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Area postrema is essential for the maintenance of normal blood pressure under cold stress in rats

Abstract No final conclusion has yet been achieved on whether the area postrema (AP) is involved in the regulation of cardiovascular activity in the rats. The aim of the present study was to investigate the role of the AP in the regulation of basal blood pressure under normal as well as abnormal (cold stress) conditions in Sprague-Dawley rats. The lesion of AP was performed by the electrolytic-lesion method. Stressed animals were subjected to chronic intermittent cold stress (2°C, 3 h/day for 14 days). The systolic blood pressure was measured by the indirect tail-cuff transducer method. The results showed that no significant difference was found between systolic blood pressure measured before and after AP-lesion surgery. The AP-lesion group had similar systolic blood pressure to both sham-operation and the control groups under normal environmental conditions. However, it was found that cold stress resulted in a significant increase in systolic blood pressure in the AP-lesion rats, but not in sham-lesion animals, within two weeks. Furthermore, there was no significant difference between blood pressures of sham-lesion rats with or without cold stress and the control animals. These results support the view that the AP plays no role in keeping basal blood pressure under normal condition and indicate as well that the AP is important in maintaining normal blood pressure under the conditions of stress (cold).

Key words Area postrema · Electrolytic lesion · Blood pressure · Cold stress

Introduction

The area postrema (AP), the most caudal-lying circumventricular organ of the brain, is located on the dorsal surface of the medulla at the obex of the fourth ventricle. The AP neurons exhibit efferent projections to neurons in the nucleus tractus soloterus, the nucleus ambiguous, the dorsal motor nuclei of the vagus, and many other brain areas (Vigier and Rouvier 1979; Spario and Miselis 1985). It has been reported that there are separate excitatory and inhibitory pathways from the AP to nucleus tractus soloterus (Cai et al. 1996). The AP also acts as a chemoreceptor zone, at which circulating blood chemicals may directly act on central nervous system tissue because the AP lacks the normal blood-brain barrier (Van Houten et al. 1983). In the AP, there are a large number of high-affinity binding sites for circulating regulators of blood pressure, such as angiotensin II, vasopressin, and atrial natriuretic peptide (Mendelsohn et al. 1984; Undesser et al. 1985; Brown and Czarnecki 1990; Papas et al. 1990; Konrad et al. 1992). These anatomic and structural characteristics of the AP strongly suggest that the AP may play an important role in the regulation of blood pressure and the baroreflex (Spario and Miselis 1985; Bonham and Hasser 1993).

However, in the rats, a final conclusion on whether the AP is involved in cardiovascular regulation has not yet been obtained. The relevant information in the literature is inconsistent. Therefore, further investigation on this topic is absolutely needed. The experiments conducted in this report were designed to investigate the effect of the AP on blood pressure under normal (without cold stress) as well as abnormal (with cold stress) conditions. Our results showed that, in our experimental conditions, the AP played no role in maintaining basal blood pressure under normal environmental conditions, but the AP is essential for keeping normal blood pressure under an abnormal (cold stress) state.

Materials and methods

Animals

Experiments were performed in male Sprague-Dawley rats with a starting weight of 178±43 g. The rats were housed three per cage, al-
lowed free access to food and water ad libitum, and maintained on a 12 h light (0600–1800)/dark (1800–0600) cycle throughout the experimental period. The animals were randomly divided into 5 groups: (1) control group (n=6); (2) the AP-lesion with-stress group (n=8); (3), the AP-lesion without-stress group (n=7); (4) sham lesion with-stress group (n=11), and (5) sham-lesion without-stress group (n=12).

AP electrolytic lesion surgery and post-mortem verification of lesion accuracy

Under pentobarbital sodium (40 mg/kg, i.p.) anesthesia, the head of the rats was immobilized in a stereotaxic frame (ASI instrument SAS-4100). The 3-dimensional positioning was followed in accordance with the de Groot coordinate system. A small pore was drilled with a blunt stainless steel syringe at the position just above the AP in order to insert the electrode. The tip of the electrode was moved downward 6 mm from the dura and exactly touched the AP. The lesion current was produced by a passage of an anodal (DC) current (2 mA for 10 s) from a lesion-making device (Ugo Basile 3500). For the sham-lesion groups, similar procedures were carried out except for the electric lesion. After surgery, a prophylactic dose of ampicillin sodium (Pamecil 25 mg/kg im) was injected to the hind legs of the rats and the animals were then returned to their cages for recovery.

On the last day of experiment, the rats were anesthetized with pentobarbital sodium (40 mg/kg, i.p.) and then killed. The brains were removed and preserved in formalin (10%). Serial sectioning was performed and the sections stained for Nissl bodies by cresyl violet. The stained brain slices were investigated to identify the accuracy of lesion location. Under the microscope, the lesion site could be found through extraordinary color from the violet background. A 90% destruction of the area was considered to be a successful lesion. For lesion groups, only data from rats with successful damage to the AP were counted as lesion rats and taken into calculation. Rats not compatible with this criteria were excluded from calculation.

Protocol of intermittent cold-restraint stress

After 1 week of recovery from surgery, the stress groups (the AP lesion and sham lesion) was subjected to daily intermittent cold stress for 2 weeks (14 days). The rats were immobilized in porous restraining cages and then exposed to cold at 2°C for 3 h (13:00–16:00) per day. After cold treatment, the rats were returned to their housing cages. For the non-stress groups (AP lesion and Sham lesion), similar procedures (including immobilization) were carried out for the same period except for the cold-stress treatment. Daily blood pressure measurements were performed in all groups.

Indirect measurement of systolic blood pressure

An indirect non-invasive method was employed to measure tail systolic blood pressure using a Letica LE5001 pressure meter. The measurements were made before surgery; day 1, 2, and 7 after lesion surgery to investigate acute effect; and then every day (0800–1200) throughout the stress period to monitor the effect of cold stress on blood pressure. Rats were immobilized in a Plexiglas restraining cage and placed on a warming plate at about 30°C. A tail cuff and a transducer were installed at the tail. After 20–30 min of adaptation, blood pressure was taken five times with an interval of 5–8 min after each measurement. All values were immediately recorded in the logbook.

Statistical analysis

All data are presented as mean and standard deviation (mean±SD). For indication of trends and validation of results, they were statistically analyzed by two-sided unpaired Student’s t-test. A P value of <0.05 was considered as significantly different.

Results

Short-term and long-term effect of the AP lesion on tail systolic blood pressure

Before lesion surgery, the systolic blood pressure (baseline value) was 161±7 mm Hg in the AP-lesion group and 163.5±6.5 mm Hg in sham-lesion group. After surgery, the AP-lesion group had 163±8 mm Hg on day 1, 164±6 mm Hg on day 2, and 167±2 mm Hg on day 7 (n=15). Correspondingly, the sham group had 164±5 mm Hg, 164±8 mm Hg, and 162±4 mm Hg (n=23). The results (Fig. 1) showed that there was no significant difference between baseline values of blood pressure in the AP-lesion, sham-lesion, and control animals.