PERSPECTIVES

Pathways to hypertension

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Hypertension remains a leading risk factor for morbidity and mortality from cardiovascular disease. Elevated sympathetic nerve activity contributes to the development and maintenance of hypertension, but the central mechanisms that lead to chronic increases in sympathetic nerve activity remain unresolved (Guyenet, 2006). Understanding these mechanisms requires detailed anatomical and physiological mapping of the relevant neurocircuitry. Recent studies highlight the importance of the paraventricular nucleus of the hypothalamus (PVN) in mediating acute and chronic increases in sympathetic nerve activity under multiple conditions including hypertension and heart failure (Benarroch, 2005; Guyenet, 2006). However, the PVN seems to have minimal influence on resting sympathetic nerve activity under normal conditions, which raises the important question: what inputs turn on the PVN (Dampney *et al.* 2005)? Recent investigations are increasing our understanding of the regulation of PVN neuronal activity. In this issue of *The Journal of Physiology*, Shi *et al.* (2008) demonstrate that a direct neural connection originating in the organum vasculosum of the laminae terminalis (OVLT) and terminating in the PVN mediates activation of PVN neurons by hyperosmolality.

Plasma osmolality is a tightly controlled variable, and hyperosmolality stimulates a number of physiological responses that alter both sodium and water balance in order to return osmolality to within normal limits (Bourque, 2008). Hyperosmolality also stimulates a stress response that includes activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis (Benarroch, 2005; Stocker *et al.* 2008). The osmoreceptors that mediate these responses are present in multiple locations including the OVLT (Bourque, 2008). The OVLT is a circumventricular organ, meaning that it is exposed to circulating factors including hormones and alterations in plasma osmolality, and also contains neurons that project into the regions of the brain that are protected by the blood–brain barrier. The OVLT mediates, in part, the increases in vasopressin and sympathetic nerve activity that result from elevations in plasma osmolality (McKinley *et al.* 2001; Shi *et al.* 2007).

Experimentally, hyperosmolality can be induced by high salt intake, and a high salt diet promotes hypertension in susceptible humans and experimental animals (Guyenet, 2006; Osborn, 2007; Stocker *et al.* 2008). Hyperosmolality can also be induced by dehydration. However, both a high salt diet and dehydration stimulate osmoreceptors throughout the body. The experiments performed by Shi *et al.* (2008) utilized intracarotid infusion of hypertonic saline to more selectively stimulate forebrain circumventricular organ osmoreceptors including those in the OVLT. They used retrograde tracing techniques to identify neurons that projected directly from the OVLT to the PVN, and they used immunohistochemistry for Fos to identify OVLT neurons that were activated by the hypertonic saline. Combining these three approaches they were able to demonstrate that increases in plasma osmolality directly activate OVLT neurons that project monosynaptically to the PVN. The results of this study are strengthened by two additional aspect of their experimental approach. First, they confirmed that the selected doses of hypertonic saline delivered to the forebrain increased sympathetic nerve activity, which is an effect that is dependent on PVN activation (Chen & Toney, 2001; Antunes *et al.* 2006). Second, they demonstrated that these doses of hypertonic saline increased arterial pressure in conscious rats, allowing for clear interpretation of the Fos data.

The results of this study provide the basis for future studies to determine the physiological role of activating the OVLT to PVN pathway in the development and maintenance of salt-sensitive hypertension. The study also raises some broader questions. (i) What other blood-borne factors can activate the neurons that project directly from the OVLT to the PVN? (ii) Are neuronal pathways that activate the sympathetic nervous system in response to a high salt diet shared with other hypertension risk factors that stimulate sympathetic outflow, such as psychological stress? If so, do they converge in circumventricular organs such as the OVLT, in the PVN or elsewhere?

It is likely that multiple converging pathways lead to hypertension, including central neural pathways that drive sustained activation of the sympathetic nervous system. Careful experiments such as those reported by Shi *et al.* (2008) will help us map these pathways, so we can then determine what turns them on.

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