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Treatment with escitalopram modulates cardiovascular function in rats

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ABSTRACT

Considering depression is three times more common in cardiac patients compared to the normal population and selective serotonin reuptake inhibitors (SSRI) as drug of choice for treating patients with cardiovascular disease and depression, our work aims to evaluate the cardiovascular effects of treatment for 21 days with escitalopram (5 mg/kg/day, ip) in rats. The treatment caused an increase in mean arterial pressure concomitant with a decrease in heart rate. Concerning heart rate variability, there was a significant reduction in the sympathetic component and an elevation of the parasympathetic component, indicating that escitalopram caused an autonomic imbalance with parasympathetic predominance. In addition, we observed a decrease in both low and very low frequency power in blood pressure variability. The cardiac autonomic blockade indicated an increase in parasympathetic modulation to the heart with escitalopram chronic treatment. However, no change was observed on baroreflex activity. On the other hand, there was a decrease in pressure response during acute restraint stress with no changes in the tachycardia response. These findings showed that despite the escitalopram be a relatively safe drug it can cause tonic effects on cardiovascular function as well as during aversive situations.

1. Introduction

An increase in the number of patients with coronary artery disease (CAD) is associated with depression (Carney et al., 2005; Frasure-Smith et al., 1995; Penninx, 2017), with about 15–20% of patients suffering a heart attack one year after showing a depressive episode (Strike and Steptoe, 2004). Furthermore, the presence of post-heart attack depression symptoms have been associated with an increased risk of adverse cardiac events and death (Carney et al., 2016; Frasure-Smith et al., 1995).

Selective serotonin reuptake inhibitors (SSRI) are widely used in anxiety and mood disorder treatment, mainly due to the supposed security and better tolerability profile compared to tricyclic antidepressants (Chang and Liu, 2017; Lars and Gram, 1994). Moreover, SSRI have a more preferable cardiovascular profile compared to tricyclic antidepressants in depressive patients with CAD (Chang and Liu, 2017; Grimsley and Jann, 1992), because its minor effect on reuptake of noradrenaline (Mago et al., 2014; Nguyen et al., 2013). SSRI change the cell membrane potential of cardiac and vascular cells (Pacher et al., 1999a, 1999b; Pacher and Kecskemeti, 2004) and the serotonin syndrome caused by the combined administration of SSRI and other serotonergic drugs is characterized by autonomic instability and hypertension (Boyer and Shannon, 2005; Buckley et al., 2014). Moreover, chronic fluoxetine treatment causes a small degree of hypertension and changes in baroreflex cardiac activity in normotensive rats (Crestani et al., 2011), as well as a decrease in arterial pressure in hypertensive rats (Fuller et al., 1979). Also, fluoxetine can still act on noradrenaline reuptake receptors and inhibit 5-HT_{2C} receptors (Pälvimäki et al., 1999), which modulate the noradrenergic and dopaminergic systems in the brain (Millan et al., 1998). However, other SSRI such as escitalopram (ESC) do not have this pharmacological feature (Sánchez et al., 2003).

ESC (S-citalopram) is the active therapeutic isomer of citalopram (Gelenberg, 2001). In a few studies that have evaluated ESC's cardiovascular security, a small degree of bradycardia was shown in humans

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(Thase et al., 2013). However, there is still a lack of studies that evaluate its effects on the cardiovascular system.

Changes in baroreflex activity have been associated with cardiac diseases (Deck et al., 1992; Gronda et al., 2016), heart attacks (Osculati et al., 1990) and hypertension (Grassi et al., 2006). Chronic fluoxetine treatment causes an increase in bradycardia response to phenylephrine and a decrease in tachycardia response to sodium nitroprusside (Crestani et al., 2011) and reduce baroreflex sensitivity (Hong et al., 2017). However, other studies did not show changes in baroreflex activity (Moffitt and Johnson, 2004; Pérgola and Alper, 1992).

There is an association between stress and depression (Hammen and Kim, 2009; Kendler et al., 1999; Zhang et al., 2017), as well as cardiovascular diseases (Edmondson and Cohen, 2014; Murphy et al., 2017). During a stressful situation, cardiovascular changes occur characterized by an increase in blood pressure and heart rate (Tavares et al., 2009). Despite evidence of SSRI-induced effects in cardiovascular responses to stress (Crestani et al., 2011; Grippo et al., 2006; Tavares et al., 2009), little is known about ESC-induced effects in animals submitted to restraint stress.

In the present study, we evaluated the cardiovascular effects of systemic ESC treatment on unanesthetized rats.

2. Materials and methods

2.1. Animals

The experiments were performed according to the protocols approved by the Ethics Committee for Animal Experimentation of the State University of Londrina (No. 15127.2013.42). Male Wistar rats (250–270 g) were housed in plastic cages at a controlled temperature of approximately 25 °C and were kept in the Animal Care Unit of the Department of Physiological Sciences, State University of Londrina. They were maintained on a controlled 12-h cycle of light and dark (lights on between 06:00 a.m. and 06:00 p.m.) and had free access to water and food.

2.2. Drugs

Escitalopram oxalate (Pharma Nostra, Rio de Janeiro, Brazil), tribromoethanol (Br_3CCH_2OH; Sigma-Aldrich, St. Louis, MO, USA), atropine methyl bromide ($C_{18}H_{26}NO_3{\cdot}Br$; Sigma-Aldrich), atenolol ($C_{14}H_{22}N_2O_3$; Sigma-Aldrich), phenylephrine hydrochloride; Sigma-Aldrich, St. Louis, MO, USA), sodium nitroprusside dehydrate; Sigma-Aldrich, and urethane ($C_3H_7NO_2$, Sigma-Aldrich) were dissolved in saline (0.9%, NaCl). Meglumine flunixine (Banamine®, Schering Plough, Santo Amaro, Brazil) was used as provided.

2.3. Escitalopram treatment

Animals were randomly divided into two groups: (i) Administration of vehicle (saline, ip) daily for 21 days; (ii) Administration of ESC (5 mg/kg/day, ip (Sağlam et al., 2006) (Pharma Nostra, Rio de Janeiro, Brazil) daily for 21 consecutive days (Wang et al., 2014). All the injections were performed between 8 and 10 a.m. The experiment was carried out 30 min after the last drug administration.

2.4. Surgical preparation

24-h before experiments, rats were anesthetized with tribromoethanol (0.25 g/kg ip; Sigma-Aldrich) and a catheter (Clay Adams, Parsippany, NJ) was inserted into the femoral artery and vein for blood pressure recording and vasoactive drug infusion, respectively. Both catheters were exteriorized at the back of the animal. After surgery, the animals were treated with an anti-inflammatory drug (meglumine flunixine 2.5 mg/kg, sc; Banamine®, Schering Plough) for postoperative analgesia.

2.5. Measurements of cardiovascular parameters

On the day of the experiment, the animals were transferred to the experimental room where they remained for 60 min to adapt to environmental conditions before starting the experiment. A constant background noise was generated by an air exhauster to minimize sound interference within the experimental room. The cannula was connected to a blood pressure transducer (Deltran®, UTAH Medical Products Inc®, Atholne, Ireland) coupled to a signal amplifier (AECAD04F/ AVS Project, São Carlos, Brazil) and to an acquisition system (AQCAD/ AVS Project) connected to a computer. Mean arterial blood pressure (MAP), systolic blood pressure, diastolic blood pressure and heart rate (HR) values were derived from the pulsatile blood pressure.

2.6. Spectral analysis of heart rate variability (HRV) and blood pressure variability (BPV)

After a minimum period of 10 min for recording basal blood pressure and HR, the variability analysis of pulse interval and systolic blood in the frequency and time domain was performed using the computer program CardioSeries v2.4 (Daniel Penteado Martins Dias, Ribeirão Preto, Brazil). Since the computer program does not perform data acquisition, blood pressure recordings were processed with the computer program LabChart 7.0 (ADInstruments, Bella Vista, Australia), which made it possible to detect inflection points in the pressure pulses and generate a series of beat-to-beat values of pulse interval and systolic pressure for each cardiac cycle.

Temporal series of pulse interval and pressure values were resampled at 10 Hz (one value every 100 ms) using cubic spline interpolation to normalize the time interval between beats. The interpolated series with pulse interval and systolic pressure values were divided into segments of 512 values each, with an overlap of 50% (Welch Protocol). The stability of pulse interval and systolic pressure values of each segment was visually examined and the segments with artifacts or transients were excluded.

After visual inspection of the segments with interpolated values of pulse interval, adequate segments were integrated in low frequency bands (LF: 0.20–0.75 Hz) and high frequency bands (HF: 0.75–3.00 Hz). For systolic pressure, adequate segments were integrated into very low frequency (VLF: 0.02–0.2 Hz) and low frequency (LF: 0.2–0.6 Hz), and the results were expressed in absolute units (ms^2 or $mmHg^2$) and normalized units (nu). The normalized values were obtained by calculating the relative power of the LF and HF bands divided by total power minus the power spectrum of the very low frequencies (VLF: $<$ 0.20 Hz). To assess cardiac sympathovagal balance, we calculated the ratio between the power of the LF and HF bands (LF/HF) of the pulse interval spectrum.

2.7. Selective autonomic blockade of heart rate

In order to evaluate the sympathetic and parasympathetic tonus influence on cardiac response to ESC treatment, animals received intravenous administration of the muscarinic receptor antagonist atropine (1 mg/kg, iv (Dos Reis et al., 2014); Sigma-Aldrich) or the selective β1-adrenergic antagonist atenolol (1 mg/kg, iv (Resstel and Corrêa, 2008); Sigma-Aldrich) after the blood pressure and HR basal recording at the experiment day. The HR was monitored for 15 min.

2.8. Baroreflex assessments

Baroreflex was tested by intravenous infusion of the selective α1-adrenoceptor agonist phenylephrine (50 μg/ml/kg, 0.34 ml/min; Sigma-Aldrich) or the nitric oxide donor sodium nitroprusside (50 μg/ml/kg; 0.8 ml/min; Sigma-Aldrich) using an infusion pump (Razel Syringe Pump - a-99 model, St. Albans, VT, USA) (Head and McCarty, 1987; Pelosi et al., 2007; Resstel and Corrêa, 2006). Infusions of

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