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BRAIN RESEARCH

Research Report

Serotonergic receptor blockade in the lateral parabrachial nucleus: Different effects on hypertonic and isotonic NaCl intake

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ABSTRACT

Hypertonic NaCl intake is produced by serotonin receptor antagonism in the lateral parabrachial nucleus (LPBN) of dehydrated rats or in rats pretreated with a mineralocorticoid, for example deoxycorticosterone (DOCA), that receive an intracerebroventricular injection (icv) of angiotensin II (ang II). The objective of the present work was to find out whether these two mechanisms are also involved with isotonic NaCl intake. Serotonin receptor blockade by methysergide in the LPBN (4 μg/0.2 μl bilaterally) had no effect on 0.15 M NaCl (methysergide: 19.3±5.2 ml/60 min; vehicle: 19.3±4.2 ml/60 min; n=7) or water (methysergide: 3.4±1.4 ml/60 min; vehicle 2.2±0.6 ml/60 min) intake induced by systemic diuretic furosemide combined with low dose of captopril (Furo/Cap). Methysergide treatment 4 days later in the same animals produced the expected enhancement in the 0.3 M NaCl intake induced by Furo/Cap (methysergide: 16.6±3.5 ml/60 min; vehicle: 6.6±1.5 ml/60 min). Similar result was obtained when another group was tested first with 0.3 M NaCl and later with 0.15 M NaCl. Isotonic NaCl intake induced by icv ang II was however enhanced by prior DOCA treatment. A de novo hypertonic NaCl intake was produced in another group by the same combined treatment. The results suggest that a facilitatory mechanism like the mineralocorticoid/ang II synergy may enhance NaCl solution intake at different levels of tonicity, while the action of an inhibitory mechanism, like the LPBN serotonergic system, is restricted to the ingestion at hypertonic levels.

1. Introduction

Preference for NaCl solutions reaches its peak at isotonic concentration in rats; the preference then decreases as the concentration increases to hypertonicity and thus the preference curve to NaCl solutions resembles an inverted "U", but sometimes with an elongated right arm (Weiner and Stellar, 1951). The shape of the preference curve is about the same for the sodium-repleted and sodium-depleted rat (Breslin et al., 1993) and thus one may predict that mechanisms that control sodium appetite operate on the amplitude, not the shape of the curve.

Thus, a mechanism that controls hypertonic NaCl intake should also control isotonic NaCl intake by a sodium-depleted animal. This makes sense if we note that, in a two-bottle test, as the NaCl solution ingested from one bottle is changed from isotonic to hypertonic, the amount of water ingested from the other bottle goes from negligible to progressive enhanced volume, proportional to the increase in tonicity of the NaCl solution ingested. Thereby an ideal isotonic assimilation of salt is

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provided to the internal environment (Nozaki et al., 2002; Stricker et al., 1991). The prediction is that any mechanism that controls sodium intake, whether facilitatory or inhibitory, would operate in a similar way whatever the concentration of NaCl solution present in the bottle; the only difference in the mechanism should relate to the intensity of the preference curve resulting in proportional ingestion of isotonic and hypertonic NaCl.

However, inhibitory mechanisms have also been considered as a safeguard against cell dehydration by restraining hypertonic intake (De Luca Jr. et al., 2003; Menani et al., 2000; Stricker and Verbalis, 1996). It is possible that inhibitory mechanisms preferentially restrain hypertonic NaCl intake but has a weak if any effect on isotonic NaCl intake (Godino et al., 2007).

The lateral parabrachial nucleus (LPBN) belongs to a putative inhibitory system that restrains sodium intake by receiving different neurotransmitter inputs. The most studied neurotransmitter is serotonin and serotonergic blockade in the LPBN enhances hypertonic NaCl intake induced by different models of dehydration (De Luca Jr. et al., 2003; Menani et al., 1996, 1998a,b, 2000). Enhanced serotonin release and its receptor blockade in the LPBN by methysergide are effective, for example, in the diuretic furosemide plus low dose captopril (Furo/Cap) dehydration model (Menani et al., 1996, 1998a; Tanaka et al., 2004). In this model, hypertonic NaCl intake is rapidly induced by combined facilitatory mechanisms, such as ang II and mild hypotension (Johnson and Thunhorst, 1997), and restrained by inhibitory mechanisms like the LPBN. It is not known whether serotonergic antagonism in the LPBN alters isotonic NaCl intake, for example, in the Furo/Cap model.

The mineralocorticoid and angiotensin II (ang II) synergy that works in sodium-depleted animals is a facilitatory mechanism of sodium intake (Epstein, 1990). In the Epstein's synergy paradigm test, a hypertonic NaCl intake is elicited when an intracerebroventricular (icv) dipsogenic dose of ang II is preceded by systemic mineralocorticoid treatment (Epstein and Sakai, 1987; Fluharty and Epstein, 1983); this paradigm produces a tendency to a post-ingestive isotonic mix (hypertonic NaCl plus water intake). However, it is possible that combined ang II and mineralocorticoid also enhance a pre-ingestive isotonic mix like the 0.15 M NaCl.

The objective of the present work was to find out whether isotonic NaCl intake is influenced by the inhibitory LPBN, in Furo/Cap-treated rats, and by the mineralocorticoid/ang II synergy paradigm.

2. Results

2.1. *Testing inhibitory effect of LPBN on sodium intake*

2.1.1. *Histology*

The LPBN injection site was centered in the central lateral and dorsal lateral portions of the LPBN (see Fulwiler and Saper,

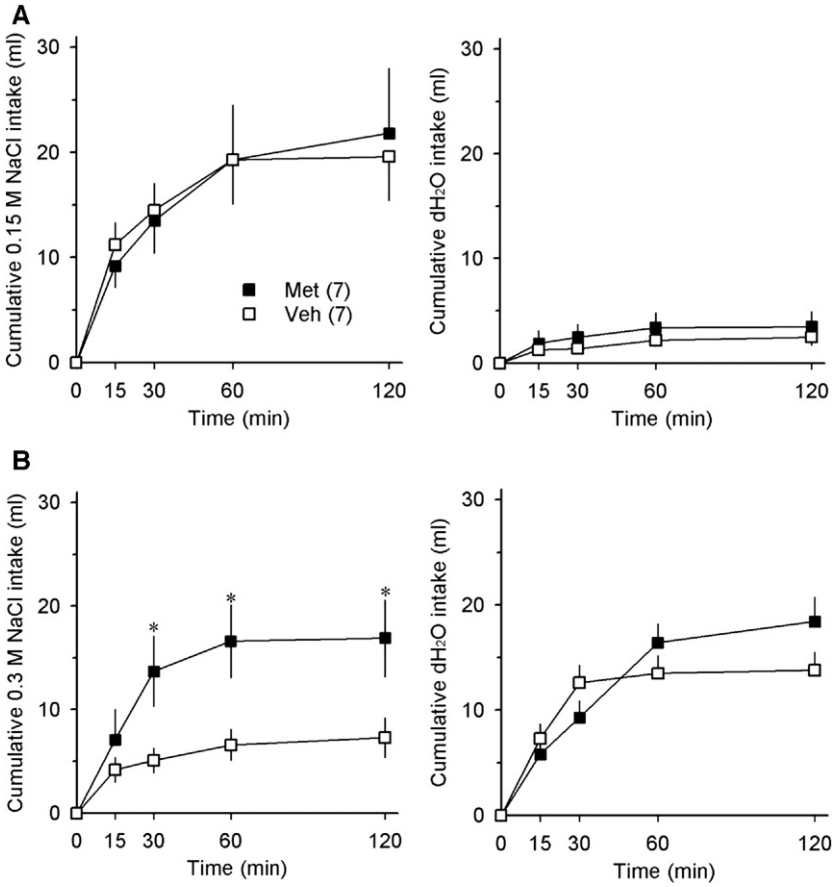

Fig. 1 – Cumulative fluid intake by Furo/Cap-treated rats that received bilateral injections of methysergide (Met) or vehicle (Veh) into the LPBN. (A) 0.15 M NaCl (left) and water (right) intake in the early tests. (B) 0.3 M NaCl (left) and water (right) intake in the late tests. *$P<0.05$ vs. vehicle. The number of animals is between parentheses.