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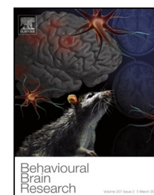

Research report

Gabaergic and opioid receptors mediate the facilitation of NaCl intake induced by α_2-adrenergic activation in the lateral parabrachial nucleus

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HIGHLIGHTS

- α_2-adrenoceptor activation in the LPBN increases sodium intake in fluid-depleted rat.
- Opioidergic receptor blockade partially reduced α_2-adrenoceptor activation effects.
- α_2-adrenoceptor activation effects are partially reduced by $GABA_A$ receptor blockade.
- Opioidergic/GABAergic blockade partially reduced α_2-adrenoceptor activation effects.
- α_2-adrenoceptor activation effects are partially dependent on opioid/$GABA_A$ receptors.

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ABSTRACT

Alpha$_2$-adrenergic, gabaergic or opioidergic activation in the lateral parabrachial nucleus (LPBN) increases sodium intake. In the present study, we investigated the effects of single or combined blockade of opioidergic and gabaergic receptors in the LPBN on the increase of 0.3 M NaCl intake induced by α_2-adrenoceptor activation in the LPBN. Male Holtzman rats (n = 5–9/group) with cannulas implanted bilaterally in the LPBN were treated with the diuretic furosemide (10 mg/kg b wt.) combined with low dose of the angiotensin converting enzyme inhibitor captopril (5 mg/kg b wt.) subcutaneously. Bilateral injections of moxonidine (alpha$_2$-adrenergic/imidazoline receptor agonist, 0.5 nmol) into the LPBN increased furosemide + captopril-induced 0.3 M NaCl intake (25.8 ± 1.4, vs. vehicle: 3.8 ± 1.1 ml/60 min). The opioidergic receptor antagonist naloxone (100 nmol) or the $GABA_A$ receptor antagonist bicuculline (5 nmol) injected into the LPBN partially reduced the increase of 0.3 M NaCl intake produced by LPBN moxonidine (11.8 ± 4.0 and 22.8 ± 4.5, respectively, vs. vehicle + moxonidine: 31.6 ± 4.0 ml/60 min, respectively). Similar to the treatment with each antagonist alone, the combined injections of naloxone (100 nmol) and bicuculline (5 nmol) into the LPBN also partially reduced moxonidine effects on 0.3 M NaCl intake (15.5 ± 6.5 ml/60 min). The $GABA_B$ receptor antagonist saclofen (5 nmol) injected into the LPBN did not change the effects of moxonidine on 0.3 M NaCl intake (24.3 ± 7.8 ml/120 min). These results suggest that the increase of 0.3 M NaCl intake by α_2-adrenergic receptor activation in the LPBN is partially dependent on $GABA_A$ and opioid receptor activation in this area.

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1. Introduction

The lateral parabrachial nucleus (LPBN) is a pontine area strongly involved with inhibitory mechanisms that control water and NaCl intake [1–7]. The LPBN is reciprocally connected to forebrain areas implicated in the maintenance of blood pressure and body fluid homeostasis, such as the paraventricular nucleus of the hypothalamus, the central nucleus of the amygdala and the median preoptic nucleus. The LPBN is also richly interconnected with medullary regions, which includes the area postrema (AP) and the medial portion of the nucleus of the solitary tract (mNTS), [8–15]. Therefore, the LPBN receives taste and visceral signals that ascend from AP/mNTS en route to forebrain

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areas involved in the control of fluid and electrolyte balance [5–7,16,17].

Studies that have investigated the involvement of the LPBN in the control of fluid-electrolyte balance demonstrated that different neurotransmitters like serotonin, cholecystokinin, glutamate and corticotrophin releasing factor (CRF) or receptors like α_2-adrenoceptors, GABAergic, opioid or purinergic receptors in the LPBN are involved with the control of sodium intake [1,3,5,18–28]. The activation of the α_2-adrenoceptors with bilateral injections of noradrenaline or moxonidine into the LPBN increases 0.3 M NaCl and water intake induced by the treatment with the diuretic furosemide (FURO) combined with low dose of the angiotensin converting enzyme inhibitor captopril (CAP) injected subcutaneously. Activation of the same receptors in the LPBN has no effect on water and hypertonic NaCl intake of satiated rats [21,25].

The activation of $GABA_A$, $GABA_B$ or opioid receptors with bilateral injections of muscimol, baclofen or β endorphin, respectively, into the LPBN strongly increases 0.3 M NaCl intake by satiated or sodium depleted rats [20,27,29,30]. Therefore, the activation of $GABA_A$, $GABA_B$, opioid receptors in the LPBN deactivates the inhibitory mechanisms, releasing sodium intake if excitatory signals were activated by sodium depletion or not [20,27,29].

It is not known if α_2-adrenoceptor, GABAergic and opioidergic mechanisms interact in the LPBN to so potently induce sodium intake. In the present study, we investigated the effect of combined antagonism of opioidergic and/or gabaergic receptor with α_2-adrenoceptor activation in the LPBN on 0.3 M NaCl and water intake induced by FURO + CAP in rats.

2. Material and methods

2.1. Animals

Male Holtzman rats weighing 290 to 310 g were used. The animals were housed in individual stainless steel cages with free access to normal sodium diet (Guabi Rat Chow, Paulinia, SP, Brazil), water and 0.3 M NaCl solution. Temperature was maintained at $23 \pm 2\,^{\circ}$C, and humidity was maintained at $55 \pm 10\%$ on a 12:12 light-dark cycle with light onset at 7:30 AM.

The experimental protocols used in the present study were approved by Ethical Committee for Animal Care and Use from Dentistry School of Araraquara–UNESP, Brazil (protocol no: 06/2006) and followed the recommendations from the National Council for the Control of Animal Experimentation (CONCEA) and the American National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH publications No. 80–23, 1996, USA). All efforts were made to minimize animal discomfort and the number of animals used.

2.2. Cerebral cannulas

Rats were anesthetized with ketamine (80 mg/kg of body weight) combined with xylazine (7 mg/kg of body weight) and placed in a Kopf stereotaxic instrument. The skull was leveled between bregma and lambda. Bilateral stainless steel 23-gauge cannulas were implanted in direction to the LPBN using the following coordinates: 9.4 mm caudal to bregma, 2.1 mm lateral to the midline, and 4.2 mm below the dura mater. The tips of the cannulas were positioned at a point 2 mm above each LPBN. The cannulas were fixed to the cranium using dental acrylic resin and jeweller screws. A 30-gauge metal obturator filled the cannulas between tests. The rats were allowed to recover 6 days before drug injections into the LPBN.

2.3. Injections into the LPBN

Injections into the LPBN were made using 5-μl Hamilton syringes connected by polyethylene tubing (PE-10) to 30-gauge injection cannulas. At time of testing, obturators were removed and the injection cannulas (2 mm longer than the guide cannulas) were introduced in the brain. The injection volume into the LPBN was 0.2 μl each site. The obturators were replaced after injection, and the rats were placed back into the cage.

2.4. Drugs

Furosemide (FURO, Sigma Chem., St Louis, MO, USA) was administered subcutaneously at 10 mg/kg of body weight. Captopril (CAP, Sigma Chem., St Louis, MO, USA) was administered subcutaneously at 5 mg/kg of body weight [7,21,31]. Moxonidine hydrochloride (a donation of Solvay Pharma, Hannover, Germany) was administered into the LPBN at the dose of 0.5 nmol/0.2 μl [19,21,24,32]. Bicuculline, ($GABA_A$ receptor antagonist, Tocris, Ellisville, MO, USA) was administered into the LPBN at the doses of 1.6 and 5.0 nmol/0.2 μl [27]; saclofen ($GABA_B$ receptor antagonist, Tocris, Ellisville, MO, USA) was administered into the LPBN at the dose of 5.0 nmol/0.2 μl [30] and naloxone hydrochloride (opioidergic receptor antagonist, Sigma Chemicals, St. Louis, MO, USA) was administered into the LPBN at the dose of 100 nmol/0.2 μl) [20].

Moxonidine, naloxone, saclofen and bicuculline were dissolved in a mix of propylene glycol/water 2:1 (vehicle). Vehicle was injected as control into the LPBN. Captopril was dissolved in isotonic saline. Furosemide was dissolved in alkaline saline (pH adjusted to 9.0 with NaOH).

2.5. Ingestive test

Rats were tested in their home cages. Water, 0.3 M NaCl and food were removed and the animals received subcutaneous FURO (10 mg/kg of body wt) + CAP (5 mg/kg of body wt) as described previously [7,21,31]. One hour later, water and 0.3 M NaCl were provided in burettes with 0.1-ml divisions that were fitted with metal drinking spouts. Cumulative water and 0.3 M NaCl intakes were measured at 15, 30, 60, 90, and 120 min (ingestive test). The injections of moxonidine or vehicle into the LPBN were performed 45 min after FURO + CAP treatment or 15 min before the rats had access to water and 0.3 M NaCl. The opioidergic and/or GABAergic antagonist, or vehicle, was injected into the LPBN 15 min before the injection of moxonidine or its vehicle.

Each group of rats was submitted to four tests, each test in a different day, at a 48-hour minimum interval. In each test the group was divided in two and each half received a different treatment into the LPBN. The sequence of the treatments into the LPBN in the different tests was randomized. All animals received a total of four treatments into the LPBN: vehicle + vehicle; vehicle + moxonidine; opioidergic and/or GABAergic antagonist + moxonidine; opioidergic and/or GABAergic antagonist + vehicle.

2.6. Histology

The animals received bilateral injections of 2% Evans blue solution (0.2 μl) into the LPBN after the fourth ingestive test. They were then deeply anesthetized with sodium thiopental (80 mg/kg of body weight) and perfused transcardially with saline followed by 10% formalin. The brains were removed, fixed in 10% formalin, frozen, cut in 50-μm sections, stained with cresyl violet, and analyzed by light microscopy to confirm the injection sites into the LPBN.

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