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

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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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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.

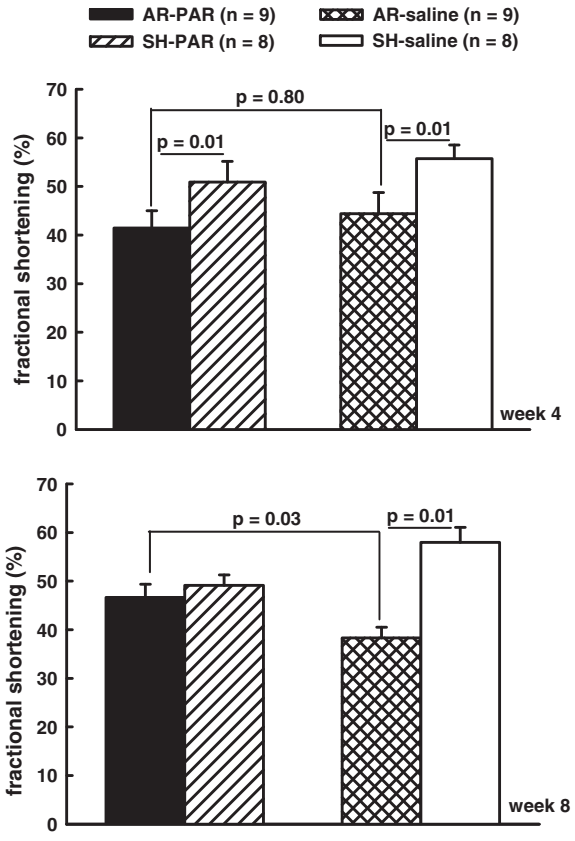

Fig. 1. Fractional shortening (%) at the weeks 4 (above, before treatment) and 8 (below, after treatment) in treated/untreated aortic regurgitation (AR) or sham (SH) rats. Data are presented as the means ± SEM. A two-way ANOVA was performed for comparisons between surgery and treatment.

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.