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Research Report

Bed nucleus of the stria terminalis α_1-adrenoceptor modulates baroreflex cardiac component in unanesthetized rats

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ABSTRACT

The bed nucleus of stria terminalis (BST) has a tonic modulating role on the baroreflex parasympathetic component. In the present study, we verified that local BST-adrenoceptors modulate baroreflex-evoked bradycardiac responses in unanesthetized rats. Bilateral microinjection of the selective α_1-adrenoceptor antagonist WB4101 (15 nmol/100 nL) into the BST increased the gain of reflex bradycardia in response to mean arterial pressure increases caused by intravenous (i.v.) infusion of phenylephrine, suggesting that BST α_1-adrenoceptors modulate baroreflex bradycardiac response. Bilateral microinjection of either the selective α_2-adrenoceptor antagonist RX821002 (15 nmol/100 nL) or the non-selective β-adrenoceptor antagonist propranolol (15 nmol/100 nL) into the BST had not affected baroreflex bradycardia. Animals were pretreated intravenously with the cholinergic muscarinic receptor antagonist homatropine methyl bromide (HMB, 1.5 mg/Kg) to test the hypothesis that activation of α_1-adrenoceptors in the BST would modulate the baroreflex parasympathetic component. Baroreflex bradycardiac responses evoked before and after BST treatment with WB4101 were no longer different when rats were pretreated with HMB. These results suggest that parasympathetic activation accounts for the effects saw after BST pharmacological manipulation and ruling out the possibility of a sympathetic withdraw. In conclusion, our data point out that local α_1-adrenoceptors mediate the BST tonic influence on the baroreflex bradycardiac response modulating parasympathetic cardiac activity.

1. Introduction

The bed nucleus of the stria terminalis (BST) is a limbic structure which is associated with autonomic, neuroendocrine and behavioral functions (Dunn, 1987; Casada and Dafny, 1991; Dunn and Williams, 1995). The BST has been reported to be involved in the central nervous system cardiovascular modulation. Electrical or chemical BST stimulation, using L-glutamate or D,L-homocysteic acid, evoked cardiovascular responses which were characterized by either blood pressure decrease (Gelsema et al., 1993; Giancola et al., 1993; Hatam and Nasimi, 2007) or increase (Gelsema and Calaresu, 1987; Dunn and Williams, 1995) in anesthetized animals. Also, activation of muscarinic receptors in the BST

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Abbreviations: ACF, artificial cerebrospinal fluid; BST, bed nucleus of the stria terminalis; HR, heart rate; HMB, homatropine methyl bromide; IA, interaural coordinate; MAP, mean arterial pressure; NTS, nucleus tractus solitarii; PAP, pulsatile arterial pressure

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evoked hypertensive and bradycardiac responses in unanesthetized rats (Alves et al., 2007).

The BST also modulates baroreflex activity (McKitrick et al., 1992; Li and Dampney, 1994; Potts et al., 1997). Previous results from our laboratory showed that bilateral microinjection of the unspecific neurotransmitter blocker $CoCl_2$ into the BST evoked reversible increase in the magnitude of the baroreflex bradycardiac response, without affecting reflex tachycardia (Crestani et al., 2006). These results suggest that synapses in the BST have a modulator role on the baroreflex bradycardiac component in rats. However, the specific neurotransmitter involved in the BST-related baroreflex modulation is yet unknown.

There is evidence of a functional noradrenergic neurotransmission in the BST. Noradrenergic terminals were identified in the BST (Phelix et al., 1992) and electrical stimulation of the BST has been reported to increase noradrenaline release in the BST (Palij and Stamford, 1992). Moreover, previous studies pointed out the presence of adrenoceptors and noradrenaline carrier in that nucleus (Sawada and Yamamoto, 1981; Matsui and Yamamoto, 1984; Egli et al., 2005; Crestani et al., 2008).

The BST-noradrenergic neurotransmission has been suggested to modulate the cardiovascular system. Noradrenaline microinjection into the BST has been reported to cause pressure responses, which are followed by reflex heart rate (HR) decrease (Crestani et al., 2007). Also, microinjection of tyramine, an indirectly acting sympathomimetic amine devoid of agonist activity, into the BST could evoke cardiovascular responses which were similar to those observed after noradrenaline injection (Crestani et al., 2007). Although the above results suggest the BST-noradrenergic neurotransmission to be involved with cardiovascular modulation, the role of this system in baroreflex modulation has never been evaluated.

Thus, the aim of the present study was to verify a possible role of the BST-noradrenergic neurotransmission modulating the bradycardiac component of the baroreflex in unanesthetized rats.

2. Results

2.1. *Effects of bilateral microinjection of artificial cerebrospinal fluid (ACF), WB4101, RX821002 or propranolol into the BST on the baroreflex bradycardiac response to i.v. infusion of phenylephrine in unanesthetized rats*

ACF—Bilateral microinjection of ACF ($n=5$) caused no changes in baseline mean arterial pressure (MAP) (98±6 vs 99±7 mmHg; $t=0.4$; $P>0.05$) or HR (340±11 vs 348±10 bpm; $t=0.6$; $P>0.05$). Microinjections of ACF also did not affect baroreflex cardiac response (−1.5±0.3 vs−1.6±0.3 bpm/mmHg, $t=0.3$, $P>0.05$).

WB4101—Bilateral microinjection into the BST of the selective α_1-adrenoceptor antagonist WB4101 ($n=5$) did not affect baseline MAP (100±4 vs 98±5 mmHg; $t=0.3$; $P>0.05$) or HR (345±10 vs 356±16 bpm; $t=0.5$; $P>0.05$). The slope of the regression line for decreases in HR as a function of MAP increases measured 10 min after WB4101 microinjection into the BST was increased when compared with the slope before WB4101 (−1.1±0.2 vs−2.1±0.3 bpm/mmHg; $F=5$, $P<0.05$) (Fig. 1). The effect of WB4101 was reversible and the HR response returned to pre-injection levels after 60 min (−1.3±0.2 bpm/mmHg; $P>0.05$) (Fig. 1). A representative recording showing the enhancing effect of WB4101 microinjection into the BST on reflex bradycardia is presented in Fig. 2.

When WB4101 was injected into structures surrounding the BST such as the anterior commissure, fornix and the internal capsule no changes were observed in the reflex bradycardiac response (−1.3±0.3 vs−1.2±0.4 bpm/mmHg; $F=0.1$; $P>0.05$).

RX821002—Bilateral microinjection into the BST of the selective α_2-adrenoceptor antagonist RX821002 ($n=5$) did not affect baseline MAP (99±4 vs 98±3 mmHg; $t=0.2$; $P>0.05$) or HR (345±10 vs 350±12 bpm; $t=0.3$; $P>0.05$). Microinjection of RX821002 into the BST did not alter the regression line for changes in HR as a function of changes in MAP (−1.3±0.3 vs −1.4±0.2 bpm/mmHg, $F=0.01$; $P>0.05$) (Fig. 1).

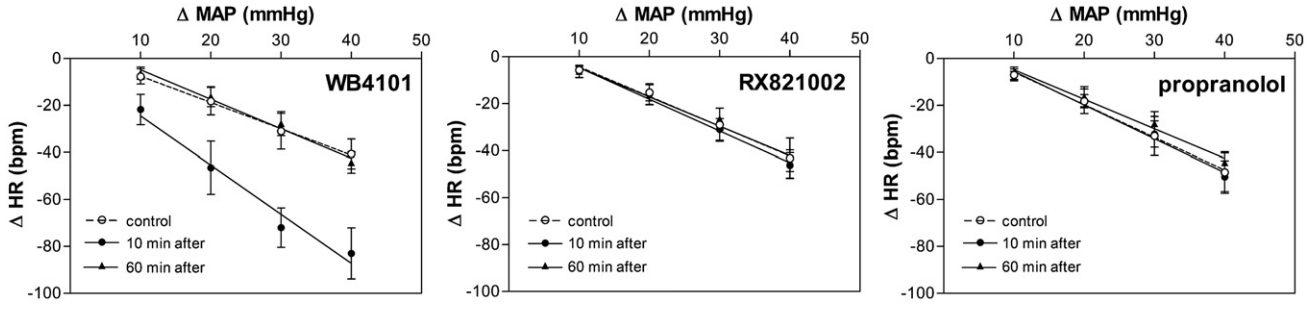

Fig. 1 – Linear regression curves showing the reflex bradycardia in response to increases in mean arterial pressure (MAP) caused by i.v. infusion of phenylephrine, measured before (control, open square dashed line) and 10 (filled circles–straight line) or 60 min (filled triangles–straight line) after bilateral microinjection of 100 nL of the selective α_1-adrenoceptor antagonist WB4101 (left panel, 15 nmol, $n=5$); the selective α_2-adrenoceptor antagonist RX821002 (middle panel, 15 nmol, $n=5$) or the non-selective β-adrenoceptor antagonist propranolol (right panel, 15 nmol, $n=5$) into the BST of unanesthetized rats. The r^2 values for the regression curves of the baroreflex bradycardiac responses were 0.7 before and 0.7 or 0.8 10 or 60 min after WB4101, respectively; 0.7 before and 0.8 or 0.8 10 or 60 min after RX821002, respectively, and 0.7 before and 0.7 or 0.8 10 or 60 min after propranolol, respectively.