



Would right atrial stretch inhibit sodium intake following GABA_A receptor activation in the lateral parabrachial nucleus?☆

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HIGHLIGHTS

- GABA_A into the lateral parabrachial nucleus (LPBN) induces sodium intake.
- Simulating volume overload with right atrial stretch decreases fluid intake.
- Influence of GABA_A into the LPBN associated with right atrial stretch was tested.
- GABA_A into the LPBN abolished the right atrial stretch effect on fluid intake.

ARTICLE INFO

Article history:

Received 3 February 2013

Received in revised form 31 July 2013

Accepted 3 August 2013

Keywords:

Right atrial stretch

Lateral parabrachial nucleus

Sodium intake

GABA_A

Cardiopulmonary volume receptors

Circulating volume

ABSTRACT

The knowledge of the mechanisms underlying circulating volume control may be achieved by stretching a balloon placed at the junction of the superior vena cava–right atrial junction (SVC–RAJ). We investigated whether the inflation of a balloon at the SVC–RAJ inhibits the intake of 0.3 M NaCl induced by GABA_A receptor activation in the lateral parabrachial nucleus (LPBN) in euhydrated and satiated rats. Male Wistar rats (280–300 g) with bilateral stainless steel LPBN cannulae and balloons implanted at the SVC–RAJ were used. Bilateral injections of the GABA_A receptor agonist muscimol (0.5 μmol/0.2l) in the LPBN with deflated balloons increased intake of 0.3 M NaCl (30.1 ± 3.9 vs. saline: 2.2 ± 0.7 ml/210 min, *n* = 8) and water (17.7 ± 1.9 vs. saline: 2.9 ± 0.5 ml/210 min). Conversely, 0.3 M NaCl (27.8 ± 2.1 ml/210 min) and water (22.8 ± 2.3 ml/210 min) intake were not affected in rats with inflated balloons at the SVC–RAJ. The results show that sodium and water intake induced by muscimol injected into the LPBN was not affected by balloon inflation at the SVC–RAJ. We suggest that the blockade of LPBN neuronal activity with muscimol injections impairs inhibitory mechanisms activated by signals from cardiopulmonary volume receptors determined by balloon inflation.

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1. Introduction

Knowledge of the mechanisms underlying the control of circulating volume may strengthen understanding of some pathophysiological processes related to edematous states such as heart failure. Cardiopulmonary volume receptors are suggested to regulate circulating volume [8,9,15,17] and may be activated by a distension of a small intravascular balloon placed at the superior vena cava–right atrial junction [SVC–RAJ, 1]. Inflation of a balloon at the SVC–RAJ attenuates water drinking in response to 24 h

water deprivation, subcutaneous injection of isoproterenol, peritoneal dialysis with hyperoncotic colloid, and *ad libitum* water intake without affecting drinking in response to intravenous hypertonic saline in rats [9]. In addition, balloon inflation also reduces sodium intake induced by overnight sodium depletion, peritoneal dialysis with hypertonic colloid, or by daily injections of deoxycorticosterone acetate [DOCA, 17]. Ablation of the ventrolateral parabrachial nucleus (LPBN) abolished the reduction in fluid intake caused by isoproterenol injection following balloon inflation [15]. Furthermore, balloon inflation at the SVC–RAJ increases immunohistochemically detected Fos expression in the LPBN following acute sodium depletion [8]. Conversely, neurons in the LPBN respond to hemorrhage [3,18]. Therefore, the LPBN is a central site involved in control of circulating volume.

The LPBN is strategically positioned in the pons and receives important visceral-related information that ascends from the area postrema/nucleus of the solitary tract (AP/NTS) being reciprocally

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connected with forebrain areas involved in behavioral and autonomic responses [5,12,15]. The NTS is the primary site in the central nervous system that receives important afferents from visceral receptors involved in the control of fluid and electrolyte balance [8]. From the NTS, the signals from visceral receptors might reach the LPBN before ascending to forebrain sites involved in the control of fluid and electrolyte balance.

The participation of the LPBN in the control of fluid intake has been extensively described for a variety of neurotransmitters such as serotonin, cholecystokinin, corticotropin-releasing hormone, glutamate, opioids, noradrenaline, and GABA [1,4,6,7,13,14,16]. The effect of GABA on the LPBN is particularly interesting, and it has been shown that bilateral injections of the GABA_A receptor agonist muscimol in the LPBN result in strong intake of 0.3 M NaCl in fluid-replete rats [4]. However, similar inhibition of the LPBN by activation of GABA_A receptors does not affect sucrose intake, suggesting that its effects on sodium are not a result of the non-specific effect of GABA_A receptor activation on the LPBN [16]. It should be noted that the effects of muscimol injection into the LPBN on sodium intake are not secondary to reductions in blood pressure or increased sodium urinary excretion [4,16].

Considering the importance of cardiopulmonary/volume receptors, their possible action through the LPBN, and the effects of the neuronal deactivation of the LPBN with muscimol on sodium and water intake, we investigated whether the inflation of a balloon at the SVC–RAJ affects 0.3 M NaCl and water intake induced by bilateral injections of muscimol into the LPBN in fluid-replete rats.

2. Methods

2.1. Animals

Male Wistar rats weighing 280–300 g were used. They were housed individually in hanging, stainless steel cages with free access to standard laboratory diet (Labina Purina® Rat Chow), water, and 0.3 M NaCl solution. Temperature was maintained at $23 \pm 2^\circ\text{C}$ and humidity at $54 \pm 10\%$, on a 12:12 light:dark cycle (onset at 6:00 am). All procedures were in accordance with the Animal Care and Use policies of the Institute of Biosciences at Botucatu, Brazil and the Brazilian College of Animal Experimentation (COBEA) policies. All efforts were made to minimize animal discomfort and the number of animals used.

2.2. Drugs

Muscimol HBr (a gabaergic receptor agonist) was purchased from Research Biochemicals International (RBI; Natick, MA). Saline was injected in the LPBN as control.

2.3. Cerebral cannulae

Rats were anesthetized with ketamine (80 mg/kg body weight, Dopalen®, Vetbrands, Jacaré, SP) combined with xilazine (7 mg/kg body weight, Anasedan®, Vetbrands, Jacaré, SP) and placed in a Kopf Model 900 stereotaxic instrument (David Kopf Instruments). The skull was leveled between bregma and lambda. Then, 23-gauge stainless steel cannulae were implanted bilaterally into the LPBN at 9.5 mm caudal to bregma, 2.2 mm lateral to the midline, and 4.1 mm below the dura mater [similar to previous studies: 6,7,13,14,16]. The tips of the cannulae were positioned at points 2 mm above each LPBN. The cannulae were fixed to the cranium using dental acrylic resin and jeweler's screws. A 30-gauge metal obturator filled the cannulae between tests. After the surgery, the rats received intramuscular injections of the analgesic ketoprofen 1% (0.03 ml/rat) and a prophylactic dose of the antibiotic penicillin (30,000 IU). Rats

were allowed to recover for four days before the surgery for balloon placement.

2.4. Balloon placement

Inflatable balloons were made of Silastic® tubing. One end of the tube was sealed with silicone glue and allowed to dry. Then, a small portion close to this end was warmed, stretched, and expanded repeatedly by injecting saline into it [according to previous studies: 8, 15]. The rats were anesthetized for balloon placement as described above for implantation of cerebral cannulae. In the rat, the left superior vena cava joins the inferior vena cava, so that placement of the balloon does not interfere with venous return from the head to the heart [9]. Thus, the right jugular vein was exposed where the inflatable balloon was inserted and positioned to terminate at the SVC–RAJ [as described in 9]. The Silastic® tube was tunneled subcutaneously, exteriorized at the nape of the neck, and fixed with suture thread. The animals were allowed three days to recover from surgery before starting the tests. During the tests, balloons were inflated by filling them with isotonic saline (0.1 ml), this inflatable portion produce an expansion of 5 mm of diameter.

2.5. Injections into the LPBN

Bilateral injections into the LPBN were made using 10 μl Hamilton syringes connected by polyethylene tubing (PE-10) to 30-gauge injection cannulae. At the time of testing the rats were removed from the home cage, the obturators were removed, and the injection cannulae were introduced into the brain. The animals were hand held as drugs were injected. Injection volume was 0.2 μl per site. After the injections, the obturators were replaced and rats were placed back into their cages.

2.6. Sodium and water intake tests

Fluid-replete rats treated with bilateral injections of saline or muscimol into the LPBN were used to test the effects of balloon inflation on water and sodium intake. The animals were tested in their home cages with continuous free access to food, water, and 0.3 M NaCl. In each test, half the animals received bilateral injections of muscimol and half received saline into the LPBN. Half the rats in each group had their balloons inflated whereas the other half had their balloons kept deflated. Thus, rats were submitted to four procedures: LPBN muscimol + balloon inflated; LPBN muscimol + balloon deflated; LPBN saline + balloon inflated; and LPBN saline + balloon deflated. Balloons were inflated immediately after rats had received injections into the LPBN. Then, rats were returned to their cages where water and 0.3 M NaCl intake started being recorded immediately. The fluids were provided from burettes with 0.1 ml divisions fitted with metal drinking spouts in front of the cages. Water and 0.3 M NaCl intake were measured at 30, 60, 90, 120, 150, 180, and 210 min. Next, the burettes were replaced by 100 ml tubes with 1 ml divisions with water and 0.3 M NaCl for the next 13 h (overnight), while balloons were kept inflated or deflated as they were in the last 210 min of the previous afternoon. The experiments started at 3:00 pm, and at 5:30 pm the burettes were replaced by 100 ml tubes which remained in place until 6:30 am in the following morning when the volume of water and 0.3 M NaCl ingested was measured and balloons were deflated. The long intake period enabled us to study the inhibitory effect of balloon distension on water and 0.3 M NaCl intake in the absence of muscimol action in the LPBN, which was necessary to determine the correct position of the balloon at the SVC–RAJ.

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