Editorial Commentary

Putative Mechanism of Salt-Dependent Neurogenic Hypertension

Cell-Autonomous Activation of Organum Vasculosum Laminae Terminalis Neurons by Hypernatremia

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Hypernatremia elicits multiple adaptive responses mediated via the central nervous system: the sensation of thirst, drinking (seeking and consuming fluids), changes in taste preference (water versus salt), and neuroendocrine responses that affect the circulatory system along with sodium and water excretion by the kidneys. In conscious humans, hyperosmotic stimuli elevate blood pressure (BP) and sympathetic tone, and this particular neurogenic response likely contributes to salt-dependent hypertension. In this issue of Hypertension, Kinsman et al1 suggest that the autonomic nervous system effects elicited by systemic hypernatremia result from a direct action of [NaCl] on neurons located within the organum vasculosum laminae terminalis (OVLT).

The OVLT along with the subfornical organ (SFO) and the median preoptic nucleus (MnPO) is an interconnected structure that line the anterior wall of the third ventricle (Figure) and orchestrate the behavioral and autonomic responses to hyperosmolality. The SFO and OVLT detect and encode the osmotic hypernatremia (2.5–10 mmol/L increase in [NaCl]). In the SFO, Na sensing requires a sodium channel (Na+, SCN7a) that is distantly related to the family of voltage-activated channels responsible for action potential generation in neurons but neither voltage operated nor tetrodotoxin sensitive. Na+ is regulated by endothelin, which shifts its operating range from supraphysiological to physiological levels of [Na+]a. In the SFO of adult mice, Na+ is primarily expressed by GFAP (glial fibrillary acidic protein)-positive glia. Lactate and 5,6-epoxyeicosatrienoic acid are among the gliotransmitters that may mediate the excitatory effect of hypernatremia on SFO GABAergic and glutamatergic neurons, respectively. Importantly, Na+ immunoreactivity and mRNA transcripts are also present in the OVLT and immediately adjacent portions of the MnPO. According to Grob et al, the ventral MnPO contains a mixture of osmosensitive (≈75% of the total) and purely sodium-sensitive neurons; the latter respond to a rise in [Na+]a in the presence of tetrodotoxin but are insensitive to mere hyperosmolality. Pharmacological and histological evidence reported by Grob et al suggests that the sodium-sensing mechanism might also depend on Na+. By analogy with the work on the SFO, the Na+ dependent excitation of MnPO neurons could well be of a paracrine nature. This mode of intercellular communication is tetrodotoxin resistant and, therefore, compatible with Kinsman et al’s results in the OVLT. In sum, the response of OVLT neurons to extracellular NaCl and the resulting autonomic effects could result from a direct effect of hyperosmolality on these neurons or they could represent a paracrine response to [Na+]a mediated by glial Na+. In the future, deleting Na+ or TRPV1 selectively from the OVLT may provide the answer.

Regardless of the precise mechanism by which hyperosmotic hypernatremia activates OVLT neurons, a key question addressed by Kinsman et al is whether these neurons respond to physiologically relevant changes in plasma [NaCl] in vivo. This is indeed the case: most OVLT neurons (72%) were

\[\text{DOI: 10.1161/HYPERTENSIONAHA.116.08470} \]
gigorously activated by injecting NaCl into the carotid artery or a lateral ventricle in a dosage range that raises [Na+]e modestly (estimate: 3–8 mmol/L). These neuronal responses were accompanied by small BP rises (≈10 mmHg for the highest NaCl dose) that were mimicked by injecting NaCl into the OVLT but not outside it. Interestingly, NaCl injections dorsal to the OVLT, which should have targeted the MnPO, were ineffective. The NaCl-responsive neurons located in the MnPO6 may, therefore, elicit responses that are not mediated by the autonomic nervous system (eg, drinking).10

NaCl injection into the OVLT changed sympathetic nerve activity (SNA) in a regionally specific manner.3 These results show that a minimal rise in [NaCl]e within the OVLT is sufficient to increase BP, probably by increasing SNA to muscle and skin arterioles, while facilitating renal sodium excretion by withdrawing renal sympathetic tone. Finally, Kinsman et al3 demonstrated that the OVLT circuitry must be fully functional for hyperosmotic hypernatremia to increase BP. Indeed, the rise in BP and SNA evoked by ICV injection of NaCl was greatly reduced by injecting the GABA-mimetic drug muscimol selectively into the OVLT. In truth, because the CVOs are all interconnected, the results of the muscimol experiment could also mean that the OVLT is a pivot for autonomic responses evoked by NaCl elsewhere (eg, SFO and MnPO).

The interpretation of the Kinsman et al data is subject to the limitations inherent to the use of anesthetized rodents. In unanesthetized mice, optogenetic stimulation of glutamatergic neurons located within the OVLT/MnPO elicits robust drinking, and the converse occurs when local GABAergic neurons are activated.10 Drinking is likely associated with arousal and cardiovascular stimulation. The BP and SNA changes observed by Kinsman et al10 could be the attenuated autonomic correlates of a behavioral response whose motor and motivational components are suppressed by anesthesia. On the contrary, it could also represent an aspect of the integrated response to hypernatremia that is independent of drinking behavior. This interpretation is tempting because the autonomic response pattern elicited by activating OVLT neurons with NaCl seems well suited to facilitate renal sodium excretion during hypernatremia (increased renal artery pressure combined with reduced renal SNA).

In conclusion, OVLT neurons are activated by modest rises in plasma or cerebrospinal fluid [NaCl]e. OVLT neurons detect [NaCl]e in a cell-autonomous manner or via the surrounding glia. The activation of OVLT neurons by NaCl elevates BP and triggers a pattern of SNA that presumably facilitates renal sodium excretion (Figure). When chronically elicited, this mechanism probably contributes to salt-dependent hypertension.

Sources of Funding
This work was supported by research grants from the National Institutes of Health (HL028785, HL HL074011).

Disclosures
None.

References


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Hypertension. 2017;69:20-22; originally published online November 28, 2016;
doi: 10.1161/HYPERTENSIONAHA.116.08470

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