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RAPID STIMULATION OF SODIUM INTAKE COMBINING ALDOSTERONE INTO THE 4TH VENTRICLE AND THE BLOCKADE OF THE LATERAL PARABRACHIAL NUCLEUS

S. GASPARINI, M. R. MELO, G. F. LEITE, P. A. NASCIMENTO, G. M. F. ANDRADE-FRANZÉ, J. V. MENANI [†] AND E. COLOMBARI [*†]

Department of Physiology and Pathology, School of Dentistry of Araraquara, São Paulo State University, UNESP, Araraquara, SP, Brazil

Abstract—Chronic infusion of aldosterone into the 4th ventricle (4th V) induces robust daily sodium intake, whereas acute injection of aldosterone into the 4th V produces no sodium intake. The inhibitory mechanism of the lateral parabrachial nucleus (LPBN) restrains sodium intake induced by different natriorexigenic stimuli and might affect the acute response to aldosterone into the 4th V. In the present study, 1.8% NaCl and water intake was tested in rats treated with acute injections of aldosterone into the 4th V combined with the blockade of the inhibitory mechanisms with injections of moxonidine (α_2 adrenergic/imidazoline agonist) or methysergide (a serotonergic antagonist) into the LPBN. Male Holtzman rats with stainless steel cannulas implanted in the 4th V and bilaterally in the LPBN were used. Aldosterone (250 or 500 ng) into the 4th V combined with vehicle into the LPBN induced no 1.8% NaClintake compared to control (1.5 ± 1.1 and 1.1 ± 0.4, respectively, vs. vehicle into 4th V: 1.0 ± 0.5 ml/2 h). However, aldosterone (250 or 500 ng) into the 4th V combined with moxonidine (0.5 nmol) into the LPBN induced strong ingestion of 1.8% NaCl (12.7 ± 4.6 and 17.6 ± 3.7 ml/2 h, respectively). Aldosterone (250 ng) into the 4th V combined with methysergide (4 μg) into the LPBN also induced 1.8% NaCl intake (17.6 ± 5.4 ml/2 h). These data suggest that the inhibitory mechanisms of the LPBN counteract the facilitation of sodium intake produced by aldosterone injected into the 4th, restraining sodium intake in this condition. **© 2017 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: sodium appetite, mineralocorticoids, hindbrain, HSD2 neurons.

INTRODUCTION

The ingestion of sodium is stimulated by body sodium deficiency and one of the main stimuli is the renin-angiotensin-aldosterone system (Fregly and Rowland, 1985; Shade et al., 2002; Johnson and Thunhorst, 2007). Aldosterone is secreted by the adrenal cortex in response to increased plasma levels of angiotensin II (ANG II) and acts in the kidney to reduce renal sodium excretion and in the brain to stimulate sodium appetite (Fregly and Rowland, 1985; Sakai et al., 2000; Shade et al., 2002; Johnson and Thunhorst, 2007).

Early studies suggested the involvement of the amygdala on sodium appetite induced by systemic administration of aldosterone or deoxycorticosterone acetate (DOCA) (Nitabach et al., 1989; Galaverna et al., 1992; Zardetto-Smith et al., 1994). More recent studies have suggested the possible action of aldosterone in hindbrain areas to control sodium appetite (Geerling et al., 2006a,b; Geerling and Loewy, 2006c, 2007). Neuroanatomical studies identified neurons that express the enzyme 11-β-hydroxysteroid dehydrogenase 2 (HSD2 neurons) in the medial portion of the nucleus of the solitary tractus (NTS) near the 4th ventricle (4th V) (Geerling et al., 2006a,b; Geerling and Loewy, 2006c, 2007). The HSD2 neurons are sensitive only to aldosterone and are activated in sodium-depleted rats and deactivated by the ingestion of hypertonic NaCl, suggesting that these neurons may play a role in the homeostasis of body sodium (Geerling et al., 2006b; Geerling and Loewy, 2006c). Functional studies showed that chronic infusion of low dose of aldosterone into the 4th V strongly increased daily 1.8% NaCl intake and the knockdown of mineralocorticoid receptors (MR) in the NTS reduced sodium intake induced by chronic infusion of aldosterone into the 4th V, suggesting the involvement of these NTS neurons in this behavioral response (Koneru et al., 2014).

Contrary to chronic infusion of aldosterone into the 4th V, acute injection of aldosterone into the 4th V induces no sodium intake. The reasons for the absence of acute natriorexigenic effect of aldosterone are not clear. It is known that acute and chronic effects of aldosterone may involve different mechanisms (Booth et al., 2002). The acute effects of aldosterone that occur within seconds to minutes might involve non-genomic action on G protein-coupled estrogen receptor (GPER) (Funder, 2011; Gros et al., 2011), whereas chronic effects may involve genomic mechanisms. However, another reason

*Corresponding author. Address: Department of Physiology and Pathology, School of Dentistry, Sao Paulo State University, UNESP, Rua Humaitá, 1680, 14801-903 Araraquara, SP, Brazil. Fax: +55-16-33016488.

E-mail address: eduardo.colombari@foar.unesp.br (E. Colombari).

[†] JVM and EC are co-senior authors.

Abbreviations: ANG II, angiotensin II; CeA, central nucleus of amygdala; DOCA, deoxycorticosterone acetate; GPER, G protein-coupled estrogen receptor; LPBN, lateral parabrachial nucleus; LV, lateral ventricle; MR, mineralocorticoid receptors; NTS, nucleus of the solitary tractus.

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for the delay in the natriorexigenic effect of aldosterone infused into the 4th V might be the action of an inhibitory mechanism such as that mediated by the lateral parabrachial nucleus (LPBN). The LPBN receives neural input from different regions, including the area postrema (AP) and the nucleus of the solitary tract (NTS). The NTS is innervated by afferents from baroreceptors, cardiopulmonary receptors, gustatory receptors and other visceral receptors that influence water and NaCl intake (Lanca and van der Kooy, 1985; Johnson and Thunhorst, 1997; Johnson, 2007). The blockade of serotonin, cholecystokinin, corticotropin releasing factor or glutamate receptors or the activation α_2 adrenergic receptors in the LPBN increases sodium intake and occasionally water drinking in fluid-depleted animals, suggesting the existence of a significant inhibitory mechanism in the LPBN controlling sodium and water intake (Menani et al., 1996; Menani and Johnson, 1998; Andrade et al., 2004; De Gobbi et al., 2007, 2009). The blockade of serotonin in the LPBN also increases DOCA-induced sodium intake (De Gobbi et al., 2000).

To investigate if the LPBN inhibitory mechanisms restrain sodium intake in rats that receive acute injections of aldosterone into the 4th V, in the present study, the ingestion of 1.8% NaCl and water was tested in rats treated with aldosterone injection into the 4th V combined with the blockade of the inhibitory mechanisms using bilateral injections of methysergide (serotonergic antagonist) or moxonidine (α_2 adrenergic/imidazoline receptor agonist) into the LPBN. To confirm the action of aldosterone in the hindbrain, it was also tested the ingestion of water and 1.8% NaCl in rats treated with injection of aldosterone into the lateral ventricle (LV) combined with bilateral injections of moxonidine into the LPBN.

MATERIAL AND METHODS

Animals

Male Holtzman rats weighing 280–320 g were housed individually in stainless steel cages in a room with controlled temperature (23 ± 2 °C) and humidity (55 ± 10%). Lights were on from 7:00 am to 7:00 pm. Normal rat chow (Biobase, Águas Frias, SC, Brazil, composed by 22 g of protein, 48 g of carbohydrates, 4 g of total fat, 8 g of fiber and 200 mg of sodium per 100 g of diet), tap water and 1.8% (0.3 M) NaCl were available *ad libitum*. The experimental protocols used in the present study were approved by the Ethics Committee for Animal Care and Use from Dentistry School of Araraquara – UNESP.

Brain surgery

Rats were anesthetized with ketamine (80 mg/kg of body weight i.p.) and xylazine (7 mg/kg of body weight i.p.). Stainless steel cannulas (12 × 0.6 mm o.d.) were implanted in the 4th V or LV and bilaterally in the LPBN using a Kopf stereotaxic instrument. The stereotaxic coordinates for the LPBN were 9.4 mm caudal to the bregma, 2.1 mm lateral to midline and 4.1 mm below the dura mater with the tips of the cannulas at a point 2 mm above the LPBN. The coordinates for the 4th V were 12.5 mm caudal to the bregma, 0.0 mm lateral to midline and 5.5 mm below the dura mater and for the LV were 0.6 mm caudal to the bregma, 1.6 mm lateral to midline and 3.6 mm below the dura mater. The cannulas were fixed to the cranium using dental acrylic resin and jeweler screws. Animals received an intramuscular injection of penicillin (30,000 IU) and a subcutaneous (s.c.) injection of the analgesic Ketoflex (ketoprofen 1%, 0.03 ml/rat) at the end of the surgery. Water and NaCl intake tests started one week after the surgery.

Drugs

Moxonidine hydrochloride, methysergide maleate and aldosterone purchased from Sigma Chemical Co, St. Louis, MO, USA were used. Moxonidine and methysergide were dissolved in propyleneglycol:distilled water (2:1) and aldosterone was dissolved in 1% ethanol in 0.9% NaCl. Moxonidine (0.5 nmol/0.2 μl), methysergide (4 μg/0.2 μl) or vehicle was injected into the LPBN and aldosterone (250 ng/2 μl or 250 ng/1 μl) or vehicle was injected into the 4th V and LV. The doses were based on previous studies that tested the effects of these drugs on water and sodium intake (Menani et al., 1998; Andrade et al., 2004; Formenti et al., 2013).

Central injections

Central injections were made using injector cannulas (0.3 mm o.d.) 2 mm longer than guide cannulas connected with a polyethylene tubing (PE-10 to a 10-μl Hamilton syringes. The volume of injection was 2 μl into the 4th V, 1 μl into the LV and 0.2 μl in each side of the LPBN.

Histology

At the end of the tests, the animals were anesthetized with sodium thiopental (60 mg/kg of body weight) and received injections of 2% Evans blue solution into the central sites. They were perfused transcardially with 10% formalin, brains were collected and fixed in 10% formalin. After at least two days, brains were frozen and cut into 60-μm sections. To confirm the central sites of injections, sections were stained with Giemsa and analyzed by light microscopy.

Statistical analysis

Two-way repeated measures ANOVA and the Neman–Keuls post-test were used to compare the results. Results were considered significantly different for $p < 0.05$.

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