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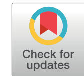
Control of cardiovascular responses to stress by CRF in the bed nucleus of stria terminalis is mediated by local NMDA/nNOS/sGC/PKG signaling



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ABSTRACT

The aims of the present study were to assess an interaction of corticotropin-releasing factor (CRF) neurotransmission within the bed nucleus of the stria terminalis (BNST) with local nitrergic signaling, as well as to investigate an involvement of activation of local NMDA glutamate receptor and nitric oxide (NO) signaling in control of cardiovascular responses to acute restraint stress by BNST CRF neurotransmission in rats. We observed that CRF microinjection into the BNST increased local NO release during restraint stress. Furthermore, bilateral microinjection of CRF into the BNST enhanced both the arterial pressure and heart rate increases evoked by restraint stress, but without affecting the sympathetically-mediated cutaneous vasoconstriction. The facilitation of both pressor and tachycardiac responses to restraint stress evoked by BNST treatment with CRF were completely inhibited by local pretreatment with either the selective NMDA glutamate receptor antagonist LY235959, the selective neuronal nitric oxide synthase (nNOS) inhibitor *N*ω-Propyl-L-arginine (NPLA), the soluble guanylate cyclase (sGC) inhibitor 1H-[1,2,4]Oxadiazolo[4,3-*a*]quinoxalin-1-one (ODQ) or the protein kinase G (PKG) inhibitor KT5823. Taken together, these results provide evidence that BNST CRF neurotransmission facilitates local NMDA-mediated glutamatergic neurotransmission and activates nitrergic signaling, and this pathway is involved in control of cardiovascular responses to stress.

1. Introduction

A coordinated and complex set of physiological changes, including cardiovascular and endocrine changes, occurs during aversive stimuli for maintenance of homeostasis (Crestani, 2016; Sterling, 2012; Ulrich-Lai and Herman, 2009). These responses are triggered by overlapping limbic circuits in the central nervous system (Dampney, 2015; Myers, 2017; Ulrich-Lai and Herman, 2009). The bed nucleus of the stria terminalis (BNST) is a limbic structure located in the prosencephalon in which has been recognized as a critical component of neural substrates of responses to aversive stimuli (Crestani et al., 2013; Myers, 2017; Ulrich-Lai and Herman, 2009). Indeed, the BNST is implicated in cardiovascular, neuroendocrine and behavioral responses to stress (Crestani et al., 2013; Davis et al., 2010). However, the local neurochemical mechanisms mediating the BNST control of stress responses are not completely understood.

The corticotropin-releasing factor (CRF) system has emerged as a crucial local neurochemical mechanism involved in BNST-mediated control of both behavioral and physiological responses evoked by aversive threats (Crestani et al., 2013; Daniel and Rainnie, 2016; Davis et al., 2010). Specifically regarding the cardiovascular responses, Nijsen et al. (2001) first reported that BNST treatment with a nonselective CRF receptor antagonist enhanced the heart rate (HR) increase evoked by contextual fear conditioning, thus indicating an inhibitory influence of BNST CRF neurotransmission on cardiac responses to conditioned stressors. Further, results from our group evidenced that microinjection of selective antagonists of either CRF_1 or CRF_2 receptor into the BNST dose-dependently decreased the arterial pressure, HR and the sympathetically-mediated cutaneous vasoconstriction evoked by restraint stress (Oliveira et al., 2015). These results provided evidence of a prominent role of CRF neurotransmission in BNST control of cardiovascular responses to aversive stimuli.

Interaction between CRF and glutamatergic neurotransmissions within the BNST has been described (Silberman and Winder, 2013). This interaction was evidenced by demonstration that CRF application onto BNST *in vitro* increased frequency, but not amplitude, of spontaneous excitatory postsynaptic currents (sEPSC) (Kash et al., 2008; Silberman et al., 2013). Pretreatment with a selective CRF_1 receptor antagonist, but not with a selective CRF_2 receptor antagonist, inhibited the ability of CRF to increase frequency of sEPSC (Kash et al., 2008).

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Taken together, these results indicated that CRF acts presynaptically via CRF_1 receptor to increase glutamatergic neurotransmission within the BNST (Silberman and Winder, 2013).

Activation of *N*-methyl-D-aspartate (NMDA) glutamate receptor in post-synaptic neurons increases Ca^{2+} influx, which in turn activates the neuronal isoform of the enzyme nitric oxide synthase (nNOS), thus resulting in nitric oxide (NO) synthesis (Garthwaite, 2008; Prast and Philippu, 2001). Despite reports of presence of neurons capable of synthesizing NO within the BNST (Guimaraes et al., 2005; Vincent and Kimura, 1992), as well as identification of CRF action facilitating glutamatergic neurotransmission in this structure (Silberman and Winder, 2013), an interaction between CRF and nitrergic neurotransmission has never been reported. Furthermore, a possible role of CRF-glutamate interaction in mediating BNST control of responses during aversive threats has never been evaluated.

Neurons synthesizing NO within the BNST are activated by aversive stimuli (Guimaraes et al., 2005), and systemic treatment with nNOS inhibitors decreases stress-evoked activation of BNST neurons (Silva et al., 2012), thus indicating a recruitment of BNST nitrergic neurotransmission during aversive threats. Furthermore, a recent study from our group reported that BNST treatment with the selective NMDA glutamate receptor LY235959 decreased the HR increase to restraint stress (Adami et al., 2017), an effect similar to that observed following BNST treatment with a CRF_1 receptor antagonist (Oliveira et al., 2015). Based on these pieces of evidence, this study aimed to evaluate the hypothesis that the facilitatory influence of BNST CRF neurotransmission in cardiovascular responses evoked by an acute session of restraint stress in rats is mediated by activation of local NMDA glutamate receptor and nNOS, as well as of signaling mechanisms related to NO effects such as soluble guanylate cyclase (sGC) and protein kinase G (PKG) (Garthwaite, 2008; Hofmann et al., 2006).

2. Materials and methods

2.1. Animals

Ninety-seven male Wistar rats weighting about 250 g (60-days-old) were used. Thirteen of these animals were excluded of the study because the microinjection sites reached structures surrounding the BNST. All animals were supplied by the breeding facility of the UNESP (Botucatu, SP, Brazil), and were housed in collective plastic cages (4 animals/cage) in a temperature-controlled room at 24 °C in the Animal Facility of the Laboratory of Pharmacology/School of Pharmaceutical Sciences-UNESP. They were kept under a 12:12 h light-dark cycle (lights on between 7:00 a.m. and 7:00 p.m.) with free access to water and standard rat chow. Housing conditions and experimental procedures were approved by local Ethical Committee for Use of Animals (School of Pharmaceutical Science/UNESP) (approval # 34/2015), which complies with Brazilian and international guidelines for animal use and welfare.

2.2. Surgical preparation

At least one week after the arrival of the animals in the laboratory, and five days before the experiment, the animals were anesthetized with tribromoethanol (250 mg/kg, i.p.), scalp was anesthetized with 2% lidocaine, and the skull was exposed. Then, using a stereotaxic apparatus (Stoelting, Wood Dale, Illinois, USA), stainless-steel cannulas (26G, 12 mm-long) were bilaterally implanted into the BNST. Stereotaxic coordinates were: antero-posterior = +7.8 mm from interaural; lateral = +4.0 mm from the medial suture, ventral = −5.8 mm from the skull, with a lateral inclination of 23° (Paxinos and Watson, 1997). Dental cement was used to fix cannulas to the skull. After surgery, the rats were treated with a poly-antibiotic containing streptomycins and penicillins to prevent infection (560 mg/ml/kg, i.m.), and the non-steroidal anti-inflammatory flunixin meglumine for post-operation analgesia (0.5 mg/ml/kg, s.c.).

One day before the trial, rats were again anesthetized with tribromoethanol (250 mg/kg, i.p.) and a polyethylene cannula (a 4 cm segment of PE-10 bound to a 13 cm segment of PE-50) (Clay Adams, Parsippany, NJ, USA) was implanted into the abdominal aorta via the femoral artery for cardiovascular recording. The catheter was tunneled under the skin and exteriorized on the animal's dorsum. After surgery, the non-steroidal anti-inflammatory flunixin meglumine was administered for post-operation analgesia (0.5 mg/ml/kg, s.c.). The animals were kept in individual cages during the post-operative period and cardiovascular recording.

2.3. Blood pressure and heart rate recording

The cannula inserted into the femoral artery was connected to a pressure transducer (DPT100, Utah Medical Products Inc., Midvale, UT, USA). Pulsatile arterial pressure (PAP) was recorded using an amplifier (Bridge Amp, ML224, ADInstruments, Australia) and an acquisition board (PowerLab 4/30, ML866/P, ADInstruments, NSW, Australia) connected to a personal computer. Mean arterial pressure (MAP) and HR values were obtained from the PAP recording.

2.4. Tail skin temperature measurement

The recording of the tail skin temperature was made using an infrared digital thermographic camera (IRI4010, InfraRed Integrates Systems Ltd, Northampton, UK). The analysis was performed using a software for thermographic analysis, and temperature was represented by color intensity variations (Busnardo et al., 2013; Vianna and Carrive, 2005). For image analysis, the temperature was measured at five points along the animal‘s tail, and the mean was calculated for each recording (Busnardo et al., 2013; Oliveira et al., 2015).

2.5. Drug microinjection into the BNST

The needles (33G, Small Parts, Miami Lakes, FL, USA) used for microinjection into the BNST were 1 mm longer than the guide cannulas and were connected to a 2 μL syringe (7002-KH, Hamilton Co., Reno, NV, USA) via a PE-10 tubing (Clay Adams, Parsippany, NJ, USA). Intra-cerebral microinjections were performed within a 5 s period, and the needle was left in the guide cannula for 1 min after the microinjection before being removed. Microinjection was performed without restraining the animals, and drugs were administrated in a final volume of 100 nL per side (Crestani et al., 2009; Oliveira et al., 2015). Photomicrograph of a coronal brain section depicting bilateral microinjection sites in the BNST of a representative animal is presented in Fig. S1.

2.6. Restraint stress

The acute restraint stress consisted of introducing the animals into plastic cylindrical tubes (diameter = 6.5 cm, length = 15 cm), which were ventilated by ½ inch holes that comprised approximately 20% of the tube. The animals were maintained for a period of 30 min into the restraint tube (Crestani et al., 2010; Oliveira et al., 2015). Each animal was submitted to only one session of stress in order to avoid habituation.

2.7. Drugs and solutions

Corticotropin-releasing factor (CRF) (TOCRIS, Westwoods Business, Park Ellisville, MO, USA; cat. # 1151), LY235959 (selective NMDA glutamate receptor antagonist) (TOCRIS; cat. # 1019), N^{ω}-Propyl-L-arginine hydrochloride (NPLA) (selective nNOS inhibitor) (TOCRIS; cat. # 1200), tribromoethanol (Sigma-Aldrich, St Louis, Missouri, USA; cat. # T48402) and urethane (Sigma-Aldrich; cat. # U2500) were dissolved in saline (NaCl 0.9%). 1H-[1,2,4]Oxadiazolo[4,3-*a*]quinoxalin-1-one

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