Serotonergic mechanisms of the lateral parabrachial nucleus on 
DOCA-induced sodium intake

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Abstract

It has been shown that the serotonergic mechanisms of the lateral parabrachial nucleus (LPBN) inhibit NaCl intake in different models of angiotensin II (ANG II)-dependent NaCl intake in rats. However, there is no information about the involvement of LPBN serotonergic mechanisms on NaCl intake in a model of NaCl intake not dependent on ANG II like deoxycorticosterone (DOCA)-induced NaCl intake. Therefore, in this study we investigated the effects of bilateral injections of serotonergic agonist and antagonist into the LPBN on DOCA-induced 1.8% NaCl intake in rats. Male Holtzman rats were treated with s.c. DOCA (10 mg/rat each every 3 days). After a period of training, in which the rats had access to 1.8% NaCl during 2 h for several days, the rats were implanted with stainless steel cannulas bilaterally into the LPBN. Bilateral injections of the serotonergic receptor antagonist methysergide (4 mg/0.2 ml each site) in the LPBN increased 1.8% NaCl intake (32.2±3.9 versus vehicle: 15.0±1.6 ml/2 h, n=10) and water intake (12.5±3.5 versus vehicle: 3.2±1.0 ml/2 h). Injections of the serotonergic 5HT2A/2C receptor agonist DOI (5 µg/0.2 µl each site) in the LPBN reduced 1.8% NaCl intake (6.8±1.7 versus saline: 12.4±1.9 ml/2 h, n=10) and water intake (2.2±0.8 versus saline: 4.4±1.0 ml/2 h). Besides the previously demonstrated importance for the control of ANG II-dependent water and NaCl intake, the data show that the serotonergic inhibitory mechanisms of the LPBN are also involved in the control of DOCA-induced NaCl intake. © 2000 Elsevier Science B.V. All rights reserved.

Theme: Neural basis of behaviour

Topic: Ingestive behaviours

Keywords: Deoxycorticosterone; NaCl intake; Water intake; 5HT; LPBN

1. Introduction

The lateral parabrachial nucleus (LPBN), a structure that lies dorsal to the superior cerebellar peduncle (SPC) in the pons has an important participation in the control of water and NaCl intake [3,6,14,19–22]. The injection of serotonin (5HT) or 2,5-dimethoxy-4-iodoamphetamine hydrochloride (DOI, a serotonergic 5HT2A/2C receptor agonist) into the LPBN reduces angiotensin II (ANG II)-induced water intake in rats [19]. Methysergide, a serotonergic receptor antagonist, injected into the LPBN increases, while DOI reduces, water and 0.5 M NaCl intake induced by sodium depletion (treatment with the diuretic furosemide injected subcutaneously (s.c.)+24 h of sodium deficient diet) or water and 0.3 M NaCl intake induced by combined s.c. treatment with furosemide (FURO) and low dose of angiotensin-converting enzyme inhibitor captopril [20,21]. Methysergide into the LPBN also increases 0.3 M NaCl intake induced by intracerebroventricular (i.c.v.) ANG II, s.c. isoproterenol and acute s.c. FURO treatment [20,22].

The LPBN receives afferent projections from the area postrema (AP) and the medial nucleus of the solitary tract (mNTS) and sends efferent projections to areas of the forebrain involved in fluid and electrolyte balance such as specific nuclei within the hypothalamus (e.g., paraventricular nucleus) and amygdala (e.g., central nucleus) [2,11–13,17,29]. Electrophysiological studies have shown projections from the parabrachial nucleus to neurotensin and galanin containing neurons of the amygdala [13], an area essential for adrenal steroid-induced salt appetite [10,31].
Earlier works from Rice and Richter (1943) and Braun-Menendez (1952) showed that systemic injection of deoxycorticosterone acetate (DOCA) produces salt appetite in rats [5]. Since then, mineralocorticoid-induced sodium appetite and/or hypertension has been extensively studied [1,8,10,16,27,28]. ANG II and aldosterone act in the brain to control sodium intake [7,8,10,27,28], and each one can activate different neural circuits [4]. It has also been suggested that pretreatment with small doses of sc DOCA associated with infusion of small doses of ANG II into the third ventricle induces appetite for sodium within minutes [8].

Considering previous studies [3,20–22] showing the importance of inhibitory LPBN serotonergic mechanisms in the control of ANG II-induced NaCl intake, in this study we investigated the effects of the treatment of the LPBN with methysergide or DOI on DOCA-induced sodium and water intake in rats.

2. Material and methods

2.1. Animals

Male Holtzman rats weighing 260–280 g were used. The animals were housed in individual stainless steel cages with free access to normal sodium diet (Purina Rat Chow) and water. Room temperature was maintained at 23±2°C, with a 12:12 light:dark cycle with light onset at 07:30 h.

2.2. Cerebral cannulas

Rats were anesthetized with tribromoethanol (200 mg/100 g body wt.) and placed in a Kopf stereotaxic instrument. The skull was leveled between bregma and lambda. Stainless steel 23-gauge cannulas were implanted bilaterally into the LPBN using the following coordinates: 9.5 mm caudal to bregma, 2.2 mm lateral to the midline and 4.1 below the dura mater [26]. 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 jeweler screws. Metal obturators (30-gauge) filled the cannulas between tests. After surgery, the rats were allowed to recover for 6 days before drug injection into the LPBN.

2.3. Injections into the LPBN

Injections into the LPBN were made using 10-µl Hamilton syringes connected by polyethylene tubing (PE-10) to 30-gauge injection cannulas. At the 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 in the LPBN was 0.2 µl each site. After injections, the obturators were replaced and the rats were placed back into the cages.

2.4. Drugs

Deoxycorticosterone acetate (DOCA, Sigma, St. Louis, MO) was dissolved in sunflower oil as a solution of 20 mg/ml and one injection of 0.5 ml/rat was performed every other 3 days. Sunflower oil was injected into control rats in the same volume.

Methysergide maleate (Research Biochemicals International, Natick, MA) was dissolved in propylene glycol/water (2:1; vehicle). The dose of methysergide was 4 µg/0.2 µl. DOI (2,5-dimethoxy-4-iodoamphetamine hydrochloride; Research Biochemicals International), was dissolved in saline, and the dose was 5 µg/0.2 µl. The doses of methysergide and DOI were the same injected into the LPBN in previous studies [3,19–22].

2.5. DOCA treatment

Daily water and 1.8% NaCl solution were provided from burettes with 1-ml divisions fitted with metal drinking spouts. Rats were allowed to adapt for 6 days to laboratory conditions with water and 1.8% NaCl measured every 24 h. Subcutaneous injections of DOCA (10 mg/rat) or sunflower oil (control) started on the sixth day, and were repeated every other 3 days until the end of all experiments. Water and 1.8% NaCl intake increased significantly within 6 days after the first injection of DOCA. Beginning on the sixth day of DOCA treatment, 1.8% NaCl solution was offered daily for only 2 h/day for training. NaCl and water intake was recorded during this 2-h period (between 14:00 and 16:00 h) using burettes with 0.1-ml divisions. The water intake during the remaining 22-h period continued to be measured in the 1-ml division burettes.

After 8 days in the 2-h training regimen, the rats were submitted to cerebral surgery to implant LPBN cannulas. Then, the daily 2-h sodium intake session was extended to a further 6 days before starting the experiments with serotonergic agonist and antagonist into the LPBN.

2.6. NaCl and water intake tests

The rats were tested in their home cages. Water and 1.8% NaCl were provided in burettes with 0.1-ml divisions fitted with metal drinking spouts. Water and 1.8% NaCl became available for rats 10 min after the injections into the LPBN. Cumulative water and 1.8% NaCl intake were measured at 15, 30, 60, 90 and 120 min. Each serotonergic drug was injected in two different test days with an interval of 2 days between the tests. In each experimental session, one half of the rats received bilateral LPBN injections of vehicle or saline and the remaining animals
received drug injections into this structure in a counterbal-
anced design.

2.7. Arterial pressure and heart rate recording

At the end of NaCl and water intake tests, the rats were
anesthetized with tribromoethanol (200 mg/kg of body
weight) and a polyethylene cannula (PE 10 connected to a
PE 50 tubing) was inserted into the abdominal aorta
through the femoral artery. The cannula was tunneled
subcutaneously and exposed on the back of the rat neck to
allow access in conscious rats. To record pulsatile arterial
pressure and mean arterial pressure (MAP) the cannula
was connected to a transducer (Stathan P23DB) coupled to
polygraph (Narco Bio System). Heart rate (HR) was
recorded using a biotachometer (Narco Bio System) acti-
vated by arterial pressure pulses. Arterial pressure and HR
were recorded 1 day following the surgery to insert the
arterial cannula.

2.8. Histology

At the end of the experiments, the animals received
bilateral injections of methylene blue solution (0.2 μl) into
the LPBN. They were then deeply anesthetized with
sodium thiopental (50 mg/kg) 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 Giemsa and analyzed by light
microscopy to confirm the injection sites into the LPBN.

2.9. Statistical analysis

The results are reported as means±S.E.M. One- or
two-way repeated measures analysis of variance (ANOVA)
and Newman–Keuls test were used for comparisons.
Differences were considered significant at P<0.05.

3. Results

3.1. Histological analysis

Similarly to previous studies [19–22], most of the
LPBN injection sites were centered in the central lateral
dorsal lateral portions of the LPBN (see Fulwiler and
Saper [9] for definitions of LPBN subnuclei) (Fig. 1).
Some injections reached the ventral lateral and external
dorsal portions, as well as the Kölliker-Fuse nucleus.
Injections also spread into the brachium (superior cerebel-
lar peduncle), or also slightly ventral to this structure,
reaching the dorsal portion of the medial parabrachial
nucleus (MPBN) in some rats. From a total of 37 rats used
in this study, 18 had injections localized as described
above and were considered rats with bilateral LPBN
injections. In order to evaluate whether the effects were
dependent exclusively on drug action into the LPBN, or
whether they were due to drug action on any other area
surrounding the LPBN, including MPBN, we also ana-
yzed: (1) the results from rats (n=8) with injections either
into the brachium, into the MPBN or both (brachium/
MPBN); (2) the results from rats (n=11) with one or both
injections rostral or dorsal to LPBN.

Fig. 1. Photomicrograph of a transverse section showing injection sites, as indicated by the arrows, in the lateral parabrachial nucleus (LPBN).
3.2. Effects of bilateral injections of methysergide or DOI into the LPBN on DOCA-induced 1.8% NaCl and water intake

Bilateral injections of the serotonergic antagonist methysergide (4 μg/0.2 μl, in each site) into the LPBN, increased DOCA-induced 1.8% NaCl intake (32.2±3.9 versus vehicle: 15.0±1.6 ml/2 h) (F(1,18)=15.67; P<0.01) (Fig. 2A). Bilateral injections of the 5HT2A/2C serotonergic agonist DOI (5 μg/0.2 μl, in each site) into the LPBN reduced DOCA-induced 1.8% NaCl intake (6.8±1.7 versus saline: 12.4±1.9 ml/2 h), (F(1,18)=10.68; P<0.01) (Fig. 2A).

Water intake also increased with bilateral injections of methysergide (4 μg/0.2 μl) into the LPBN (12.5±3.5 versus vehicle: 3.2±1.0 ml/2 h) (F(1,18)=6.69; P<0.05) (Fig. 2B). Bilateral injections of DOI (5 μg/0.2 μl) into the LPBN reduced water intake (2.2±0.8 versus saline: 4.4±1.0 ml/2 h) (F(1,18)=6.28; P<0.05) (Fig. 2B).

Bilateral injections of methysergide into the LPBN did not alter 1.8% NaCl intake (F(1,14)=0.01; P>0.05) and water intake (F(1,14)=2.53; P>0.05) in rats that received s.c. injections of vehicle (Fig. 3). Injections of DOI into the LPBN in the same rats also did not alter 1.8% NaCl intake (F(1,14)=0.01; P>0.05) and water intake (F(1,14)=0.34; P>0.05).

3.3. Temporal evolution of daily DOCA-induced 1.8% NaCl and water intake

Fig. 4A shows the results of 24- and 2-h 1.8% NaCl intake induced by s.c. DOCA or vehicle. The 24 h NaCl intake significantly increased in rats treated with sc DOCA (10 mg/rat), compared to the NaCl intake of the same rats before treatment (F(11,99)=11.46; P<0.01) (Fig. 4A). Vehicle did not alter 1.8% NaCl intake (F(11,77)=0.92; P>0.05).

![Fig. 2. (A) Cumulative 1.8% NaCl intake, and (B) cumulative water intake induced by s.c. DOCA (10 mg/rat every other 3 days) in rats treated with bilateral injections of methysergide (methy, 4 μg/0.2 μl) or vehicle (veh), DOI (5 μg/0.2 μl) or saline (sal) into the LPBN. Results are expressed as means±S.E.M., n=number of rats. *Different from veh or sal (P<0.05, Newman–Keuls test).](image1)

![Fig. 3. (A) Cumulative 1.8% NaCl intake, and (B) cumulative water intake in rats treated with s.c. sunflower oil (0.5 ml/rat each 3 days) following bilateral injections of methysergide (methy, 4 μg/0.2 μl) or vehicle (veh), DOI (5 μg/0.2 μl) or saline (sal) into the LPBN. Results are expressed as means±S.E.M., n=number of rats.](image2)
In comparison to vehicle-treated rats, the 24-h NaCl intake ($F(1,16)=16.05; P<0.01$) or 2-h NaCl intake ($F(1,16)=38.05; P<0.01$) of DOCA-treated animals was also enhanced (Fig. 4A).

Daily 24 h water intake increased in rats treated with s.c. DOCA compared to the intake before treatment ($F(33,306)=6.08; P<0.01$), or compared to vehicle treated rats ($F(1,456)=108.17; P<0.01$) (Fig. 4B). Two-hour/day water intake also increased in rats treated with s.c. DOCA (2.6±0.6 versus vehicle: 1.5±0.3 ml/2 h on the 13th day, and 3.0±0.9 versus vehicle: 0.6±0.2 ml/2 h on day 33) ($F(1,120)=9.65; P<0.01$). Bilateral injections of methysergide (4 mg/0.2 ml) or DOI (5 μg/0.2 μl) into the brachium/MPBN did not change DOCA-induced 1.8% NaCl and water intake (Table 1). DOCA-induced 1.8% NaCl and water intake was also not altered in rats in which one or both injections of methysergide were performed in sites rostral or dorsal to LPBN (Table 2). DOI reduced DOCA-induced 1.8% NaCl intake in rats with one or both injections rostral or dorsal.

3.4. Effects of injections of methysergide or DOI outside the LPBN on DOCA-induced 1.8% NaCl and water intake

The specificity of LPBN as the site where injections of methysergide or DOI produced the reported effects was confirmed by results from rats in which the injections were not performed into the LPBN. Bilateral injections of methysergide (4 μg/0.2 μl) or DOI (5 μg/0.2 μl) into the brachium/MPBN did not change DOCA-induced 1.8% NaCl and water intake.
Table 1
Cumulative 1.8% NaCl and water intake in rats treated with DOCA (10 mg/rat every other 3 days) s.c. and bilateral injections of methysergide (4 μg/0.2 μl) or vehicle, DOI (5 μg/0.2 μl) or saline into the brachium/MPBN.

<table>
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<tr>
<th>LPBN treatments</th>
<th>Time (min)</th>
<th>15</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
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<td>1.8% NaCl intake (ml)</td>
<td>Vehicle</td>
<td>7.8±1.4</td>
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<td>12.3±3.9</td>
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<td>Saline</td>
<td>9.0±2.0</td>
<td>10.9±2.4</td>
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<td></td>
<td>DOI</td>
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<td>7.2±1.4</td>
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<tr>
<td>Water intake (ml)</td>
<td>Vehicle</td>
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<td>Saline</td>
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<td>DOI</td>
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<td>0.6±0.3</td>
<td>1.0±0.4</td>
<td>1.5±0.5</td>
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* Results are expressed as means±S.E.M. ANOVA indicated no significant difference in 1.8% NaCl intake comparing methysergide and vehicle (F(1,14)=1.78; P>0.05) or DOI and saline (F(1,14)=2.81; P>0.05). ANOVA also indicated no significant difference in water intake comparing methysergide and vehicle (F(1,14)=0.83; P>0.05) or DOI and saline (F(1,14)=0.33; P>0.05). n=8 rats.

to LPBN (Table 2), an effect possible to obtain with unilateral injection of the agonist into the LPBN.

4. Discussion

Bilateral injections of the serotonergic receptor antagonist methysergide into the LPBN increased 1.8% NaCl intake, and the injection of the serotonergic 5HT2A/2C receptor agonist DOI into the LPBN reduced 1.8% NaCl intake induced by sc DOCA treatment in rats. Methysergide into LPBN also produced a 4-fold increase in water intake while DOI reduced water intake.

The participation of the inhibitory serotonergic mechanisms of the LPBN on the control of hypertonic NaCl and water intake induced by ANG II-dependent stimuli (e.g., i.c.v. ANG II, ANG II in the SFO, FURO+CAP, 24 h sodium depletion, 24 h water deprivation, s.c. isoproterenol) has been previously demonstrated [3,19–22]. The present results extend the importance of the inhibitory serotonergic mechanisms of the LPBN to mineralocorticoid-dependent NaCl intake.

Bilateral injections of methysergide in rats that received sunflower oil did not change 1.8% NaCl intake. This is consistent with previous observations showing that the deactivation of the inhibitory serotonergic mechanisms of the LPBN alone has no effect on NaCl intake, i.e., methysergide into the LPBN did not change NaCl intake in satiated rats [20,21]. In the present work the animals were tested during a 2-h period of access to 1.8% NaCl, instead of 24-h free access used in previous studies, and thereby showed some intake of this solution in this short period of time without any treatment. It is important to point out that 2-h 1.8% NaCl intake was not enhanced by LPBN

Table 2
Cumulative 1.8% NaCl and water intake induced by s.c. DOCA (10 mg/rat each 3 days) in rats in which one or both injections of methysergide (4 μg/0.2 μl) or vehicle, DOI (5 μg/0.2 μl) or saline were performed in sites rostral or dorsal to LPBN.

<table>
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<th>LPBN treatments</th>
<th>Time (min)</th>
<th>15</th>
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<th>90</th>
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<td>Vehicle</td>
<td>10.6±2.4</td>
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<td>Saline</td>
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<td>Water intake (ml)</td>
<td>Vehicle</td>
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* Results are expressed as means±S.E.M. ANOVA indicated no significant difference in 1.8% NaCl intake (F(1,20)=0.32; P>0.05) and water intake (F(1,20)=0.27; P>0.05) comparing methysergide and vehicle. No significant difference was also observed on water intake comparing DOI and saline (F(1,20)=0.55; P>0.05). Significant differences in 1.8% NaCl intake were observed comparing DOI and saline (F(1,20)=9.58; P<0.05). *Different from saline (Newman–Keuls test). n=8 rats.
methysergide treatments when animals were in a need-free state. This is in spite of the fact that there is measurable NaCl intake when control and experimental animals are given access to the hypertonic NaCl for the 2-h period. Therefore, it seems as if LPBN 5-HT related mechanisms only modulate the NaCl and water intake induced by dehydration/sodium depletion states or conditions (e.g., increased hormones) mimicking those states of depletion.

Mineralocorticoid-induced NaCl intake has been shown to depend on central actions of mineralocorticoids and amygdala is an important site for their effects [10,28]. Neurons from the LPBN project to forebrain areas related to sodium taste and mineralocorticoid control of sodium appetite, like amygdala and preoptic area [2,12,13,17,30]. Amygdala is one of the brain regions with the highest uptake of aldosterone [23] and efferent discharges of distinct subnuclei of the parabrachial nucleus seem to control distinct subnuclei in the amygdala [15]. Chemical or electrolytic lesions of specific parts of the amygdala, like central and medial nuclei, reduce sodium, but not water intake, induced by ANG II and mineralocorticoids [10]. Injections of antisense nucleotides for mineralocorticoid receptors into the medial amygdala also reduce 3% NaCl intake induced by DOCA [28]. Further, DOCA also increases the number of preoptic neurons specifically excited by salty solutions applied to the tongue [24]. Thus, since the LPBN also receives projections from AP and mNTS, including projections from primary gustatory relay neurons from the NTS [11,18,25,29] and sends projections to forebrain areas, it is in a position to intermediate the sensory information from the hindbrain to forebrain areas controlling sodium intake.

In an ascending pathway from AP/mNTS to LPBN 5HT has been identified as a neurochemical component [18]. Menani et al. [20] have proposed that the pathway from AP/mNTS to LPBN may convey information related to blood pressure and blood volume signaled from cardiopulmonary and/or arterial baroreceptor afferent information that plays inhibitory role on NaCl and water intake. Therefore methysergide injections into the LPBN might impair this central pathway, removing the inhibitory signals that control ANG II or mineralocorticoid-induced water and NaCl intake.

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