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Research Report

Insular cortex α_1-adrenoceptors modulate the parasympathetic component of the baroreflex in unanesthetized rats

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ABSTRACT

The insular cortex (IC) has been reported to modulate the cardiac parasympathetic activity of the baroreflex in unanesthetized rats. However, which neurotransmitters are involved in this modulation is still unclear. In the present study, we evaluated the possible involvement of local IC-noradrenergic neurotransmission in modulating reflex bradycardiac responses. Bilateral microinjection of the selective α_1-adrenoceptor antagonist WB4101 (15 nmol/100 nL), into the IC of male Wistar rats, increased the gain of reflex bradycardia in response to mean arterial pressure (MAP) increases evoked by intravenous infusion of phenylephrine. However, bilateral microinjection of equimolar doses of either the selective α_2-adrenoceptor antagonist RX821002 or the non-selective β-adrenoceptor antagonist propranolol into the IC did not affect the baroreflex response. No effects were observed in basal MAP or heart rate values after bilateral microinjection of noradrenergic antagonists into the IC, thus suggesting no tonic influence of IC-noradrenergic neurotransmission on resting cardiovascular parameters. In conclusion, these data provide evidence that local IC-noradrenergic neurotransmission has an inhibitory influence on baroreflex responses to blood pressure increase evoked by phenylephrine infusion through activation of α_1-adrenoceptors.

1. Introduction

The prefrontal cortex is a limbic region, which has been implicated in autonomic nervous system modulation (Anand and Dua, 1956; Delgado, 1960; Neafsey, 1990; Resstel and Correa, 2006). In rats, the prefrontal cortex has been anatomically divided into two main regions: the lateral prefrontal cortex or insular cortex (IC) and the medial prefrontal cortex (MPFC), (Krettek and Price, 1977; Leonard, 1969).

The IC integrates sensory and visceral information from peripheral receptors (Saper, 1982). This cortical region has connections with brain areas that are involved in autonomic control, such as the nucleus of the solitary tract (NTS), the hypothalamus, and medullary areas that contain preganglionic parasympathetic neurons (Cechetto and Saper, 1987; Ruggiero et al., 1987; Yasui et al., 1991). Its stimulation has been reported to cause either pressor or depressor responses, a discrepancy that could be related to differences among the IC regions stimulated; experimental conditions, such as the use of anesthetized animals or the type of IC stimulation, either chemical or electrical (Allen and Cechetto, 1995; Hardy and Holmes, 1988; Hardy and Mack, 1990; Ruggiero et al., 1987; Yasui et al., 1991). Also, previous studies indicated involvement of the IC in baroreflex modulation. It has been reported

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that IC unilateral electrolytic lesion or its bilateral inhibition by local microinjection of lidocaine affected bradycardiac reflex responses, but not tachycardiac reflex responses in anesthetized animals (Saleh and Connell, 1998; Zhang et al., 1998). Moreover, previous results from our laboratory pointed out that either a non-selective synaptic inhibition or a selective NMDA glutamatergic receptor antagonism of the IC may evoke a reversible decrease of bradycardiac reflex responses without affecting reflex tachycardia, thus suggesting an IC facilitatory influence on the parasympathetic component of the baroreflex, which is mediated by NMDA glutamatergic receptors (Alves et al., 2009b).

Central noradrenergic neurotransmission is also involved in baroreflex modulation in areas such as the paraventricular nucleus (PVN; Hwang et al., 1998) and bed nucleus of stria terminalis (BST; Crestani et al., 2008b). The IC has a dense network of noradrenergic neural terminations (Morrison et al., 1979; Ungerstedt, 1971). Moreover, it has also been reported that microinjection of a β-adrenoceptor agonist into the IC increased basal heart rate (HR), whereas administration of a β-adrenoceptor antagonist reduced the increase in HR evoked by tail pinching (Funk and Stewart, 1996). Although brain noradrenergic pathways seem to be important for baroreflex modulation and there is evidence suggesting the existence of functional noradrenergic neurotransmission in the IC, its role in baroreflex modulation has not yet been evaluated.

The aim of the present study was to test the hypothesis that IC-noradrenergic neurotransmission modulates bradycardiac baroreflex responses in unanesthetized rats. For this, the baroreflex response was evaluated before and after microinjection of selective adrenoceptor antagonists into the IC.

2. Results

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

2.1.1. ACSF

Bilateral microinjection of ACSF ($n=5$) into the IC did not affect baseline MAP (100±2 vs 99±3 mmHg; $t=0.4$; $P>0.05$) or HR (351±6 vs 367±9 bpm; $t=1.2$; $P>0.05$), nor did it affect the baroreflex response (−1.4±0.3 vs −1.3±0.2 bpm/mmHg, $t=0.2$, $P>0.05$).

2.1.2. WB4101

Bilateral microinjection of the selective α_1-adrenoceptor antagonist WB4101 ($n=5$) into the IC did not affect baseline MAP (100±2 vs 103±4 mmHg; $t=0.6$; $P>0.05$) or HR (374±8 vs 358±10 bpm; $t=1.1$; $P>0.05$). The slope of the linear regression of HR decreased as a function of MAP increase, recorded 10 min after WB4101 microinjection into the IC, increased as compared with the slope of linear regression from data obtained before WB4101 microinjection (−1.3±0.2 vs −1.9±0.2 bpm/mmHg; $F=5$, $P<0.05$) (Figs. 1 and 2). The effect of WB4101 was reversible and the bradycardiac reflex returned to the preinjection level 60 min after WB4101 microinjection (−1.2±0.1 bpm/mmHg; $P>0.05$) (Fig. 2). The maximal bradycardiac response evoked by an increase in MAP, recorded 10 min after WB4101 microinjection into the IC, also returned to control levels when measured 60 min after treatment with WB4101 (Table 1).

No changes were observed in the bradycardia reflex (−1.4±0.3 vs −1.6±0.4 bpm/mmHg; $t=0.4$; $P>0.05$) when WB4101 was injected into the structures surrounding the IC ($n=5$), such as the primary motor cortex or the forceps minor of the corpus callosum.

2.1.3. RX821002

Bilateral microinjection of the selective α_2-adrenoceptor antagonist RX821002 ($n=5$) into the IC did not affect baseline MAP (97±3 vs 99±3 mmHg; $t=0.3$; $P>0.05$) or HR (347±6 vs 359±7 bpm; $t=1.2$; $P>0.05$). Microinjection of RX821002 into the IC caused no changes in the linear regression of changes in HR as a function of changes in MAP (−1.3±0.2 vs −1.2±0.1 bpm/mmHg, $F=0.02$; $P>0.05$) (Fig. 2). IC treatment with RX821002 also did not affect maximal bradycardia evoked by infusion of phenylephrine (Table 1).

2.1.4. Propranolol

Bilateral microinjection of the non-selective β-adrenoceptor antagonist propranolol ($n=5$) into the IC did not affect the baseline of either MAP (103±4 vs 99±3 mmHg; $t=0.6$; $P>0.05$) or HR (339±8 vs 357±6 bpm; $t=1.7$; $P>0.05$). Microinjection of propranolol into the IC caused no changes in the linear regression of changes in HR as a function of changes in MAP (−1.5±0.2 vs −1.6±0.3 bpm/mmHg, $F=0.05$; $P>0.05$) (Fig. 2). IC treatment with propranolol also did not affect maximal bradycardia evoked by infusion of phenylephrine (Table 1).

2.2. *Effect of unilateral microinjection of noradrenaline into the IC on the bradycardiac baroreflex response to i.v. infusion of phenylephrine in unanesthetized rats*

Unilateral infusion of noradrenaline ($n=5$) into the IC did not affect the baseline of either MAP (96±1 vs 97±2 mmHg; $t=0.07$; $P>0.05$) or HR (350±8 vs 342±6 bpm; $t=0.74$; $P>0.05$). However, the slope of the linear regression for decreases in HR as a function of increase in MAP during noradrenaline infusion into the IC was decreased when compared with the slope before noradrenaline infusion (−1.2±0.2 vs −0.7±0.2 bpm/mmHg; $F=15$, $P<0.001$) (Fig. 3). Moreover, the effect of NA infusion on the cardiac baroreflex response was blocked by IC pretreatment with the selective α_1-adrenoceptor antagonist WB4101 (−1.7±0.2 vs −1.6±0.1 bpm/mmHg; $F=15$, $P>0.05$). A representative photomicrograph of one coronal brain section showing the microinjection site into the IC and a diagrammatic representation of the IC indicating microinjection sites of ACSF, WB4101, RX821002, propranolol and noradrenaline into the IC and WB4101 into the structures surrounding the IC are presented in Fig. 4.

3. Discussion

In the present study, it was observed that IC α_1-adrenoceptor inhibition facilitated reflex bradycardiac response in unanesthetized rats. In addition, noradrenaline infusion into the IC evoked opposite effects on reflex bradycardia when compared