Neuroscience 297 (2015) 78–88

TEMPORAL DISSOCIATION BETWEEN SODIUM DEPLETION AND SODIUM APPETITE APPEARANCE: INVOLVEMENT OF INHIBITORY AND STIMULATORY SIGNALS

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Abstract—Our aim was to analyze the participation of inhibitory and stimulatory signals in the temporal dissociation between sodium depletion (SD) induced by peritoneal dialysis (PD) and the appearance of sodium appetite (SA), particularly 2 h after PD, when the rats are hypovolemic/natremic but SA is not evident. We investigated the effects of bilateral injections of the serotonin (5-HT) receptor antagonist, methysergide, into the lateral parabrachial nucleus (LPBN) on hypertonic NaCl and water intake 2 h vs. 24 h after PD. We also studied plasma renin activity (PRA) and aldosterone (ALDO) concentration 2 h vs. 24 h after PD. Additionally, we combined the analysis of brain Fos immunoreactivity (Fos-ir) with the detection of double immunoreactivity in 5HT and oxytocinergic (OT) cells 2 h after PD. Bilateral LPBN injections of methysergide (4 μg/200 nl at each site) increased NaCl intake when tested 2 h after PD compared to controls. We found a significant increase in PRA and ALDO concentration after PD but no differences between 2 and 24 h after PD. We also found for the first time a significant increase 2 h after PD in the number of Fos-ir neurons in the brainstem nuclei that have been shown to be involved in the inhibition of SA. In summary, the results show that 5HT-mechanisms in the LPBN modulate sodium intake during the delay of SA when the renin angiotensin aldosterone system (RAAS) is increased. In addition, the activation of brainstem areas previously associated with the satiety phase of SA is in part responsible for the temporal dissociation between SD and behavioral arousal.
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Key words: sodium depletion, sodium appetite, temporary dissociation, lateral parabrachial nucleus, serotonergic system.

INTRODUCTION

Thirst and *sodium appetite* (SA) are the motivational states in animals that lead to the search for and consumption of water and sodium (Na) respectively in order to reestablish hydroelectrolyte balance. There is a temporal dissociation between sodium depletion (SD) and the appearance of SA behavior. Previous studies from our laboratory have shown that acute SD by peritoneal dialysis (PD) produces a rapid and significant drop in volemia and Na concentration in serum and CSF within 1–4 h after PD. Sodium concentration rises gradually until 20 h later when the animals not only recover the normal blood volume and extracellular Na values (possibly by mobilizing body sodium reservoirs) but also the specific SA becomes evident (Ferreyra and Chiaraviglio, 1977).

It is widely known that the renin angiotensin aldosterone system (RAAS) is the principal system involved in the genesis of SA and thirst 24 h after PD or other SA induction procedures such as central injection of Angiotensin II (ANGII). However, the temporal pattern of this system activity after SD has not been described.

The lack of evidence for a specific stimulus that increases SA (in a physiologically relevant model) suggested that it is stimulated primarily by ANGII, but that the appetite for salt is usually held in check by a dominant inhibitory signal. In agreement with this hypothesis and with previous evidences, it has been shown that the

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Abbreviations: 5-HIAA, hydroxyindolacetic acid; 5HT, serotonergic system; 5-HT-ir, 5-HT immunoreactivity; AC, anterior commissure; ALDO, aldosterone; ANGII, Angiotensin II; AP, area postrema; BNSTL, lateral division of the bed nucleus of the stria terminalis; CD, control dialyzed or sham-depleted rats; CeA, central amygdaloid nucleus; CVOs, circumventricular organs; DAB, diaminobenzidine hydrochloride; DRD, dorsal subdivision of DRN; DRN, dorsal raphe nucleus; DRV, ventral subdivisions of DRN; DRVL, ventrolateral subdivision of DRN; EDTA, ethylenediaminetetraacetic acid; Fos-ir, Fos immunoreactivity; LC, locus coeruleus; LPBN, lateral parabrachial nucleus; Methy, methysergide maleate; MnPO, median preoptic nucleus; Na, sodium; NHS, normal horse serum; NTS, nucleus of the solitary tract; OT, oxytocinergic system; OT-ir, OT immunoreactivity; OVLT, organum vasculosum of the lamina terminalis; PaDC, dorsomedial cap; PaMM, medial magnocellular group; PaMP, medial parvocellular group; PaPo, posterior paraventricular subnucleus; PaV, ventral paraventricular subnucleus; PB, phosphate buffer; PD, peritoneal dialysis; PeM, periventricular nucleus; PRA, plasma renin activity; PVN, paraventricular nucleus; RAAS, renin angiotensin aldosterone system; RIA, radioimmunoassay; SA, sodium appetite; SD, sodium depletion; SFO, subfornical organ; SON, supraoptic nucleus; Veh, vehicle.

http://dx.doi.org/10.1016/j.neuroscience.2015.03.059
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satiety or inhibitory mechanisms of SA may involve: (1) *brainstem nuclei* (Contreras and Stetson, 1981; Watson, 1985; Curtis et al., 1996, 1999; Wang and Edwards, 1997; Franchini and Vivas 1999; Olivares et al., 2003; Callera et al., 2005; Godino et al., 2007); (2) *oxytocinergic (OT) neurons* (Stricker and Jalowiec, 1970; Stricker and Verbalis, 1987, 1996; Stricker et al., 1992; Franchini and Vivas 1999; Amico et al., 2001; Godino et al., 2007; Vivas et al., 2013); and (3) *serotonergic (5HT) neuron circuits* (Margatho et al., 2002; Castro et al., 2002, 2003; Franchini et al., 2002; Olivares et al., 2003; Tanaka et al., 2003, 2004; Cavalcante-Lima et al., 2005a,b; Reis, 2007; Badaue-Passos et al., 2007; Fonseca et al., 2009; Godino et al., 2007, 2010, 2013; Menani et al., 2014).

In our studies of the brain areas and neurochemical systems involved in the control of SA (Franchini and Vivas, 1999; Franchini et al., 2002; Godino et al., 2007; Vivas et al., 2013), the circumventricular organs (CVOs) of the lamina terminalis, subfornical organ (SFO) and organum vasculosum of the lamina terminalis (OVLT), were found activated (as shown by Fos immunoreactivity (Fos-ir)), during SA stimulation (24 h after PD). The brainstem nuclei (such as the nucleus of the solitary tract (NTS), area postrema (AP) and lateral parabrachial nucleus (LPBN)) and 5HT and OT neurons in the dorsal raphe nucleus (DRN) and hypothalamic nuclei respectively, were also found activated during the inhibition or satiety phase of SA (after sodium intake induced by 24 h after PD). Although the areas and neurochemical systems associated with SA appearance and satiation are well known, the neurochemical circuit responsible for the temporal dissociation between hyponatremia/hypovolemia and the appearance of SA behavior is still unknown.

Our recent results indicate that the LPBN appears to be an integrative region involved in the processing of information derived from receptive and integrative areas during the satiety or inhibition phase of SA, during blood volume expansion, and modulates the regulatory responses to achieve body fluid homeostasis under these stimuli (Margatho et al., 2008; Godino et al., 2010). Connectional studies also demonstrate that the LPBN is monosynaptically connected with the AP and DRN (Lanca and van der Kooy 1985; Petrov et al., 1992). Serotonin from these nuclei can be released into the LPBN and, in turn, can facilitate this inhibitory pathway, related to the modulation of sodium intake and excretion (Lanca and van der Kooy, 1985; Godino et al., 2010). In addition, a study by de Gobbi et al. (2008), suggests that the LPBN participates in the inhibitory process of SA during extracellular volume expansion, as the stimulation of cardiopulmonary receptors (simulating blood volume expansion) increased the number of Fos-ir neurons along the LPBN and reduced the sodium intake caused by furosemide-captopril treatment.

Taking this into account, the present work focused on the possible areas or systems involved in the temporary dissociation between SD and the appearance of SA. With this purpose, we analyzed the participation of the stimulatory and inhibitory signals of SA at 2 h after PD when the rats were hypovolemic/hyponatremia but SA was not evident, as follows: (1) plasma renin activity (PRA) and plasma aldosterone (ALDO) concentration 2 h vs. 24 h after PD; (2) the effect of serotonergic antagonism at the LPBN (Methysergide, a nonselective 5-hydroxytryptamine (5-HT)1/2 receptor antagonist), on sodium intake 2 h after PD; and (3) the brain Fos-ir pattern and the neurochemical (OT and 5-HT) mechanisms involved in SA regulation, 2 h after PD.

EXPERIMENTAL PROCEDURES

Animals

For the experiments, we used adult male Wistar rats, born and reared in the breeding colony at Instituto Ferreyra (INIMEC-CONICET-UNC, Córdoba, Argentina). Animals weighing 250–300 g were housed singly in metabolic cages with free access to normal sodium diet (Purina Rat chow), distilled water and hypertonic NaCl solution. Room lights were on for 12 h/day and temperature was controlled at 23 °C. All experimental protocols were approved by the appropriate animal care and use committee of our institute, following the guidelines of the international Public Health Service Guide for the Care and Use of Laboratory Animals.

SD

The PD technique, (described in Ferreyra and Chiaraviglio, 1977), consisted of an intraperitoneal injection of 5% glucose solution warmed to 37 °C, at a volume equivalent to 10% of the rat body weight. After 1 h, a needle was inserted into the peritoneal cavity and an equivalent volume of ascitic fluid was withdrawn. In control dialyzed or sham-depleted rats (CD), no injection was given but the needle was inserted into the peritoneal cavity.

PD and CD rats were returned to their individual metabolic home cages without food and with distilled water as the only drink for the following hours prior to the drinking test.

Electrolyte assays and protein determination

The blood was centrifuged and 1 ml of plasma was extracted and stored at −20 °C. The sodium concentration of these samples was analyzed by flame photometry (Hitachi 911, automatic analyzer). Plasma volume was inferred by the plasma protein concentration, measured according to Lowry et al. (1951).

Determination of PRA and ALDO concentration

The trunk blood was collected in chilled plastic tubes containing EDTA. PRA was measured by radioimmunoassay (RIA) of angiotensin I (DiaSorin, Saluggia, Italy) in the presence of reagents that inhibit angiotensin I-converting enzyme and angiotensinases. Intra- and inter-assay coefficients of variation were below 8% and below 6.66%, respectively.

ALDO was measured in plasma samples using a commercial kit (Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). Intra- and inter-assay

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