cuff method (IITC Life Science Inc. Woodland Hills, CA). Hypertensive rats were considered as those animals with SBP levels above 160 mm Hg.

Extraction of total RNA

Total RNA was extracted from tissues using Trizol, a commercially available mixture of phenol and guanidine isothiocyanate, according to the protocol described by the manufacturer (Life Technologies, Carlsbad, CA). The concentration and purity of the RNA were determined by measurement of the optical densities at 260 and 280 nm. A ratio of 1.8 A260/A280 was required for these studies. The RNA solutions were diluted to a working concentration of 1 mg/ml in nuclease-free water with the addition of RNase inhibitor.

Quantification of receptors mRNA expression

For the reverse transcription synthesis of cDNA, we used the reverse transcription system kit (Promega Corporation, Woods Hollow Road, Madison, WI) using oligodT primers, following the manufacturer's recommendations. We performed the polymerase chain reaction using the universal probe library (Roche Applied Science, Manheim, Germany); the reaction of PCR was performed in a thermocycler time CFX-96 (Bio-Rad, Hercules, CA, USA .S.), using 96-well microplates under the following conditions: 95°C for 2 min; 45 cycles at 95°C for 15 s, 60°C for 30 s. The following primers and probes were used: GPR88 gene (NM_031696.1) TTCAGACTGCATGTTGATTTCC (Forward), CCATAAAGCAACAGCGAACA (Reverse) universal probe library #63; GPR124 gene (XM_003751617.4) GGGAGTGCGT CTCCTCAG (Forward), GAGCTCAGTCACCTGGACAAG (Reverse) universal probe library #67; housekeeping Hprt1 (NM_012583.2) CCCGCGAGTACAACCTTCT (Forward), CGTCATCCATGGCGAACT (Reverse) universal probe library #22. Negative control was obtained by performing real-time RT-PCR without cDNA. The GPR88 and GPR124 receptors mRNA expression levels were determined by the Livak method commonly known as the "delta delta Ct", normalizing expression with Hprt1.

Bioinformatic identification of potential G protein coupled to receptor GPR88 and GPR124

The predicted g protein-coupling specificity for the orphan receptors GPR88 and GPR124 was determined by the software PRED-COUPLE 2.00 that uses a method for the prediction of g-protein coupled receptors (GPCRs) coupling specificity to g proteins using refined profile Hidden Markov Models (18).

Statistical analysis

Data were expressed as the mean ± standard error of the mean (SEM). Comparisons were made between groups of SHR of 6–8 weeks of age with their WKY control of 6–8 weeks of age and SHR of 10–12 weeks of age with their WKY control of 10–12 weeks of age, respectively, in addition to one comparison between groups using a one-way ANOVA and Tukey's post hoc test. Significant values were * $p \leq 0.05$ vs. WKY, ** $p < 0.01$ vs. WKY, and # $p \leq 0.05$ vs. SHR of 6–8 weeks of age.

Physiological parameters

Analysis of body weight showed that rats of 6–8 weeks of age did not show significant differences with respect to their control; however, in the group of 10–12 weeks of age there was a significant decrease in the weight of the SHR compared with their WKY control. On the other hand, the analysis of SBP showed that the SHR of 6–8 weeks did not present significant differences with respect to their WKY control; however, at the age of 10–12 weeks a higher SBP was observed in the SHR with respect to their WKY control. In the case of heart rate, the SHR presented a significantly higher frequency at the age of 6–8 weeks with respect to their WKY control (Table 1).

Expression of orphan receptor GPR88

Expression of GPR88 showed that the SHR group of 6–8 weeks had a significant lower expression in the aorta (Figure 1A); on the contrary, the left atrium had a higher expression (Figure 2B) compared to their control. However,

Table 1. Physiological parameters.

Groups	N	BW	SBP	HR
WKY 6–8 weeks old	4	161 ± 4.86	106 ± 8.75	315 ± 37.75
SHR 6–8 weeks old (Prehypertensive)	4	167 ± 4.51	120 ± 4.41	440 ± 28.28*
WKY 10–12 weeks old	4	293 ± 10.68	116 ± 1.44	375 ± 15.00
SHR 10–12 weeks old(Hypertensive)	4	257 ± 6.02*	174 ± 2.40*	405 ± 57.45

BW: Body weight; SBP: Systolic blood pressure; HR: Heart rate. Values are expressed as mean ± standard error. * $p \leq 0.05$ vs. controls.

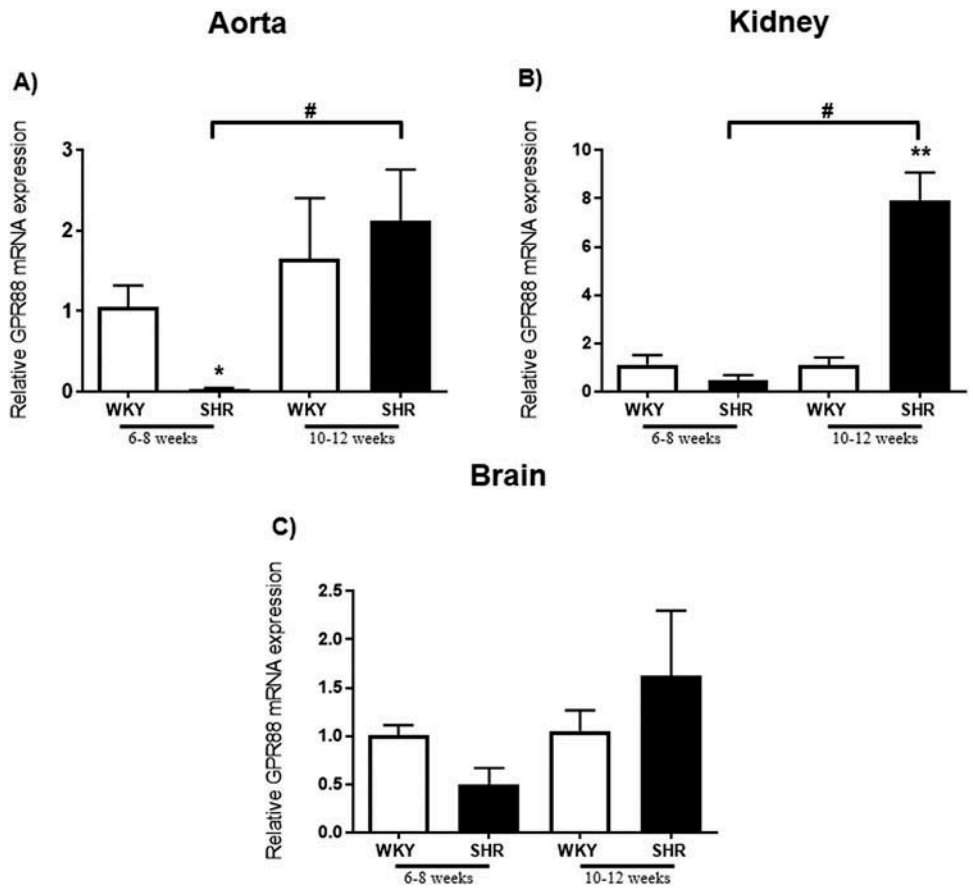

Figure 1. Relative expression of the orphan receptors GPR88 in A)aorta, B)kidney and C)brain of rats with 6-8 and 10-12 weeks of age. Values are expressed as mean ± standard error. *P ≤ 0.05 vs WKY, # P ≤ 0.05 vs SHR of 6-8 weeks of age.

in the tissues of the kidney, brain, right atrium, and ventricles, there were no significant differences (Figure 1B, C, 2A, C, D). On the other hand, the SHR of 10–12 weeks of age showed a significant increase in kidney and left atrium with respect to their control (Figures 1B and 2B), while the right atrium and the right ventricle showed a significant decrease (Figure 2A, C) and no significant differences were observed in the aorta, brain, and left ventricle (Figures 1A, C, and 2D).

Expression of orphan receptor GPR124

Expression analysis of the GPR124 receptor showed that the SHR of 6–8 weeks of age had a significant increase in aorta compared with their control (Figure 3A); on the other hand, a significant decrease was observed in kidney and left ventricle (Figures 3B and 4D). However, brain, atrium, and right ventricle did not show significant differences (Figures 3C and 4A, B, C). On the other hand, the SHR of 10–12 weeks of age presented a significant increase in kidney and left atrium with respect to their control (Figures 3B and 4B), whereas in the aorta, brain, right atrium, and ventricles no significant differences were observed (Figure 3A, C and 4A, C, D).

Discussion

Our results show that the SHR present less weight at the age of 10–12 weeks; this agrees with previous studies (19,20), where they associate this effect with sympathetic hyperactivity observed in the SHR because this effect causes an increase in lipolysis and a decrease in the accumulation of triglyceride-rich lipoproteins in adipose tissue, in addition to the activation by β3-adrenergic receptors that stimulate thermogenesis, increasing energy expenditure (21). It is important to mention that this difference is not observed in rats of 6–8 weeks because at that age the SHR and WKY rats show no difference

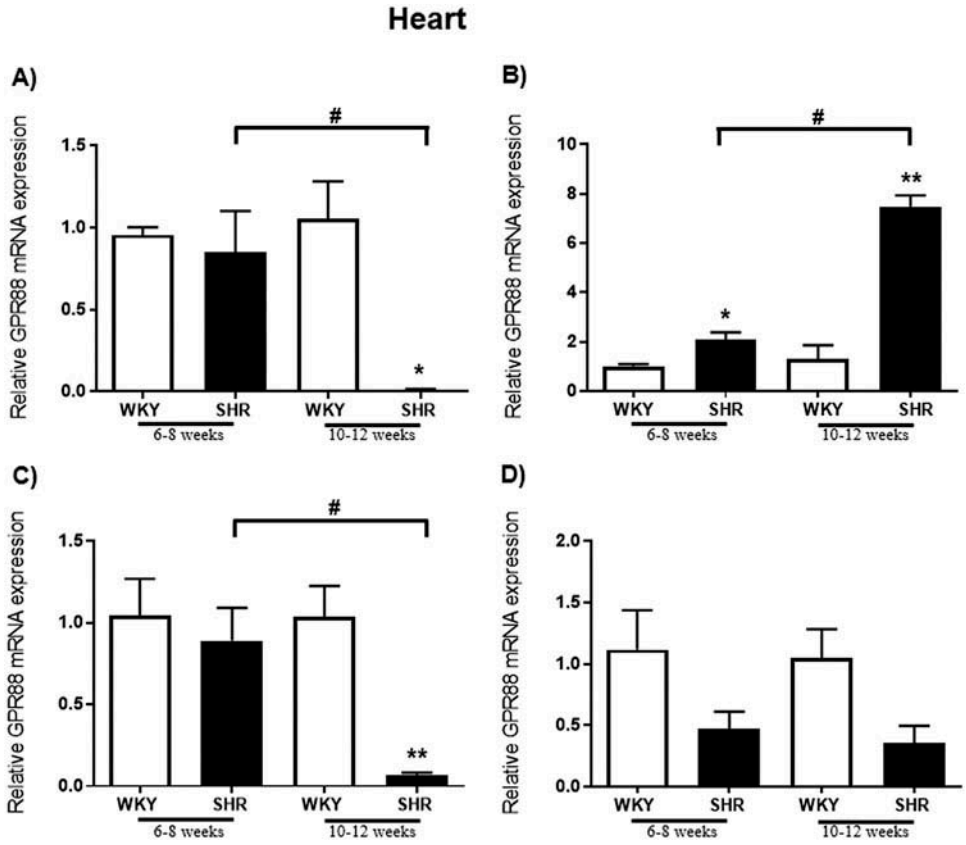

Figure 2. Relative expression of the orphan receptor GPR88 in A) right atrium, B)left atrium, C)right ventricle and D) left ventricle of rats with 6-8 weeks of age. Values are expressed as mean ± standard error. *P ≤ 0.05 vs WKY, # P ≤ 0.05 vs SHR of 6-8 weeks of age.

in SBP, suggesting that at that age they did not initiate sympathetic hyperactivity (22,23).

On the other hand, measurements of SBP showed that the SHR at the age of 6–8 weeks does not differ from their WKY control; there are studies in which they mention that at the age of 6–8 weeks, the SHR can be considered prehypertensive, so their pressure does not show differences with respect to WKY rats (24,25). However, as they increase in age, there are changes in this type of rats that lead to HBP (26,27). This increase has been associated with an increase in peripheral vascular resistance (28) and sympathetic activity (29,30) as well as a decrease in vasodilators agents such as nitric oxide and prostacyclin (31,32). With regard to heart rate, only an increase in the SHR was observed at the age of 6–8 weeks; this agrees with other studies where they report that the frequency tends to increase and the fact that the pressure does not increase at that age is because the vasculature retains its capacity to be a counterbalance to the increased frequency and as age increases, this counterbalance is lost and therefore an increase is observed only at older ages (33,34).

With respect to the expression of the orphan receptors, we found that these receptors are expressed ubiquitously; however, they present differences in profile expression between them. The expression of GPR124 showed that this receptor is expressed in the aorta, heart, kidney, and brain; these results are in agreement with other studies, where the presence of this receptor has been reported in brain (35,36), heart, and kidney (36), although our results show that this receptor tends to change its expression, increasing in the left atrium and left ventricles due to the HBP. Interestingly, bioinformatic analysis suggests that this receptor is coupled to Gi proteins; this is the first time that this receptor is associated with a signaling cascade. The fact that it increases its expression in the heart suggests that this receptor might be over-expressing in order to decrease cardiac damage due to HBP (37), because Gi signaling in the heart is related to a decrease in the force of contraction (38); on the other hand, we cannot rule out that perhaps overexpression of this receptor promotes neovascularization, which has been reported to occur during HBP (39).

In the case of the GPR88 receptor, there are previous studies that have reported its presence in different regions of the brain and especially in dopaminergic regions (12,15,40); our study agrees with these studies, although we did not make analysis in all the regions, on the other hand, we found that this receptor was expressed in all the tissues analyzed however did not observe differences between the groups, although this receptor has been involved in different pathologies such as schizophrenia (40), Parkinson's (12) and depression (41), being this a psychiatric disease that has been associated with HBP (42–44), possibly these results are due to the fact that specific regions were not considered. *In silico* analysis we showed that this receptor is associated with Gi proteins, which is in agreement with the previous results where it was shown that this receptor decreases the cAMP levels (45,46). At the central level, this receptor would be decreasing the sympathetic discharges on the basis of its

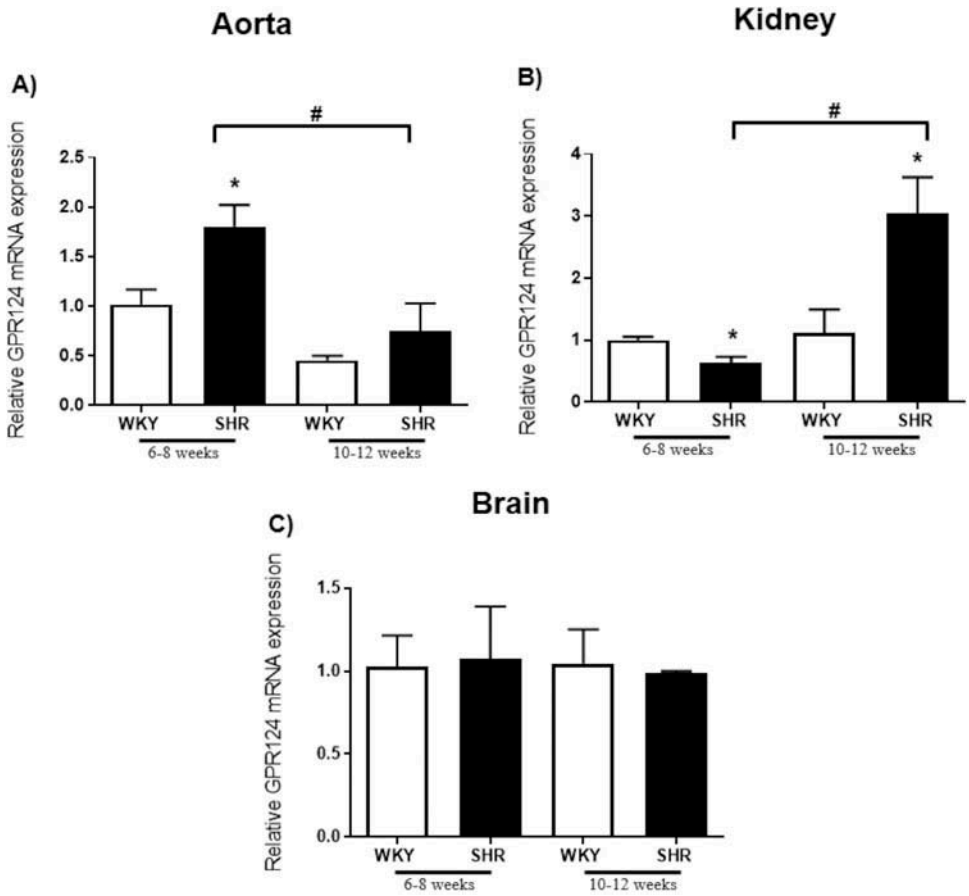

Figure 3. Relative expression of the orphan receptor GPR124 in A) aorta, B) kidney and C) brain of rats with 6-8 and 10-12 weeks of age. Values are expressed as mean ± standard error. *P ≤ 0.05 vs WKY, # P ≤ 0.05 vs SHR of 6-8 weeks of age.

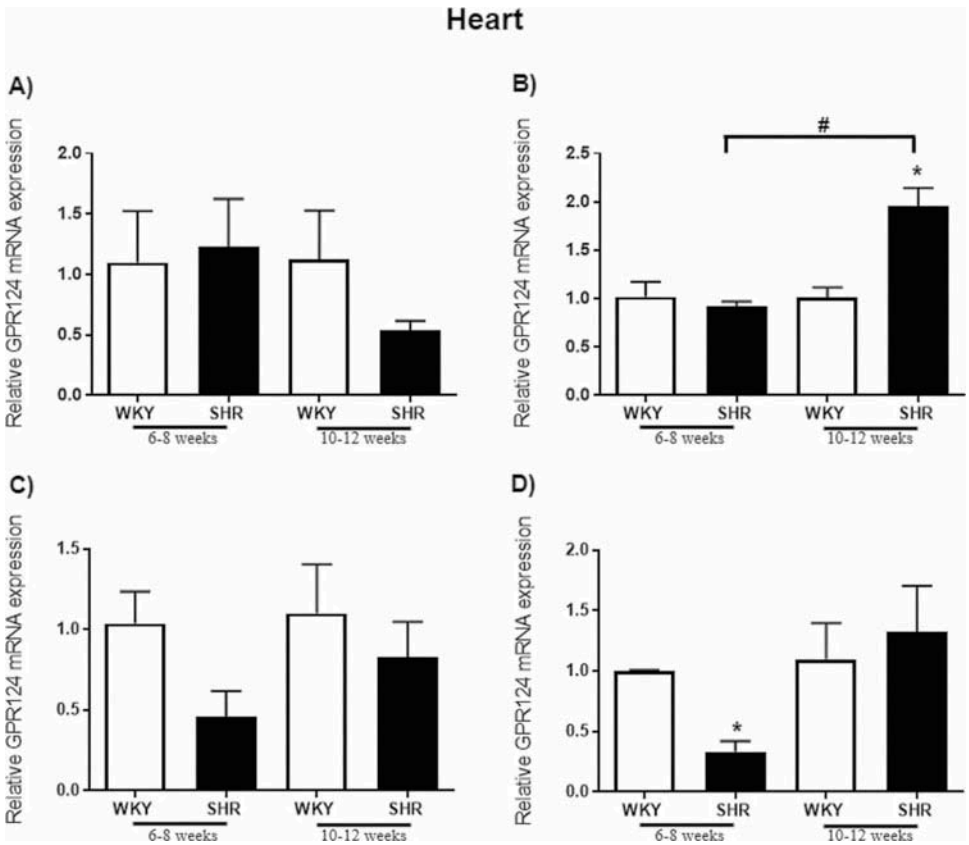

Figure 4. Relative expression of the orphan receptor GPR124 in A) right atrium, B) left atrium and C) right ventricle and D) left ventricle of rats with 6-8 and 10-12 weeks of age. Values are expressed as mean ± standard error. * P ≤ 0.05 vs WKY, # P ≤ 0.05 vs SHR of 6-8 weeks of age.

signaling cascade (46); perhaps we did not observe differences because in our rats of 10–12 weeks of age the activity has increased (47), which suggests that this receptor is not modulating that activity. The GPR88 receptor was not described previously at the cardiovascular level. Our study demonstrated that this receptor is present in important tissues of the regulation of arterial pressure; on the one hand, we find that the atrium and right ventricle tend to decrease their expression due to HBP, while in the atrium it tends to increase its expression. The mediated signaling by Gi coupled receptors in the heart produces negative chronotropism and negative inotropism (48,49). The fact that this receptor tends to decrease in the regions of the heart may favor the increase of blood pressure, which is observed in HBP. On the other hand, the fact that this receptor is overexpressed in the kidney in the SHR suggests that it can try to avoid damage at the renal level because receptors with Gi signaling tend to increase renin secretion (50,51). Perhaps this receptor is overexpressed trying to decrease the increase of this secretion since these rats present an increase of plasma renin levels (52); we do not rule out that this receptor could have a compensatory effect.

Conclusion

Based on the above discussions, we conclude that GPR88 and GPR124 receptors are ubiquitously expressed at the cardiovascular level and their expression profile in some tissues is dependent on the stage of HBP.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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