Role of the lateral parabrachial nucleus in the control of sodium appetite

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Menani JV, De Luca LA Jr, Johnson AK. Role of the lateral parabrachial nucleus in the control of sodium appetite. Am J Physiol Regul Integr Comp Physiol 306: R201–R210, 2014. First published January 8, 2014; doi:10.1152/ajpregu.00251.2012.—Instates of kidney, brain, and peripheral systems, animals continuously lose water and electrolytes to the external environment, but specific autonomic, hormonal, and behavioral mechanisms operate continuously to adjust and restore body fluid-electrolyte balance. The rate of loss from the kidneys is primarily controlled by neural and hormonal actions, but loss may also occur passively through the largely uncontrolled processes of respiration (evaporation), perspiration, transpiration, and salivation. These later modes of loss are referred to as insensible loss because they cannot be easily measured. Severe loss of both sodium and water may also occur in disorders associated with emesis and diarrhea. However, despite such ongoing challenges, the osmolarity and volume of body fluids are maintained within reasonably narrow limits, thus allowing normal metabolic and cardiovascular functions. Although renal mechanisms can slow water and sodium loss, the restoration of fluid homeostasis is only made possible by the mobilization of behaviors that result in the ingestion of water and sodium (usually NaCl). The behavioral responses of seeking out and consuming water and salty substances involve the motivational states of thirst and salt appetite. Salt appetite is also frequently referred to as sodium appetite and salt or sodium hunger. The state of sodium appetite can be experimentally induced, tested, and operationally defined by the ingestion of hypertonic NaCl solutions (in most cases 0.3 or 0.5 M NaCl) at concentrations that are usually aversive to rats in sodium balance (5, 50, 76, 77).

The behavioral, endocrine, and autonomic mechanisms that control sodium balance involve an extensive central circuitry composed of both forebrain and hindbrain structures (5, 50, 76, 77). Within this brain circuitry, the lateral parabrachial nucleus (LPBN) stands as an important hindbrain region playing a pivotal role in the control of water and sodium intake. This review begins by presenting an overview of the neural and humoral mechanisms controlling behaviors associated with body fluid homeostasis. It then turns to focus on 1) the role of the LPBN in the control of sodium intake by the rat, 2) how different neurotransmitters acting in the LPBN are related to behavioral inhibitory mechanisms, and 3) a current understanding of how LPBN-dependent inhibitory mechanisms interact with facilitatory processes to control sodium intake.
BODY-BRAIN SIGNALING AND THE CENTRAL NERVOUS SYSTEM NEURAL NETWORK MAINTAINING BODY FLUID HOMEOSTASIS

The subfornical organ (SFO) and the organum vasculosum of the lamina terminalis (OVLT), located in the forebrain, and the area postrema (AP) and the nucleus of the solitary tract (NTS), located in the hindbrain, are sensory portals through which body fluid-related information enters the brain to be processed to coordinate mechanisms that control water and sodium intake. Areas comprising this neural network include the median preoptic nucleus (MnPO), septal area (SA), medial and lateral hypothalamus, bed nucleus of the stria terminalis (BNST), nucleus acumbens, parvocellular ventral postero medial thalamic nucleus, and parabrachial nucleus (PBN) (2–5, 27, 32–44, 75–77, 86, 88–97, 105, 106, 108, 113, 115–117, 120, 132, 133).

A decrease in blood volume releases humoral factors that act on the brain to facilitate sodium and water intake. Specifically, angiotensin II (ANG II) acts in conjunction with mineralocorticoids (aldosterone) to generate sodium intake (50, 76, 77) and hyperosmolality to produce thirst (76, 77). In contrast, blood volume expansion releases humoral factors, such as atrial natriuretic peptide (ANP), which inhibit salt and water intake (5, 6, 14, 49). Other agonists and receptor subtypes, such as oxytocin and α2-adrenergic receptors, act in the brain to inhibit behavioral responses that expand body fluids (12, 13, 39, 40, 48, 93, 123, 125).

ANG II and hyperosmolality act on sites that function as sensory structures, specifically the OVLT, SFO, and AP, which are located outside the blood-brain barrier. In some cases they also act on structures located within the blood-brain barrier such as the supraoptic nucleus of the hypothalamus (25, 26, 75–77, 84, 86, 118, 119). ANG II acts on angiotensin type I receptors (AT1-R), which are present in neurons and which by activating two different intracellular pathways have been proposed to lead to either water or sodium intake (31, 75–77, 86). Hyperosmolality activates nonselective cation channels (e.g., transient receptor potential vanilloid-related channels) and hypernatremia activates Na+ channels (25, 26, 84, 118, 119).

The NTS contains the first synapse in the central nervous system (CNS) that receives input from systemic visceral receptors. Signals that arise from peripheral high- and low-pressure baroreceptors (23, 30) can inhibit thirst and sodium appetite when blood volume is expanded or blood pressure is high and facilitate thirst and salt intake when pressure and volume are low (79, 112, 128, 129). Other systemic visceral receptors and afferents including osmoreceptors, taste receptors (36, 67, 76, 77), and possibly renal receptors (127) also influence thirst and sodium intake.

Mineralocorticoid receptors (MR) implicated in the control of sodium intake are located in both the forebrain and hindbrain at areas, which have direct anatomical and physiological links with the LPBN (53, 60, 62–67, 102, 115, 117, 132, 133). In the forebrain, electrolytic lesions or injections of antisense oligodeoxynucleotides against MR into components (medial or central nuclei) of the amygdala abolish sodium appetite induced by the peripheral administration of aldosterone (ALDO) or deoxycorticosterone acetate (DOCA) (60, 102, 115, 117, 133). Direct administration of aldosterone or DOCA into the amygdala of sodium-replete rats also induces hypertonic NaCl intake (115). In addition, lesions of the BNST, an anatomical extension of central amygdala, reduce experimentally induced sodium intake (108, 132).

In the hindbrain, ALDO-sensitive neurons of the NTS have been implicated in the control of sodium intake (62–67). These neurons, referred to as HSD2 neurons, coexpress MR and the enzyme 11 β-hydroxysteroid dehydrogenase type 2 (HSD2) (62–67). The HSD2 enzyme inactivates endogenous glucocorticoids and thus allows only ALDO to access the MR (104). HSD2 neurons connect with the LPBN and amygdala (64, 65) and are likely to play a role in sodium homeostasis because they are activated in sodium-depleted rats and inactivated by sodium ingestion (62–67). Chronic infusions of ALDO into the fourth ventricle strongly increase daily sodium intake, whereas the injection of the mineralocorticoid antagonist RU 28318 into the fourth ventricle acutely reduces sodium depletion-induced NaCl intake (53). This suggests that ALDO acting on MR in the hindbrain, and most likely on cells containing HSD2 in the NTS, activates an important mechanism involved in the control of sodium appetite (53).

Major Neurohumoral Factors Inhibiting Water and/or Sodium Intake

**Oxytocin.** There is an inverse correlation between oxytocin secretion from the posterior pituitary and sodium appetite. Oxytocin release in the brain seems to parallel the secretion of this hormone into the blood, and oxytocin in both systems is activated by similar stimuli, including ANG II (12, 45, 46, 123). However, the oxytocin found and released in the CNS inhibits sodium appetite (12–14, 121–124). Intracerebroventricular (icv) injections of oxytocin reduce sodium intake (12–14), and central delivery of an oxytocin receptor antagonist, or the destruction of brain neurons containing oxytocin receptors by oxytocin conjugated to the cytotoxic ricin, increase hypertonic NaCl intake in rats treated with a central injection of ANG II (12, 123). The inactivation of central neurons containing oxytocin receptors also reduces hyperosmolarity-induced inhibition of sodium intake (13, 14). The central release of oxytocin by ANG II might explain why acute administration of ANG II immediately induces thirst, and only later when oxytocin release is reduced as a result of the dilution of body fluids by the ingested water is sodium appetite expressed (12).

**Atrial natriuretic peptide.** ANP and oxytocin are both secreted under conditions of body fluid volume expansion. In addition to the inhibition of water and sodium intake, both peptides act on the kidney to increase diuresis and natriuresis (5). The intracerebroventricular injection of ANP reduces water and sodium intake induced by water deprivation, sodium depletion, or central injections of ANG II (5, 6, 49). Central administration of antibodies against ANP or the inactivation of brain neurons containing ANP receptors with intracerebroventricular injections of ANP conjugated to the cytotoxin ricin increase hypertonic NaCl intake in response to ANG II or hypovolemia (14, 56).

**Central α2 adrenergic mechanisms.** Norepinephrine acting centrally has a dual role in the control of sodium and water intake. Acting on forebrain α1- or hindbrain α2-adrenoceptors, norepinephrine facilitates both behaviors. In contrast, acting on forebrain α2-adrenoceptors, norepinephrine inhibits them (10,
Similar to norepinephrine, either intracerebroventricular or forebrain parenchymal injections into the lateral hypothalamus, medial septal area, or preoptic area of $\alpha_2$-adrenoceptor agonists (e.g., $\alpha$-methylnorepinephrine) or of $\alpha_2$-adrenergic-imidazoline receptor agonists (e.g., clonidine or moxonidine) also inhibit water and sodium intake (39, 40, 47, 93, 125). The effects of $\alpha_2$-adrenoceptor or $\alpha_2$-adreno/imidazoline receptor agonists on sodium and water intake are reversed by the pretreatment with $\alpha_2$-adrenoceptor antagonists (e.g., yohimbine, RX 821002, or SK&F86466), which suggests that the activation of $\alpha_2$-adrenoceptors plays a role in the inhibition of water and sodium intake (40, 47, 93, 125). The increased efficacy provided by the imidazoline moiety to several $\alpha_2$-adrenoceptor agonists and antagonists suggests a synergic action between imidazoline receptors and $\alpha_2$-adrenoceptors acting to inhibit water and salt intake (40, 93, 125).

Peripheral administration of clonidine and moxonidine also inhibits water and sodium intake, whereas peripheral administration of yohimbine has the opposite effect (40, 57, 93, 132). Central antagonism of $\alpha_2$-adrenoceptors by yohimbine or RX 821002 reduces the antinatriorexigenic effects of lipopolysaccharide, which suggests that central adrenergic mechanisms are involved in the inhibition of sodium intake in pathological conditions such as bacterial or viral infections (1).

Serotonin. Serotonin receives particular attention here because it is associated with the initial findings and subsequent work that focuses research on the role of the LPBN in the control of salt and water intake. Several pharmacological studies indicate that endogenous serotonin acts on different receptor subtypes (e.g., 5HT1, 5HT2, 5HT3), particularly in the forebrain, to inhibit sodium appetite (19, 29, 52, 58, 114). Drinking studies in the pigeon suggest that an homologous serotonergic system inhibits fluid intake in both birds and mammals (18). Consistent with the inhibitory effect that serotonin receptor activation has on sodium appetite, early studies also showed that when given systemically, agonists that reduce serotonin release or antagonists that act on 5HT2 receptors increase sodium intake (29, 114).

Studies showing enhanced sodium intake in rats with electrolytic or ibotenic acid lesions in the dorsal raphe nucleus (DRN) suggest that the DRN is a source of endogenous serotonin that inhibits salt appetite (20, 21). Such inhibition is possibly linked to reduced ANP release and modulation of forebrain activity in circumventricular organs (9, 87, 109, 110). Moreover, in sodium-depleted rats, the ingestion of hypertonic or isotonic saline results in reduced activity in serotonin neurons of the DRN (54, 69). Together these results suggest that DRN serotonergic neurons are associated with the process of satiating sodium appetite.

**IMPORTANCE OF THE PBN FOR THE CONTROL OF WATER AND SODIUM INTAKE**

The PBN is a pontine structure composed of several cell groups located around the superior cerebellar peduncle, which is also known as the brachium. In the human brain, the PBN is divided into the medial and lateral parabrachial nuclei (MPBN and LPBN, respectively) according to its position in relation to the brachium. According to Paxinos and Watson (107), the same divisions also apply for the rat brain. However, because of the position of the brachium in the rat brain, the MPBN and LPBN lie ventromedial and dorsolaterally to the brachium, respectively (see Fig. 1 for the position of these structures in the rat brain).

The PBN receives projections from the NTS and AP. These inputs convey information arising from peripheral receptors, and the PBN in turn projects to other hindbrain and forebrain areas controlling water and sodium intake (76, 77). The PBN is
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LPBN INHIBITORY MECHANISMS FOR SODIUM INTAKE

Neurotransmitter and Receptor Distribution in the LPBN: Basis for Neuropharmacological Studies

Serotonergic, adrenergic, and noradrenergic neurons are present in projections from the AP/NTS to the LPBN, and binding and immunohistochemical studies indicate the presence of 52-adrenergic sites in the LPBN (70, 83, 98). There is evidence from both receptor binding and in situ hybridization studies indicating that there are GABA receptors in the PBN (7, 16). Opioid receptors and enkephalin are present in the LPBN, and the activation of GABA and -opioid receptors in LPBN increases potassium conductance, inhibiting neural activity as a result of hyperpolarization (22, 130). Whole cell electrophysiological recordings in rat brain slices also showed that most (62%) LPBN neurons tested responded to GABA superfusion, and in most cases this response was attenuated by the GABAA antagonist bicuculline (80). Glutamate, cholecystokinin (CCK), and corticotropin-releasing factor (CRF) have also been identified in the parabrachial nucleus (15, 68, 78).

In rat, serotonergic, catecholaminergic, glutamatergic, cholecystokininergic, opioid, and CRF immunoreactive neurons are found in the pathway from the AP/NTS to the LPBN (68, 72, 83, 85, 98, 111). GABAergic and CRF immunoreactive neurons are present in the projections from the CeA to the LPBN (74, 99). It is also likely that there are GABAergic interneurons in the LPBN. Among other neuropeptides, enkephalin- and CRF-like immunoreactive neurons are particularly numerous within areas of the BNST that project to the PBN (100). Enkephalin-, dynorphin-, and CRF-immunoreactive neurons are also described in the projections from several hypothalamic nuclei to the PBN (101).

LPBN and thirst. Initial studies on the role of the LPBN in the control of fluid and electrolyte balance were directed at investigating hindbrain control of water intake. Results from these experiments showed that electrolytic or neurotoxic lesions of the LPBN increased thirst induced by manipulations that are related to the depletion of extracellular fluid but not to the reduction of intracellular volume (44, 105, 106). Also the inactivation of LPBN neurons with bilateral injections of lidocaine or by nonselective antagonism of serotonin receptors by injecting methysergide into the LPBN increased ANG II-induced water intake (94). Such results suggested that inhibitory mechanisms in the LPBN are involved in the control of the magnitude of drinking induced by ANG II (94) and paved the way for studies that demonstrated an inhibitory role for the LPBN in the control of sodium appetite.

LPBN and sodium appetite: enhanced sodium intake associated with accompanying dipsogenic or natriorexigenic challenges. When the LPBN was injected with methysergide at the same time ANG II was injected intracerebroventricularly, rats with access to both water and 0.3 M NaCl showed remarkably large intakes of normally aversive hypertonic NaCl (96). Usually, acute intracerebroventricular injections of dipsogenic doses of ANG II produce only modest, if any, intake of 0.3 or 0.5 M NaCl. However, ANG II (50 ng/µl) injected intracerebroventricularly 15 min after bilateral LPBN injections of methysergide (4 µg/0.2 µl) induces a robust ingestion of 0.3 M NaCl that is accompanied by increased water intake (Fig. 2; 96). These results suggest that serotonin acts in the LPBN to inhibit both ANG II-induced sodium appetite and thirst. The typical sites of bilateral LPBN injections are illustrated in Fig. 1. Besides increasing intracerebroventricular ANG II-induced water and 0.3 M NaCl intake, bilateral LPBN injections of methysergide also increase water and/or 0.3 M NaCl intake induced by several other natriorexigenic and dipsogenic treatments (Table 1).

Methysergide injections into the LPBN increase sodium appetite induced by ANG II administered into the SFO or by different treatments that activate the circulating renin-angiotensin system such as sodium depletion, water deprivation, acute subcutaneous injection of the diuretic furosemide (Furo), or a combined treatment of subcutaneous Furo with a low subcutaneous dose of the angiotensin-converting enzyme inhibitor captopril (CAP) (27, 90–92, 94, 96). In contrast to the effects of methysergide, LPBN injections of the 5HT2 receptor agonist 2.5-dimethoxy-4-iodoamphetamine hydrochloride (DOI) reduces Furo + CAP-induced 0.3 M NaCl intake (96). Consistent with these functional results, the release of serotonin and its metabolite 5-hydroxyindoleacetic acid is reduced in the PBN after Furo + CAP treatment and enhanced by 0.3 M NaCl intake (126).

Further investigation also showed that the enhancing effects of methysergide are not restricted to the effects of ANG II on hypertonic sodium chloride intake. Methysergide injected into the LPBN also increases sodium appetite in rats treated with subcutaneous DOCA (37). Interestingly, the combination of methysergide injected into the LPBN along with intragastric 2 M NaCl also results in what seems a paradoxical ingestion of 0.3 M NaCl (38). Treatments that induce cellular dehydration typically only produce water intake. Although intracerebroven-
tricular carbachol, subcutaneous isoproterenol, or intracerebroventricular relaxin usually only elicit water intake, they induce a significant sodium appetite when combined with LPBN methysergide injections (88, 89, 92).

It is important to emphasize that bilateral LPBN injections of methysergide by itself in fluid replete rats produces no water or hypertonic NaCl intake. This indicates that only blocking the action of serotonin in the LPBN without the presence of some type of facilitating factor is not sufficient to induce sodium or water intake. On the other hand, sodium intake is easily generated when attenuation of LPBN serotonergic inhibitory mechanisms is combined with either a dipsogenic or a natriorexigenic stimulus. This suggests that the LPBN acts strongly to inhibit sodium intake (27, 90–92, 94, 96).

Other neurotransmitters in addition to serotonin act to inhibit sodium intake under dipsogenic or natriorexigenic conditions. Similar to methysergide, blockade of CCK, CRF, or glutamate receptors, or activation of either α2-adrenoceptors or purinergic P2 receptors in the LPBN increases 0.3 M NaCl intake induced by Furo + CAP or 24 h sodium depletion (2, 33–35, 61, 95, 97). Just like methysergide, LPBN injections of these agents have no effect on sodium appetite or thirst in rats unless they are accompanied by a dipsogenic or natriorexigenic treatment (2, 33–35, 61, 95, 97).

**LPBN and sodium appetite: “de novo” sodium intake under sodium-replete and euhydrated conditions.** In contrast to the effect that serotonin, CCK, CRF, or glutamate antagonists have in the presence of a dipsogenic or natriorexigenic signal, LPBN injections of GABA_A, GABA_B, or opioid receptor agonists produce sustained salt and water intakes lasting 3 to 4 h without the need for any concomitant treatment (3, 17, 41, 42, Fig. 3). These results suggest that blocking LPBN neuronal activity with the injections of GABA or opioid receptor agonists attenuates a tonic inhibitory mechanism that normally restrains sodium appetite and thirst.

**Significance of Multiple Neurotransmitter Receptors in the Control of Sodium Appetite**

The various neurotransmitter/neuromodulators involved in inhibitory mechanisms acting within the LPBN can be grouped under those that act in the presence of a dipsogenic/natriorexigenic signal and those that act in the absence of such signals. Whereas the deactivation of LPBN inhibitory mechanisms produced by the blockade of serotonin, CCK, CRF, or glutamate receptors, or the activation of α2-adrenoceptors or purinergic receptors, requires the presence of additional signals associated with sodium and water deficits, GABAergic or opioid activation in the LPBN is sufficient to drive fluid replete rats to ingest hypertonic saline in quantities that easily surpass the amount ingested by sodium-depleted animals.

It is possible that the manipulation of those neurotransmitters/receptors that require the synergistic assistance of accompanying dehydration or sodium deficiency does not elicit sodium intake in hydrated animals because, in contrast to GABAergic activation, it does not remove a sufficient amount of tonic inhibition. It seems reasonable to speculate that the manipulation of those neurotransmitters/receptors that require the synergistic assistance of accompanying dehydration or sodium deficiency would be effective in fluid replete rats if a critical number of other restraining inhibitory influences were also blocked. Without sufficient suppression of multiple inhibitory influences that converge on the LPBN, the threshold for removing the tonic inhibitory influence projected to the fore-
The effects of GABAA receptor activation may depend on the interaction between LPBN and angiotensinergic mechanisms (27, 90). This type of interaction between LPBN and angiotensinergic mechanisms has been recently explored in relation to the effects of the GABA<sub>A</sub> agonist muscimol on hydrated rats.

Brain is not reached and sodium intake is not released in fluid replete rats.

A possibility to consider is that the various types of inhibitory input that converge on the LPBN use different neurochemical codes. For example, input from arterial baroreceptors might use serotonin as an inhibitory signal, whereas inhibition generated by the taste of a highly concentrated salt solution might use CCK as an inhibitory signal. Experiments testing such a hypothesis have yet to be conducted.

Interaction between different neurotransmitters/receptors is also possible as suggested by preliminary results showing that the increased sodium intake produced by the activation of α<sub>2</sub>-adrenoceptors in the LPBN depends at least partially on GABA<sub>A</sub>, opioid, and purinergic receptor activation. In addition, the effects of GABA<sub>A</sub> receptor activation may depend partially on opioid receptor activation.

Some neurotransmitters like serotonin and CCK may act in the LPBN based on a model of cooperativity and interdependence (35). According to this model, elevated serotonin release and action tend to increase the release and effects of CCK and vice versa. The interdependence assumption is that both 5-HT and CCK acting at their respective receptors is a necessary condition for the normal inhibition of ingestive behaviors.

**INTERACTION BETWEEN FOREBRAIN FACILITATORY AND LPBN INHIBITORY MECHANISMS CONTROLLING SODIUM INTAKE**

Early indications that the LPBN interacts with forebrain mechanisms derived from functional studies where angiotensinergic antagonism in the forebrain was combined with muscimol injection into the LPBN (27, 90). This type of interaction between LPBN and angiotensinergic mechanisms has been recently explored in relation to the effects of the GABA<sub>A</sub> agonist muscimol on hydrated rats.

Muscimol injected into the LPBN induces large intakes of water and 0.3 M NaCl in fluid replete rats (8, 113). This effect is almost abolished by the blockade of either AT<sub>1</sub> or muscarinic receptors with intracerebroventricular injections of losartan or atropine (8, 113). This suggests that the increase in water and hypertonic saline intake produced by LPBN muscimol injections must depend on a combination of blockade of LPBN inhibitory mechanisms, while at the same time there must be facilitation that arises from tone generated by angiotensinergic and cholinergic mechanisms (8, 113). However, at the present time it is not known whether that tone is tonic or phasic in nature. That is, whether the tone is always present or is actually produced by deactivation of a LPBN inhibitory mechanism.

The importance of forebrain facilitatory mechanisms for the ingestion of 0.3 M NaCl and water induced by deactivation of LPBN inhibitory mechanisms has also been demonstrated by studies that tested the interaction between the LPBN and the CeA for the control of sodium intake. The ingestion of hypertonic NaCl induced by different treatments such as sodium depletion, intracerebroventricular injection of renin, subcutaneous DOCA, or subcutaneous yohimbine is significantly reduced by bilateral electrolytic lesions of the CeA. This suggests that important facilitatory mechanisms for sodium intake are present in the CeA (60, 102, 117, 132, 133). There are reciprocal connections between the amygdala and the LPBN (73, 103). Bilateral electrolytic lesions of the CeA abolishes 0.3 M NaCl intake produced by bilateral LPBN injections of muscimol in fluid replete rats (3) and by bilateral LPBN injections of moxonidine or muscimide in rats previously treated with subcutaneous Furo + CAP (4). Therefore, similar to the need for a functional central angiotensinergic pathway, CeA facilitatory activity is also essential for enhanced natriorexigenic responses induced by deactivation of the inhibition produced by the LPBN (3, 4).

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**Table 1. Changes in water and hypertonic NaCl intake in rats induced by different natriorexigenic/dipsogenic stimuli combined with different treatments in the LPBN**

<table>
<thead>
<tr>
<th>Pharmacological Class</th>
<th>Drug Injected LPBN</th>
<th>Natriorexigenic/Dipsogenic Stimulus</th>
<th>Water Intake</th>
<th>Hypertonic NaCl Intake</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT antagonist</td>
<td>Methysergide</td>
<td>Furo + CAP</td>
<td>↑</td>
<td>↑</td>
<td>96</td>
</tr>
<tr>
<td>5-HT agonist</td>
<td>DOI</td>
<td>Furo + CAP</td>
<td>↑</td>
<td>↑</td>
<td>96</td>
</tr>
<tr>
<td>5-HT antagonist</td>
<td>DOI</td>
<td>DOCA</td>
<td>↑</td>
<td>↑</td>
<td>37</td>
</tr>
<tr>
<td>CCK antagonist</td>
<td>Proglumide</td>
<td>ANG II icv</td>
<td>↑</td>
<td>↑</td>
<td>95</td>
</tr>
<tr>
<td>CRH antagonist</td>
<td>αβmATP</td>
<td>Sodium depletion</td>
<td>↑</td>
<td>↑</td>
<td>97</td>
</tr>
<tr>
<td>CRH antagonist</td>
<td>Endorphin</td>
<td>Fluid-replete rats</td>
<td>↑</td>
<td>↑</td>
<td>41</td>
</tr>
<tr>
<td>CRH antagonist</td>
<td>Muscimol</td>
<td>Sodium-replete rats</td>
<td>↑</td>
<td>↑</td>
<td>17</td>
</tr>
<tr>
<td>CRH antagonist</td>
<td>Baclofen</td>
<td>Sodium-replete rats</td>
<td>↑</td>
<td>↑</td>
<td>42</td>
</tr>
<tr>
<td>GABA antagonist</td>
<td>Furo + CAP</td>
<td></td>
<td>↑</td>
<td>↑</td>
<td>34</td>
</tr>
<tr>
<td>Opioid antagonist</td>
<td>Naloxone</td>
<td>Sodium depletion</td>
<td>↑</td>
<td>↑</td>
<td>33</td>
</tr>
<tr>
<td>Opioid antagonist</td>
<td>β Endorphin</td>
<td>Fluid-replete rats</td>
<td>↑</td>
<td>↑</td>
<td>41</td>
</tr>
<tr>
<td>Opioid antagonist</td>
<td>Muscimol</td>
<td>Sodium-replete rats</td>
<td>↑</td>
<td>↑</td>
<td>41</td>
</tr>
<tr>
<td>Opioid antagonist</td>
<td>Baclofen</td>
<td>Sodium-replete rats</td>
<td>↑</td>
<td>↑</td>
<td>42</td>
</tr>
</tbody>
</table>

LPBN, lateral parabrachial nucleus; αβmATP, αβ methyl adenosine triphosphate; α<sub>2</sub>, α<sub>2</sub>-adrenoceptor; ANG II, angiotensin II; CAP, captopril; CCK, cholecystokinin; CRH, corticotrophin-releasing factor; DNQX, 6,7-dinitroquinoxaline-2,3(1-H,4H)-dione; DOCA, deoxycorticosterone; DOI, 2,5- dimethoxy-4-iodoamphetamine; Furo, furosemide; 5-HT, serotonin; icv, intracerebroventricular; Hypertonic NaCl, 0.3 or 0.5 M NaCl; SFO, subfornical organ.
The marked reduction of sodium and water intakes with the blockade of central AT1-R and muscarinic receptors or CeA lesions suggests that activity of facilitatory mechanisms produces signals that drive normovolemic rats to ingest sodium and water when treated with LPBN injections of muscimol. If under basal conditions, LPBN mechanisms are normally active, facilitatory mechanisms are inhibited by signals from the LPBN to retrain the ingestion of water and NaCl. The inactivation of LPBN inhibition releases forebrain facilitatory mechanisms resulting in increased water and sodium intake. In other words, the behavioral systems that defend blood volume and blood pressure are tonically “armed” to respond rapidly when homeostasis is challenged, but these behaviors are restrained by LPBN-associated inhibitory mechanisms. Such a “primed for action” intake system can in some ways be viewed as analogous to the control of heart rate and blood pressure by arterial baroreceptors. When afferent inputs from high pressure baroreceptors are interrupted, the tonic inhibitory control of sympathetic outflow is immediately released to produce the acute onset of hypertension (43, 82).

MULTIPLE NEUROTRANSMITTER MECHANISMS IN THE LPBN: A MODEL FOR THE CONTROL OF SODIUM APPETITE

The previously described mechanisms involved in the control of sodium intake in rats can be summarized in a model represented by Fig. 4. In this model, the LPBN belongs to a brain circuit whose primary purpose is to inhibit sodium intake. The core of the model accounts for two key aspects of the LPBN inhibitory mechanism; that is, its modulation and interaction with the facilitatory mechanisms. Modulation of the LPBN inhibitory mechanism depends on ascending visceral or humoral signals generated through primary relays located in the hindbrain (AP, NTS). Those signals modulate the release of two sets of neurotransmitters, some (serotonin, CCK, CRF, and glutamate) that increase the inhibitory signals and others (GABA, opioids, norepinephrine, and ATP) that reduce them. Reduction of inhibitory signals generated in the LPBN can occur by direct inhibition of output neurons or reduced release from interneurons of neurotransmitters such as serotonin, CCK, CRF, and glutamate. Interaction between the LPBN inhibitory mechanism and facilitatory mechanisms depends on signals sent to brain integrative areas. A candidate area to integrate those signals is the amygdala, particularly the CeA. There, signals from LPBN inhibit facilitation produced, for example, by ANG II or hyperosmolality acting on the SFO and/or OVLT.

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AUTHOR CONTRIBUTIONS


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