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Research Report

Activation of serotonergic 5-HT_{1A} receptors in the lateral parabrachial nucleus increases NaCl intake

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Abstract

Previous studies using non-specific serotonergic agonists and antagonists have shown the importance of serotonergic inhibitory mechanisms in the lateral parabrachial nucleus (LPBN) for controlling sodium and water intake. In the present study, we investigated whether the serotonergic 5-HT_{1A} receptor subtype in the LPBN participates in this control. Male Holtzman rats had cannulas implanted bilaterally into the LPBN. Bilateral injections of the 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT, 0.1, 1.25, and 2.5 μg/0.2 μl), into the LPBN enhanced 0.3 M NaCl and water intake of rats injected subcutaneously with the diuretic furosemide (10 mg/kg bw) and a low dose of the angiotensin-converting enzyme inhibitor, captopril (5 mg/kg bw). The increase in NaCl intake produced by 8-OH-DPAT injections was reduced in dose-related manner by pre-treating the LPBN with the selective 5-HT_{1A} serotonergic antagonist, WAY-100635 (WAY, 1 and 2 μg/0.2 μl). In contrast, WAY did not affect water intake produced by 8-OH-DPAT. WAY-100635 injected alone into the LPBN had no effect on NaCl ingestion. Injections of 8-OH-DAPT (0.1 μg/0.2 μl) into the LPBN also increased 0.3 M NaCl intake induced by 24-h sodium depletion (furosemide, 20 mg/kg bw plus 24 h of sodium-free diet). Serotonin (5-HT, 20 μg/0.2 μl) injected alone or combined with 8-OH-DPAT into the LPBN reduced 24-h sodium depletion-induced 0.3 M NaCl intake. Therefore, the activation of serotonergic 5-HT_{1A} receptors in the LPBN increases stimulated hypertonic NaCl and water intake, while 5-HT injections into the LPBN reduce NaCl intake and prevent the effects of serotonergic 5-HT_{1A} receptor activation.
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1. Introduction

The lateral parabrachial nucleus (LPBN) is a pontine structure that lies dorsolateral to the superior cerebellar peduncle. Recent studies have shown the existence within the LPBN of important serotonin-related control mechanisms for water and NaCl intake [5,10,11,25–29]. For example, injections of the non-selective serotonin (5-HT) receptor antagonist, methysergide, directly into the LPBN markedly increase NaCl intake following several experimental procedures, including injections of angiotensin II (ANG II) either icv or into the subfornical organ (SFO), water deprivation, sodium depletion, and injections of deoxycorticosterone acetate (DOCA) [5,10,25,27]. Injections of the 5-$HT_{2A/2C}$ receptor agonist 2,5-dimetoxy-4-iodoamphetamine hydrobromide (DOI) into the LPBN reduce water and NaCl intake after acute sodium depletion [26] or DOCA treatment [10]. A recent microdialysis study showed that levels of 5-HT and its metabolite, 5-hydroxy-

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indoleacetic acid (5-HIAA), increased in the LPBN of acute fluid depleted rats that were permitted to drink water and concentrated (0.3 M) NaCl. Levels of these substances significantly decreased in the LPBN if rats were not allowed to drink [35]. The results of these studies using drug injections and microdialysis strongly suggest the existence of a serotonergic mechanism in the LPBN related to the control of water and NaCl intake.

The role of specific serotonergic receptor subtypes in the control of water and NaCl intake has been investigated mainly by injecting specific serotonergic agonists or antagonists systemically or into forebrain areas. Peripheral treatments with the selective serotonergic 5-HT_{1A} receptor agonists gepirone, ipsapirone, and 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) increase stimulated NaCl intake, while peripheral administration of the serotonergic 5-HT_{2C} receptor agonist MK-212 inhibits water and NaCl intake [6–9]. Water and NaCl intake are also inhibited by the serotonergic 5-$HT_{2B/2C}$ receptor agonist mCPP and by injection of the serotonergic 5-HT_3 receptor agonist *m*-chlorophenylbiguanide into the 3rd cerebral ventricle [2,3]. The effects of DOI injected into the LPBN are similar to the effects produced by injections of 5-HT_2 receptor agonists peripherally or into the forebrain. It is likely that the effects of peripheral injections of the serotonergic 5-HT_{1A} receptor agonists are due to their central action, but no previous studies have reported the effects of injections of 5-HT_{1A} agonists and antagonists into specific brain structures on water and NaCl intake.

Serotonergic 5-HT_{1A} receptors are located pre-synaptically as somatodendritic receptors on 5-HT neurons, mainly in the dorsal and median raphe nuclei. They are also located post-synaptically in other brain regions, notably in limbic and cortical regions [12]. Despite close proximity of the LPBN to the raphe nuclei, 5-HT_{1A} receptors in the LPBN have not been characterized regarding their pre-synaptic or post-synaptic location. Activation of 5-HT_{1A} receptors causes neuronal hyperpolarization, thus reducing 5-HT release [1,20]. In the ventral tegmental area, the 5-HT_{1A} and 5-HT_{2A} receptors are localized pre- or post-synaptically, especially in dopaminergic neurons [13,14].

Considering the importance of LPBN serotonergic mechanisms in the control of water drinking and NaCl intake and the effects of peripheral injections of the serotonergic 5-HT_{1A} receptor agonist 8-OH-DPAT on sodium appetite, the present study investigated the involvement of LPBN 5-HT_{1A} receptors in the control of water and 0.3 M NaCl intake. For this purpose, we tested the effects of bilateral injections of 8-OH-DPAT into the LPBN either alone or combined with the specific serotonergic 5-HT_{1A} receptor antagonist WAY-100635 (WAY) on water and 0.3 M NaCl intake induced by acute fluid depletion produced by combining subcutaneous (sc) injections of the diuretic furosemide (Furo) and a low dose of the angiotensin-converting enzyme inhibitor captopril (Cap) [11,17,26,35–37]. In addition, no previous study has investigated the effects of serotonin (5-HT) injected into the LPBN on sodium intake or whether serotonergic 5-HT_{1A} receptor activation affects water and NaCl intake by reducing 5-HT release within the LPBN. Therefore, we also tested the effects of 8-OH-DPAT and 5-HT injected alone, or together, into the LPBN on 0.3 M NaCl intake induced by 24-h sodium depletion.

2. Material and methods

2.1. Animals

Male Holtzman rats weighing 280–300 g were used. The animals were housed in individual stainless steel cages with free access to standard sodium diet (Purina Rat Chow), water and 0.3 M NaCl solution. Rats were maintained on a 12:12 light/dark cycle (light onset at 7:30 AM) in a room with controlled temperature (23 ± 1 °C) and humidity (55 ± 10%).

2.2. Cerebral cannulas

Rats were anesthetized with tribromoethanol (200 mg/100 g bw) 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 mm below the dura mater [32]. 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. A 30-gauge metal obturator filled the cannulas between tests. After surgery, the rats were allowed to recover 6 days before drug injections into the LPBN.

2.3. 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 cannulas. At the time of testing, the rats were removed from the home cage, the obturators were removed, and the injection cannulas were introduced into the brain. The injection cannulas extended 2 mm beyond the tips of the guide cannulas upon insertion. The animals were held by hand during the injections. The injection volume was 0.2 μl per site. After the injections, the obturators were replaced, and the rats were placed back into their cages.

2.4. Drugs

Furosemide and captopril were purchased from Sigma Chem. Co., St. Louis, MO. The 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*n*-propylamino) tetralin hydrobromide (8-OH-DPAT), the 5-HT_{1A} receptor antagonist, *n*-[4-(2-

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