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Research Report

AV3V lesions reduce the pressor response to L-glutamate into the RVLM

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ABSTRACT

Neurons from the rostral ventrolateral medulla (RVLM) directly activate sympathetic pre-ganglionic neurons in the spinal cord. Hypertensive responses and sympathetic activation produced by different stimuli are strongly affected by lesions of the preoptic periventricular tissue surrounding the anteroventral third ventricle (AV3V region). Therefore, in the present study, we investigated the effects of acute (1 day) and chronic (15 days) electrolytic lesions of the AV3V region on the pressor responses produced by injections of the excitatory amino acid L-glutamate into the RVLM of unanesthetized rats. Male Holtzman rats with sham or electrolytic AV3V lesions and a stainless steel cannula implanted into the RVLM were used. The pressor responses produced by injections of L-glutamate (1, 5 and 10 nmol/100 nl) into the RVLM were reduced 1 day (9 ± 4, 39 ± 6 and 37 ± 4 mm Hg, respectively) and 15 days after AV3V lesions (13 ± 6, 39 ± 4 and 43 ± 4 mm Hg, respectively, vs. sham lesions: 29 ± 3, 50 ± 2 and 58 ± 3 mm Hg, respectively). Injections of L-glutamate into the RVLM in sham or AV3V-lesioned rats produced no significant change in the heart rate (HR). Baroreflex bradycardia and tachycardia produced by iv phenylephrine or sodium nitroprusside, respectively, and the pressor and bradycardic responses to chemoreflex activation with iv potassium cyanide were not modified by AV3V lesions. The results suggest that signals from the AV3V region are important for sympathetic activation induced by L-glutamate into the RVLM.

1. Introduction

Important mechanisms related to cardiovascular regulation are present in the forebrain and hindbrain areas (Agarwal and Calaresu, 1993; Brody et al., 1978; 1980, 1984; Brown and Guyenet, 1984; Dampney et al., 2003; De Paula and Machado, 2001; Guyenet et al., 1990; Pyner and Coote, 1997; Spyer, 1972; Willete et al., 1983; Wyss et al., 1999). In the hindbrain, a medullary circuitry that provides the basic control of cardiovascular system includes the rostral ventrolateral medulla (RVLM), nucleus of the solitary tract (NTS), caudal ventrolateral medulla (CVLM) and nucleus ambiguous (NA) (Agarwal and Calaresu, 1993; Ciriello et al., 1994; De Paula and Machado, 2001; Finley and Katz, 1992; Guyenet et al., 1990; Machado, 2001; Willete et al., 1983). The RVLM localized ventrally to the nucleus ambiguous is the main central site that sends signals to activate sympathetic pre-ganglionic neurons in the intermediolateral column (IML) in the spinal cord (Araújo et al.,

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1999; Brown and Guyenet, 1984; Dampney et al., 2000, 2003; De Paula and Machado, 2001; Guertzenstein and Silver, 1974; Guyenet et al., 1990; Willete et al., 1983).

Among the forebrain areas, the preoptic periventricular tissue surrounding the anteroventral third ventricle (AV3V region) has been shown to play an important role in cardiovascular regulation and fluid–electrolyte balance (Bealer, 1995; Brody et al., 1978, 1980, 1984; Colombari et al., 1992a,b; Johnson, 1985; Johnson et al., 1978; Johnson and Loewi, 1990; Menani et al., 1988a,b, 1990; Valladão et al., 1992; Vieira et al., 2004). Besides the periventricular preoptic nuclei, the AV3V region also includes the organum vasculosum of the lamina terminalis (OVLT), an area lacking blood–brain barrier and rich in angiotensin II (ANG II) receptors (Brody et al., 1978, 1980, 1984; Johnson, 1985; Johnson and Loewi, 1990). In rats, AV3V lesions affect sympathetic activation and vasopressin secretion and reduce arterial pressure in different models of experimental hypertension, the pressor responses to bilateral common carotid occlusion and the pressor responses to central angiotensinergic and cholinergic activation (Brody et al., 1978, 1980, 1984; Colombari et al., 1992a,b; Johnson, 1985; Johnson et al., 1978; Johnson and Loewi, 1990; Menani et al., 1988a,b, 1990; Valladão et al., 1992).

A recent study from our laboratory shows that AV3V lesions also abolish the pressor responses, but not the bradycardia, produced by injection of the excitatory amino acid L-glutamate into the NTS in unanesthetized rats, without changing baro or chemoreflexes (Vieira et al., 2004). These effects of AV3V lesions on the pressor responses to L-glutamate into the NTS suggest that the AV3V region is also important for the increase in sympathetic activity that results from the activation of an area that is part of the medullary circuitry related to cardiovascular regulation. Therefore, it seems that the control of sympathetic activity by the medullary circuitry depends not only on signals that arise from peripheral receptors. Descending signals from the forebrain, especially from the AV3V region, might affect the activity of the medullary circuitry and the autonomic discharges to the cardiovascular system.

In spite of the importance of the RVLM for the control of sympathetic activity and the strong involvement of the AV3V region on cardiovascular regulation, particularly on the pressor responses that depend on increases in sympathetic activity (Brody et al., 1978, 1980, 1984; Colombari et al., 1992a,b; Dampney et al., 2000, 2003; Guyenet et al., 1990; Johnson and Loewi, 1990; Menani et al., 1988a,b, 1990; Valladão et al., 1992), no previous study investigated the possible functional interaction between these two areas for cardiovascular regulation. Therefore, in the present study, we investigated the effects of electrolytic lesions of the AV3V region on the pressor responses produced by injections of L-glutamate into the RVLM. Besides L-glutamate into the RVLM, peripheral chemo and baroreflex were also tested in AV3V-lesioned rats.

2. Results

2.1. *Histological analysis*

Fig. 1 shows the typical AV3V lesion and the site of injections into the RVLM in one rat representative of the lesioned groups.

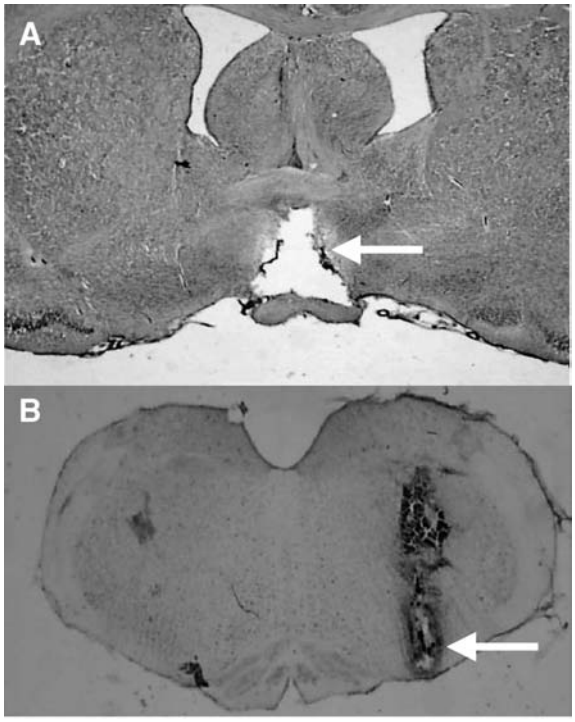

Fig. 1 – Photomicrograph of brain slices from one rat representative of the groups studied showing (arrows) the typical (A) AV3V lesion and (B) site of injection into the RVLM.

The AV3V lesions were located between the anterior commissure and the floor of the third ventricle with bilateral periventricular tissue damage from the lamina terminalis through the preoptic area and anterior hypothalamus, never extending caudally to the arcuate nucleus or medial hypothalamus (Brody et al., 1978, 1980, 1984; Colombari et al., 1992a; Menani et al., 1988a,b, 1990). The brain structures that were consistently destroyed by AV3V lesions were the preoptic periventricular nuclei, the ventral part of median preoptic nucleus and the anterior wall of the third ventricle with the associated organum vasculosum of the lamina terminalis. Partial destruction of the medial preoptic nuclei and the medial region of the anterior hypothalamic nuclei was also observed in some rats.

Injections into the RVLM were ventral to the nucleus ambiguous and approximately 200 to 400 μm caudal to facial nucleus, where the injection of L-glutamate induces pressor responses in rats (Araújo et al., 1999; De Paula and Machado, 2001).

From a total of 35 rats submitted to AV3V lesions and injections into the RVLM, 19 rats had lesions and injections positioned in the correct sites. A total of 40 rats with sham lesions were submitted to injections into the RVLM and 25 of them had correct injections into the RVLM area.

2.2. *Effects of AV3V lesions on the pressor responses induced by L-glutamate into the RVLM*

Acute (1 day) and chronic (15 days) AV3V lesions did not modify baseline MAP (120 ± 3 and 117 ± 3 mm Hg, respectively,