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Antidepressant treatment decreases daily salt intake and prevents heart dysfunction following subchronic aortic regurgitation in rats ☆

Juliana Irani Fratucci De Gobbi [a,*], Ana Carolina Mieko Omoto [a], Tamires Ferreira Siqueira [a], Luiz Shigueto Matsubara [b], Meliza Goi Roscani [b], Beatriz Bojikian Matsubara [b]

[a] Department of Physiology, Institute of Bioscience, UNESP-Botucatu, Brazil
[b] Department of Internal Medicine, Botucatu Medical School, UNESP, Brazil

HIGHLIGHTS

- Selective serotonin reuptake inhibitors (SSRI) may improve heart disease outcomes.
- Aortic regurgitation (AR) decreases systolic function.
- Paroxetine (SSRI) treatment effects were investigated in AR rats.
- Paroxetine improves systolic function and decreases sodium intake in AR rats.

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ABSTRACT

Depression is a predictor of poor prognosis in patients with heart failure. Selective serotonin (5-HT) reuptake inhibitors (SSRIs) may improve these outcomes. Left ventricular volume overload induced hypertrophy that is associated with aortic regurgitation (AR) leads to ventricular dysfunction and heart failure. The aim of this study was to verify the effects of the SSRI paroxetine on cardiac function, as well as on fluid intake and excretion, in subchronic AR. Male Wistar rats (260 to 280 g) received sham (SH) surgery or AR induced by retrograde puncture of the aortic valve leaflets. The presence of AR was confirmed by echocardiography (ECHO) exams. Four weeks after AR surgery, subcutaneous injections of paroxetine (PAR: 10 mg/kg 3 times in a week) or saline were administered. The rats were randomly divided into the following 4 groups and treated for 4 weeks: AR-PAR, ARsaline, SH-PAR and SH-saline. At the end of the treatment period, fractional shortening was preserved in AR-PAR, compared to AR-saline (46.6 ± 2.7% vs 38.3 ± 2.2%, respectively). Daily 0.3 M NaCl intake was reduced in PAR-treated rats. Natriuresis was increased in weeks 2-3 after PAR treatment. Our results suggest that augmentation of central 5-HT neurotransmission has a beneficial effect on cardiovascular remodeling following volume overload. The mechanisms underlying this effect are unknown.

1. Introduction

Aortic regurgitation (AR) causes a progressive dilatation and hypertrophy of the left ventricle (LV). Over time, AR leads to LV dysfunction and eventually heart failure after a prolonged lack of symptoms [1]. Valve heart disease remains a prevalent issue in Brazil, as this rheumatic heart disease is a leading cause of AR, particularly in young patients [1,2]. Furthermore, its incidence is increasing in developed countries as a consequence of senile degeneration [2]. Heart failure, independent of underlying disease, is associated with the activation of several neurotransmitter systems that lead to further ventricular dysfunction and death.

Depression, a mood disorder, is a co-morbidity commonly associated with cardiovascular disease [3–5]. This medical condition also causes an activation of neurohumoral systems, which could facilitate the transition to heart failure. Alterations in the metabolism of serotonin (5-HT) are particularly implicated in this process [6,7]. Four weeks of fluoxetine treatment, a selective serotonin reuptake inhibitor (SSRI), can prevent cardiovascular changes associated with moderate chronic stress in rats [7]. SSRIs are widely prescribed, and they show advantages over classic antidepressants, including dose safety and good tolerability, as well as

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* Corresponding author at: Department of Physiology, Institute of Bioscience, UNESP, São Paulo State University, UNESP, Distrito de Rubião Junior s/n, 18618-000 Botucatu, SP, Brazil.
E-mail address: jdegobbi@ibb.unesp.br (J.I.F. De Gobbi).

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improving the safety of patients with heart disease by reducing the probability of arrhythmias and platelet function [6,8]. Panic patients treated with the SSRI paroxetine (PAR) present with increased heart rate variability [9]. The administration of a selective 5-HT_3 receptor agonist in the forebrain exerts a tonic sympathoinhibitory action on the pressor component of the baroreflex [10], suggesting a potential beneficial role for SSRI treatment in heart disease.

Sodium intake reductions are well recognized as important steps to improve both the clinical outcome and the quality of life of cardiac patients [11,12]. The involvement of 5-HT in sodium balance, intake and excretion behaviors is well documented. The depletion of 5-HT through intraperitoneal administration of p-chlorophenylalanine, an amino acid that competes with tryptophan for the same transporter on serotonergic neurons, increases sodium appetite in salt-depleted rats [13]. Chemical lesions of the dorsal raphe nucleus, a midline structure comprising the main source of central 5-HT [14], increase sodium intake for a variety of protocols, for instance sodium depletion and angiotensin II brain activation [15]. Taken these observations in account the present study was designed to investigate the effects of PAR treatment in subchronic AR in relation to heart function and fluid intake and excretion.

2. Materials and methods

2.1. Animal model of AR

Male Wistar rats (260 to 280 g) had sham (SH) or AR surgeries induced by retrograde puncture of the aortic valve leaflets under anesthesia [ketamine 80 mg/kg of body weight (bw) plus xylazine 7 mg/kg bw, Vetbrands, Jacareí-SP]; these surgeries are described elsewhere [16,17]. One week after surgeries, the rats were analyzed by echocardiogram, and the rats meeting the inclusion criteria (see below) were assigned to experimental groups. The rats were randomly divided into 4 groups: AR-PAR, AR-saline, SH-PAR and SH-saline. Drug treatment was initiated 4 weeks after the surgical procedure, as this is a period when the heart has already been exposed to an overload that continues for 4 weeks. Animals were observed daily to collect the drinking and weekly weight data. At the end of the protocol, the animals were euthanized and their hearts were removed and weighed. All procedures were in accordance with the Animal Care and Use policies of the Institute of Biosciences of Botucatu, which follows the Brazilian College of Animal Experimentation (COBEA) polices. All efforts were made to minimize animal discomfort and the number of animals used.

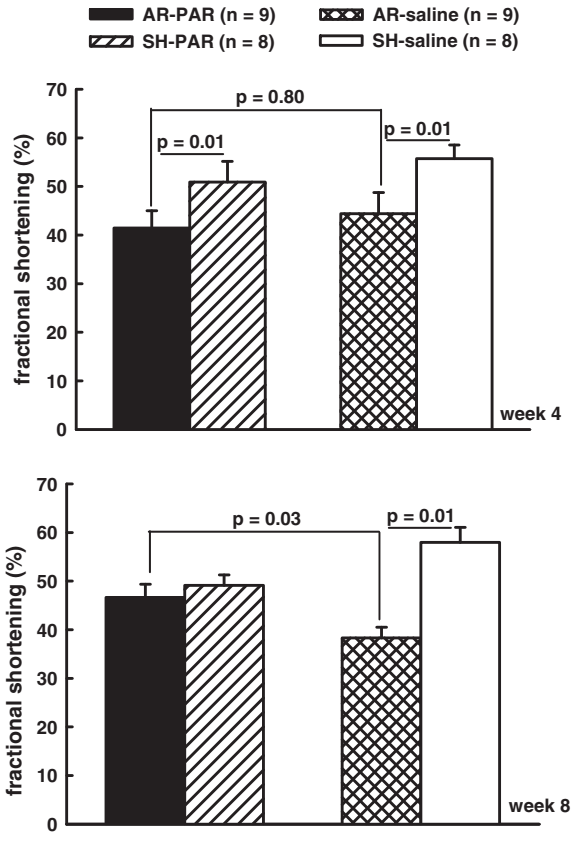

Fig. 1. Fractional shortening (%) at the weeks 4 (above, before treatment) and 8 (below, after treatment) in treated/untreated aortic regurgitation (AR) or sham (SH) rats. Data are presented as the means ± SEM. A two-way ANOVA was performed for comparisons between surgery and treatment.

2.2. Echocardiography

A complete M-mode, 2D, and Doppler echocardiogram (ECHO) were performed on the animals under anesthesia (ketamine 50 mg/kg with xylazine 5 mg/kg) using a 12-MHz probe with a Sonos 5500 echograph (Philips Medical Imaging, Andover, Mass) one week after surgery to confirm AR presence and severity. The ECHO was repeated at weeks 4 and 8 after surgery to collect morphofunctional variables. ECHO inclusion criteria included a ratio of regurgitant jet width to LVOT diameter >50% of a retrograde holo-diastolic flow in the proximal descending aorta (Fig. 1), and animals that failed to meet these criteria were excluded. We analyzed LV dimensions, wall thickness, ejection fraction, diastolic function, and cardiac output (i.e., ejection volume in the LV outflow tract-heart rate), as previously reported [18].

2.3. Drugs

Paroxetine chloride (PAR, 10 mg/kg bw, PharmaNostra, Rio de Janeiro, Brazil) was dissolved in saline vehicle, which was used as a control. PAR was injected subcutaneously (sc) every three days over 4 weeks.

2.4. Daily water and 0.3 M NaCl intake and excretion

The rats were kept in individual metal cages. Water and 0.3 M NaCl were provided from burettes with 1 ml divisions that were fitted with metal drinking spouts, with free access to a standard laboratory diet (Labina Purina® Rat Chow). Temperature was maintained at 23 ± 2 °C and humidity at 54 ± 10% with a 12:12 light:dark cycle (onset at 06:10). During PAR treatment, the water and 0.3 M NaCl solution volumes were measured daily. Overnight urine samples were collected weekly from weeks 5–8. Each night, the animals were moved to metabolic cages and given access only to water. Urine samples were analyzed by a flame photometer to quantify Na^+ and K^+ in milliequivalents (mEq). In order to calculate sodium and potassium excretion the urinary volume was multiplied by the mEq.

2.5. Blood pressure and heart rate

Mean arterial pressure (MAP) and heart rate (HR) were recorded in unanesthetized rats. Four days after collecting ECHO variables at week 8, the rats were anesthetized again with ketamine (80 mg/kg bw) combined with xylazine (7 mg/kg bw), as described for AR surgeries. After anesthesia onset, polyethylene tubing (PE-10 tube connected to a PE-50 tube, Braintree Scientific, Inc. MA, USA) was inserted into the abdominal aorta through the femoral artery. Arterial catheters were tunneled sc and exposed on the back of the rats to allow access in unrestrained, freely moving rats. To record pulsatile arterial pressure, MAP and HR, the arterial catheter was connected to a pressure transducer (TSD104A, Biopac Systems) coupled to a pre-amplifier (model M100A-CE, Biopac Systems Santa Barbara, CA, USA), and monitored by a BIOPAC computer data acquisition system.

Table 1
Echocardiographic data before paroxetine treatment, 4 weeks following AR.

Variables — 4 weeks	AR-PAR n = 9	AR-saline n = 8	SH-PAR n = 9	SH-saline n = 8
LVSD (mm)	5.13 ± 0.38*	5.12 ± 0.53*	3.46 ± 0.40	2.62 ± 0.26
LVDD (mm)	8.74 ± 0.31*	9.07 ± 0.39*	7.01 ± 0.33	5.95 ± 0.29
LAV (cm^3)	0.180 ± 0.020*	0.189 ± 0.033*	0.075 ± 0.009	0.080 ± 0.019
Relative wall thickness	0.39 ± 0.02	0.35 ± 0.02	0.43 ± 0.03	0.48 ± 0.01
LA/Ao	1.44 ± 0.11*	1.61 ± 0.13*	1.22 ± 0.06	1.05 ± 0.04
Sphericity index	0.81 ± 0.01*	0.87 ± 0.02*	0.66 ± 0.02	0.63 ± 0.01
Body weight (g)	378.4 ± 12.9	369.3 ± 6.2	371.3 ± 14.3	362.8 ± 9.9

LVSD = left ventricle end-systolic diameter (mm, $p < 0.001$); LVDD = left ventricle end-diastolic diameter (mm, $p < 0.01$); LAV = left atrium volume (cm^3, $p < 0.01$); LA/Ao = left atrium normalized area ($p < 0.01$). Treatment initiated after this ECHO measurement. Data are presented as the means ± SEM. *Different from SH.

2.6. Data analysis

Two-way ANOVA was used to analyze the ECHO data, daily water and 0.3 M NaCl intake, blood pressure and urinary variables for each week of treatment, with surgery and treatment as independent factors. Two-way repeated measures ANOVA was used to compare the effect of time on the presence or absence of AR. Tests were combined with the Student–Newman–Keuls post-hoc test when appropriate. A probability of less than 0.05 was required for significance. Data are expressed as the means ± standard error of the mean (SEM).

3. Results

3.1. Echocardiographic data

Tables 1 and 2 summarize the echocardiographic data for weeks 4 and 8, respectively. It was important to demonstrate that the groups were homogeneous before the PAR treatment. A 4-week treatment period prevented a further reduction in LV function in the AR-PAR group, compared with AR-saline (Figs. 1 and 2). That is, fractional shortening in AR-PAR was similar to the control groups, whereas it decreased in the AR-saline group (Fig. 1). Interestingly, this protective effect occurred in association with decreases in daily sodium intake, even in the presence of LV dilation. PAR treatment prevented a time-dependent progression of LV dysfunction in the AR rats (Fig. 2), data are represented as median and percentiles and a two-way repeated measures ANOVA was performed to compare treatment and time and highlight the differences in the time evolution of the AR–PAR and AR–saline on fractional shortening (%). However, PAR had no effect on the LV function index in rats without cardiac dysfunction (Fig. 2).

Table 2
Echocardiographic data at the end of paroxetine treatment, 8 weeks following AR.

Variables — 8 weeks	AR-PAR n = 9	AR-saline n = 8	SH-PAR n = 9	SH-saline n = 8
LVSD (mm)	4.73 ± 0.35*+	5.86 ± 0.45*	3.84 ± 0.23	2.85 ± 0.22
LVDD (mm)	8.82 ± 0.33*	9.45 ± 0.54*	7.54 ± 0.17	6.71 ± 0.15
LAV (cm^3)	0.168 ± 0.019*	0.164 ± 0.018*	0.102 ± 0.009	0.065 ± 0.009
Relative wall thickness	0.34 ± 0.02*	0.35 ± 0.03*	0.37 ± 0.03	0.41 ± 0.03
LA/Ao	1.38 ± 0.08*	1.57 ± 0.05*	1.15 ± 0.04	1.26 ± 0.07
Sphericity index	0.806 ± 0.026*	0.856 ± 0.017*	0.670 ± 0.024	0.637 ± 0.031
Body weight (g)	431.9 ± 19.8	419.5 ± 7.4	448.2 ± 19.3*	414.0 ± 14.1

LVSD = left ventricle end-systolic diameter (mm, $p < 0.001$ for surgery and $p = 0.003$ for treatment); LVDD = left ventricle end-diastolic diameter (mm, $p < 0.01$); LAV = left atrium volume (cm^3, $p < 0,01$); LA/Ao = left atrium normalized area ($p < 0.01$). Data are presented as the means ± SEM. *Different from SH, +different from AR-saline.

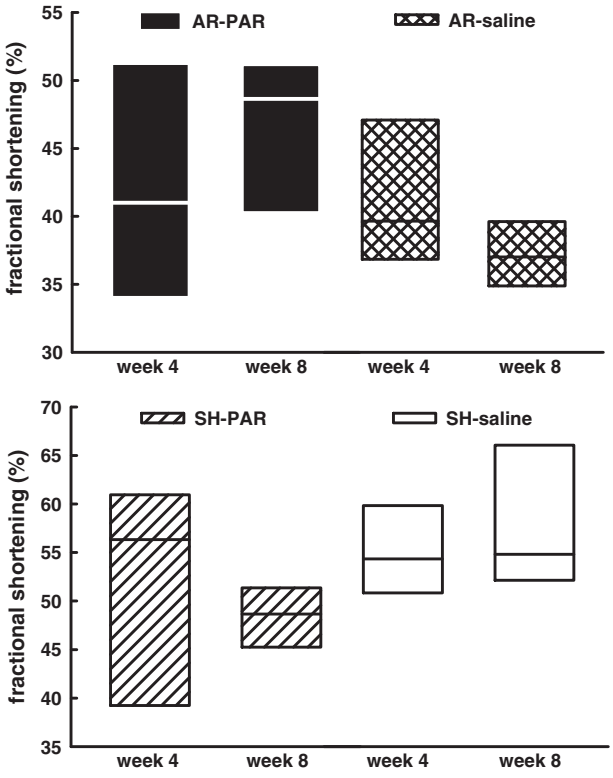

Fig. 2. Comparison of the effect of time on fractional shortening (%) in weeks 4 and 8 in aortic regurgitation (AR) or sham (SH) rats. Data are presented as the means ± SEM. A two-way repeated measures ANOVA was performed to compare AR or SH and time with fractional shortening (%) as the dependent variable: AR, $p = 0.041$ and SH, $p = 0.496$.

3.2. Fluid balance

Daily 0.3 M NaCl intake was reduced in the groups that received PAR, compared with the groups receiving saline injections, $p < 0.01$. In contrast, daily water intake was not altered by surgery or treatment, $p = 0.128$ (Fig. 3).

Paroxetine treatment mediated diureses in AR and SH animals in weeks 1–3, and AR-saline presented with diureses only in week 4 (Fig. 4). Sodium excretion was greater in AR-PAR, as compared to SH-PAR in week 1 ($p = 0.034$, Fig. 4). Natriureses were present in weeks 2–3 to AR-PAR and SH-PAR, as compared to saline groups (AR-saline and SH-saline) and returned to control levels at week 4 (Fig. 4). Kaliureses were present in week 2 for the AR-PAR compared to the AR-saline groups ($p = 0.037$), (Fig. 4).

3.3. Blood pressure

Systolic blood pressure was similar in AR groups (AR-PAR: 165 ± 4 vs AR-saline: 166 ± 3 mm Hg, $p = 0.212$); however, PAR treatment decreased BP in controls (SH-PAR: 138 ± 6 vs SH-saline: 156 ± 6 mm Hg, $p = 0.008$). Diastolic blood pressure was reduced in rats with AR compared to SH, regardless of treatment status (AR-PAR: 72 ± 5 vs SH-PAR: 85 ± 1 mm Hg, $p = 0.03$; AR-saline: 65 ± 4 vs SH-saline: 98 ± 3 mm Hg, $p = 0.01$, Fig. 5). Heart rate was not altered by condition or treatment, with AR-PAR = 346.3 ± 10.5, SH-PAR = 327.4 ± 10.5, AR-saline = 327.9 ± 12.8 and SH-saline = 343.4 ± 15.3 beats per minute.

3.4. Heart weight

At the cessation of experiments, the animals were sacrificed, and the hearts were removed, and the chambers were separated for comparisons. There were no significant group differences between the AR

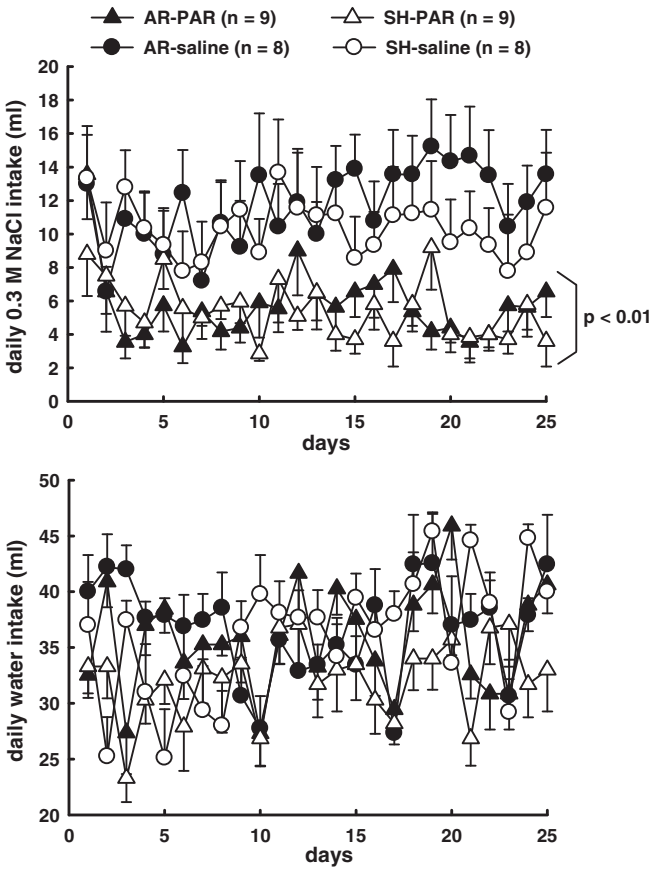

Fig. 3. Daily 0.3 M NaCl intake (above) and water intake (below) in treated/untreated aortic regurgitation (AR) or sham (SH) rats. Data are presented as the means ± SEM.

conditions for the atrium ($p = 0.239$), right ventricle ($p = 0.108$) or body weight ($p = 0.776$), (Table 3). However, there was a bw difference in the SH groups between treatments ($p = 0{,}037$). Furthermore, the LV weight was higher in the AR groups than the SH groups ($p < 0.001$), (Table 3).

4. Discussion

Our results indicate that chronic SSRI treatment with paroxetine prevented LV systolic dysfunction and reduced daily sodium intake in AR rats. In addition, an increase in natriureses was observed during weeks 2–3 of treatment, with the values returning to basal levels at week 4. Paroxetine reduced systolic pressure in the SH animals, with no effect on AR rats. Diastolic pressure was reduced in AR, compared to SH rats, and paroxetine did not alter this group difference. To the best of our knowledge, no other treatment has been proven effective in restoring shortening fraction by itself.

Depression is a frequent co-morbidity associated with heart diseases [3–5]. It is interesting to note that the association between mood disorders and cardiovascular disease is independent of other traditional risk factors for cardiovascular diseases, such as hypertension, overweight status, hypercholesterolemia, or history of heart disease [3,4]. The SSRIs are the most commonly prescribed antidepressants throughout the world due to dosage safety, good tolerability, and superior safety when used in patients with heart disease given a reduction in the probability of arrhythmias [6,8]. The accepted and hypothesized mechanism of action for SSRIs is based on the downregulation of somatodendritic 5-HT_{1A} receptors. Serotonin neurotransmission is involved in inhibition of sodium intake and excretion regulation. Intracerebroventricular administration of 5-HT2 agonists in rats increases sodium renal excretion [19]. Treatment with p-chlorophenylalanine, a

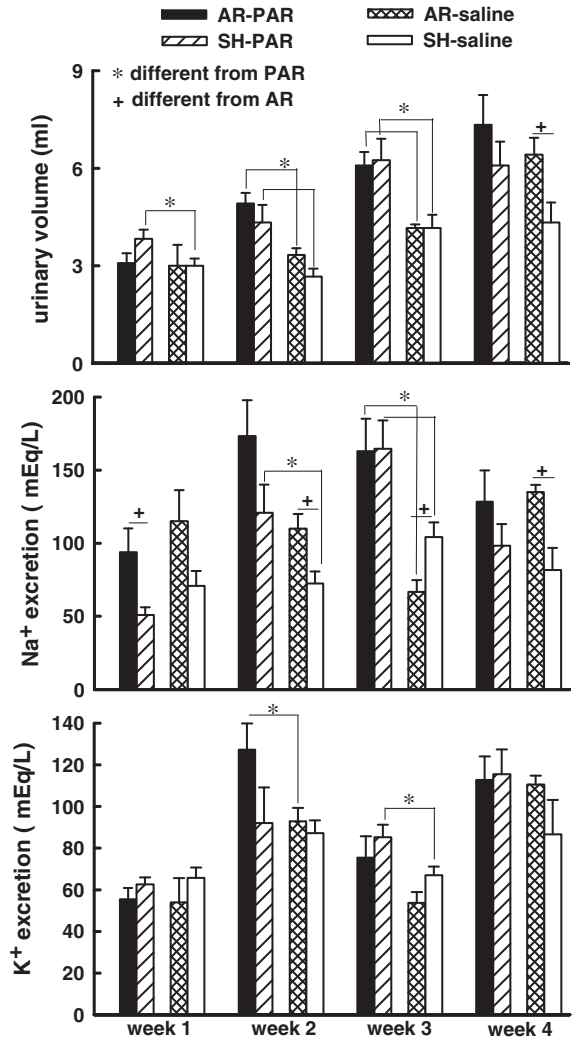

Fig. 4. Weekly diureses (ml) and Na^+ and K^+ (mEq) excretion in treated/untreated aortic regurgitation (AR) or sham (SH) rats. Data are presented as the means ± SEM. Diurerses week 1 $p = 0.043$, week 2 $p = 0.008$, week 3 $p = 0.012$; natriureses week 1: $p = 0.034$, week 2: $p = 0.03$, week 3: $p = 0.026$; kaliureses: week 2 $p = 0.037$.

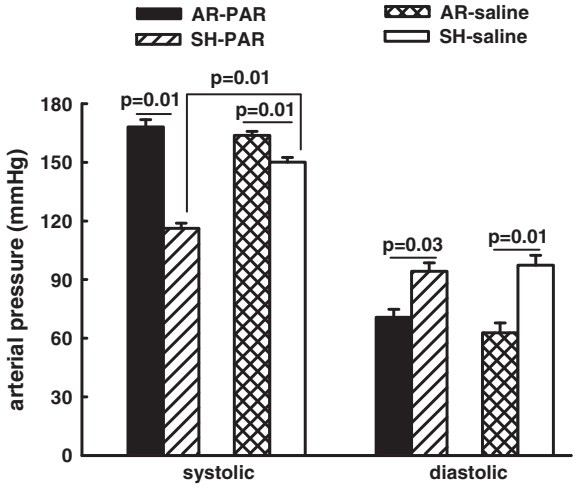

Fig. 5. Systolic (left) and diastolic (right) arterial pressure (mm Hg) in treated/untreated aortic regurgitation (AR) or sham (SH) rats. Data are presented as the means ± SEM.

Table 3
Heart weight comparisons between groups.

Variables − 8 weeks	AR-PAR n = 8	AR-saline n = 7	SH-PAR n = 8	SH-saline n = 8
Body weight (bw, g)	438.5 ± 16.0	420.4 ± 10.2	453.7 ± 12.0*	412.9 ± 13.1
A/100 g bw	0.027 ± 0.002	0.032 ± 0.002	0.025 ± 0.003	0.027 ± 0.002
RV/100 g bw	0.071 ± 0.005	0.069 ± 0.003	0.066 ± 0.004	0.059 ± 0.003
LV/100 g bw	0.276 ± 0.013*	0.320 ± 0.023*	0.210 ± 0.004	0.208 ± 0.006

A = atrium; RV = right ventricle and LV = left ventricle. Data are presented as the means ± SEM. *Different from SH.

competitive and irreversible inhibitor of tryptophan hydroxylase, induces natriorexigenic responses even for a paradoxical salt appetite model that is dependent on beta-adrenergic stimulation [13]. Chemical lesions of the raphe nuclei, which contain one of the largest populations of serotonergic neurons, increase sodium intake [15]. Thus, our results are in agreement with those previous studies. In the present results we had reductions of daily sodium intake and natriureses in weeks 2–3 in both AR and SH animals. It is reasonably postulated that PAR treatment increased the central 5-HT neurotransmission and this augmentation produced the changes in sodium and excretion behaviors.

Central 5-HT neurotransmission is also involved in the cardiovascular control. Interestingly, prosencephalic activation of the 5-HT3 agonist receptor exerts an inhibitory action on the pressor part of the baroreflex function [10]. Healthy individuals with family histories of coronary arterial disease receiving PAR treatment presented with lower blood pressure during psychosocial stress tests, suggesting a cardio-protective effect [20]. Using SSRI to control panic syndrome in humans seems to be beneficial to the heart by increasing heart rate variability [9]. In patients with post-myocardial infarction studies the SSRIs increase heart rate variability [21] and improve outcomes [22]. On the other hand, antidepressant drugs, including tricyclic, serotoninergic or noradrenergic drugs, may decrease heart rate variability [23,24]. Thereby there are still controversies concerning the SSRIs on heart function, such as heart disease etiology, dosing, administration route, and the type of molecule used. Meanwhile, our results demonstrated a preservative effect on systolic dysfunction following SSRI treatment, seen by the improvement in fractional shortening in AR–PAR compared to AR–saline at week 8. To the best of our knowledge no other treatment was able to preserve the systolic function as it was seen in the present results. Moreover, it is worth noting that the sphericity index did not change after paroxetine treatment, indicating that LV geometric shape was still affected by volume overload, whilst systolic function was preserved. We might even speculate whether decreases in the sodium intake would be beneficial to heart function. The causal relationships linking these observations might be complex, and our data do not allow us to make further conclusions underlying this protective effect.

In conclusion, the data demonstrate that the antidepressant paroxetine is beneficial to cardiovascular function with exposure to volume overload by preventing systolic dysfunction and reducing sodium daily intake. These observations may relate to increased central 5-HT neurotransmission. Future experiments would be needed to elucidate the central involvement of 5-HT with circulating hormones that improve cardiac function.

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