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The medial amygdaloid nucleus modulates the baroreflex activity in conscious rats

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ABSTRACT

The medial amygdaloid nucleus (MeA) is involved in cardiovascular control. In the present study we report the effect of MeA pharmacological ablations caused by bilateral microinjections of the nonselective synaptic blocker $CoCl_2$ on cardiac baroreflex responses in rats. MeA synaptic inhibition evoked by local bilateral microinjection of 100 nL of $CoCl_2$ (1 mM) did not affect blood pressure or heart rate baseline, suggesting no tonic MeA influence on resting cardiovascular parameters. However, 10 min after $CoCl_2$ microinjection into the MeA of male Wistar rats, the reflex bradycardic response evoked by intravenous infusion of phenylephrine was significantly enhanced when compared with the reflex bradycardic response observed before $CoCl_2$. The treatment did not affect the tachycardic responses to the intravenous infusion of sodium nitroprusside (SNP). Baroreflex activity returned to control values 60 min after $CoCl_2$ microinjections, confirming a reversible blockade. The present results indicate an involvement of the MeA in baroreflex modulation, suggesting that synapses in the MeA have an inhibitory influence on the bradycardic component of the baroreflex in conscious rats.

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1. Introduction

The amygdaloid complex is a limbic structure associated with autonomic, neuroendocrine and behavioral responses (Fortaleza et al., 2011; Ma and Morilak, 2005; Price et al., 1987; Sah et al., 2003) that is located in the temporal lobe between the external capsule and the hypothalamus. Based on its cytoarchitecture and chemoarchitecture, it has been divided into subnuclei having extensive internuclear and intranuclear connections (Krettek and Price, 1978b; Price et al., 1987). The amygdaloid complex is divided into three groups: (1) the deep or basolateral group, which includes the lateral, basal and the accessory basal nucleus; (2) the superficial or cortical-like group, which includes the cortical nucleus and the nucleus of the lateral olfactory tract; and (3) the centromedial group, composed by the medial and central nuclei (Pitkanen et al., 1997; Sah et al., 2003).

Among the amygdaloid complex nuclei, the medial amygdaloid nucleus (MeA) is involved in cardiovascular control and modulates stress responses (Fortaleza et al., 2009, 2011, 2012b; Gelsema et al., 1987; Kubo et al., 2004; Morilak et al., 2005).

Electrical stimulation of the MeA has been reported to evoke mean arterial pressure (MAP) and heart rate (HR) increases in anesthetized rats (Faiers et al., 1975). In addition, we have previously shown that microinjection of noradrenaline into the MeA caused cardiovascular changes, and that stress-evoked heart rate increases are modulated by different types of adrenoceptors in the MeA (Fortaleza et al., 2011, 2012b), suggesting its involvement in central cardiovascular control.

Baroreceptor activity provides an essential feedback to the central nervous system (CNS) for moment-to-moment control of the cardiovascular function, in order to maintain arterial pressure within a narrow functional range (Michelini, 1994; Sved and Gordon, 1994). Moreover, it has been proposed that a resetting of baroreflex activity towards higher blood pressure values mediates, at least in part, autonomic and cardiovascular changes during physical exercise and stress situations (Crestani et al., 2010b; Dampney et al., 2008; DiCarlo and Bishop, 1992). Defensive reactions are associated with changes in cardiovascular activity. Cardiovascular changes include increases in MAP, HR, sympathetic nerve activity and skeletal muscle blood flow (Coote et al., 1979). These simultaneous enhancements in MAP, HR, and sympathetic vasomotor activity imply in a reset of the baroreceptor reflex (Coote et al., 1979; Hatton et al., 1997; Hilton and Zbrozyna, 1963; Nunomura et al., 1983; Porter, 2000; Schlor et al., 1984; Turnbull et al., 1993).

The MeA is connected with medullary structures that appear to be the primary site involved in baroreflex responses (Dampney, 1994; Krettek and Price, 1978a; Michelini, 1994; Schreihofer and Guyenet, 2002; Sved and Gordon, 1994). Moreover, it sends projections to several limbic structures that are involved in baroreflex modulation, such as the medial prefrontal cortex (Resstel and Correa, 2006; Sevoz-Couche et al., 2006), the bed nucleus of the stria terminalis (Crestani et al., 2006), the

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periaqueductal grey area (Pelosi et al., 2007), the hypothalamus (Crestani et al., 2010a; Sevoz-Couche et al., 2006), lateral septal area (Scopinho et al., 2007, 2012) and the diagonal band of Broca (Crestani et al., 2008b).

There is functional evidence showing a possible MeA involvement in the basal control of baroreflex activity, resulting from power spectral analysis that evaluates variability of the HR and MAP (Neckel et al., 2012; Quagliotto et al., 2008), or in BPH/2J mice, a neurogenic model of hypertension, in which the MeA was proposed to participate in cardiac baroreflex sensitivity control (Jackson et al., 2014), consequently it would be relevant to evaluate the role of MeA in the modulation on baroreflex activity response evoked by intravenous infusion of phenylephrine (Phe) or sodium nitroprusside (SNP) in conscious rats.

The hypothesis of the present study is that the MeA is involved in baroreflex modulation in conscious rats. To investigate this hypothesis, we analyzed the effect of the blockade of synaptic transmission in the MeA, caused by local microinjection of $CoCl_2$ that reduces pre-synaptic Ca^2+ influx leading to inhibition of neurotransmitter release, on the cardiac baroreflex response evoked by the intravenous infusion of either Phe or SNP.

2. Material and methods

2.1. Animal preparation

Twenty male Wistar rats weighing 230–270 g were used. Animals were kept in the Animal Care Unit of the Department of Pharmacology, School of Medicine of Ribeirão Preto, University of São Paulo. Rats were housed individually in plastic cages under standard laboratory conditions; a 12 h light–dark cycle, and free access to food and water. Housing conditions and experimental procedures were approved by the Institution's Animal Ethical Committee (Proc 128/2010).

Four days before experiments, rats were anesthetized with tribromoethanol (250 mg/kg i.p.). After scalp anesthesia with 2% lidocaine, the skull was exposed and stainless steel guide cannulas (26G) were stereotaxically implanted bilaterally into the MeA. Coordinates for cannula implantation into the MeA were: AP = +6.2 mm; L = +3.4 mm from the medial suture and V = −8.8 mm, based on the rat brain atlas of Paxinos and Watson (1997). One day before the experiment, rats were anesthetized with tribromoethanol and a catheter was inserted into the abdominal aorta through the femoral artery for MAP and HR recording. A second catheter was implanted into the femoral vein for infusion of either phenylephrine or SNP. Catheters were tunneled under the skin and exteriorized on the animal's dorsum.

2.2. Measurement of cardiovascular responses

Experiments were carried out between 08:00–12:00 h. On the day of the experiment, animals were allowed a 15 min period to adapt to experimental room's conditions, such as sound and illumination, before starting blood pressure and HR recording. Another 15 min period was allowed before beginning the experiments. The room was acoustically isolated and had constant background noise provided by an air exhauster. Care was taken to start injections when stable blood pressure and specially heart rate recordings were observed. The injection needle was slowly introduced into the guide cannula without touching or restraining the animals. Pulsatile arterial pressure of freely moving animals was recorded using an HP-7754A preamplifier (Hewlett Packard, Palo Alto, Califórnia, USA) and an acquisition board (MP100A, Biopac Systems Inc, Santa Barbara, Califórnia, USA) connected to a computer. MAP and HR values were derived from the blood pressure recordings and processed online.

2.3. Drug injection

Drugs were dissolved in artificial cerebrospinal fluid (aCSF) with the following composition: NaCl 100 mM; Na_3PO_4 2 mM; KCl 2,5 mM; $MgCl_2$ 1,0 mM; $NaHCO_3$ 27 mM; $CaCl_2$ 2,5 mM (pH = 7.4). Needles (33G, Small Parts, Miami Lakes, Flórida, USA) that were used for microinjection into the MeA were 1 mm longer than guide cannulas and were connected to a 1 μL syringe (7002H, Hamilton, USA) through PE-10 tubing. $CoCl_2$ or vehicle was injected in a final volume of 100 nL in each side of the MeA. After a 20 s period, the needle was removed and inserted into the second guide cannula for microinjections into the contralateral side.

2.4. Baroreflex stimulation

Baroreflex was activated by intravenous infusion of phenylephrine (Phe, 50 μg/kg; 0.34 mL/min) or SNP (50 μg/kg; 0.8 mL/min), using an infusion pump (K.D. Scientific, Holliston, Massachusetts, USA).

2.5. Method of baroreflex evaluation

HR values matching MAP variations were determined. Paired values of MAP and HR variations, evoked by Phe or SNP, were plotted to generate sigmoid curves (Head & McCarty, 1987) for each rat, which were used to determine baroreflex activity. Commercial software (Prism, Prism, GraphPad, San Diego, California, USA) was used to generate curves.

To study bradycardic and tachycardic responses separately, HR values matching 10, 20, 30 and 40 mm Hg MAP changes were calculated. Values were plotted to create linear regression curves for each rat (Crestani et al., 2006; Resstel et al., 2004) and their slopes were compared to verify changes in baroreflex gain. The delay in reflex bradycardia and tachycardia was about 1.2 s because of the time of baroreflex synapse processing that is 700 ms according to Su et al. (1992) and the integration factor of the recording system that was about 500 ms.

2.6. Drugs

The following drugs were used: phenylephrine-HCl; CoCl2 (Sigma, St. Louis, Missouri, USA); sodium nitroprusside; urethane (Sigma, St Louis, Missouri, USA) and tribromoethanol (Aldrich, St Louis, Missouri, USA).

2.7. Experimental protocols

All animals used in this study received three infusions of either phenylephrine or SNP to determine control baroreflex response. One group received bilateral microinjections of aCSF into the MeA and infusions of phenylephrine or sodium nitroprusside were repeated 10 min after this procedure. A second group received bilateral microinjections of $CoCl_2$ (1 mM; Crestani et al., 2006) into the MeA, and phenylephrine or nitroprusside infusions were repeated 10 and 60 min after injection. A third group received bilateral microinjections of $CoCl_2$ (1 mM) into structures surrounding the MeA, and phenylephrine or nitroprusside infusions were repeated 10 min after injection. The order of infusions was randomized. $CoCl_2$ interferes with synaptic Ca^{2+} and consequently causes nonspecific synaptic blockade. Its effectiveness is accepted as indicative of synaptic involvement (Kretz, 1984).

2.8. Histological procedure

At the end of the experiments, rats were anesthetized with urethane (1.25 g/kg, i.p.) and 100 nL of 1% Evan's blue dye was bilaterally injected into the MeA to label injection sites. The chest was surgically opened, the descending aorta occluded, the right atrium severed and the brain perfused with 10% formalin through the left heart ventricle. Brains

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