Is the RVLM a key site for sex-related differences in blood pressure regulation? Focus on “Sex differences in angiotensin signaling in bulbospinal neurons in the rat rostral ventrolateral medulla,” by Wang et al.

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IT IS WELL KNOWN THAT ARTERIAL blood pressure and the prevalence of hypertension and other cardiovascular diseases is higher in men than in age-matched premenopausal women, although after menopause these differences are reduced or even reversed (10). It is likely that many factors contribute to these sex-related differences in blood pressure regulation, but recent studies have focused on the role of central neural mechanisms, in the light of evidence that increased sympathetic activity has a critical role in the development and maintenance of at least some types of hypertension and other cardiovascular disorders, such as heart failure (4, 6).

In the last 30 years, there have been several key discoveries that have had a major impact on our current understanding of the central mechanisms that regulate the sympathetic outflow in both the short and long term. Three of these discoveries are particularly relevant to the article by Wang et al. (13). First, work in the 1970s and early 1980s established that bulbospinal neurons in the rostral ventrolateral medulla (RVLM), including catecholamine neurons of the C1 group, have a critical role in the tonic and reflex control of sympathetic activity and blood pressure (1, 2). Second, it was discovered that there is a renin-angiotensin system within the brain and that angiotensin (ANG) receptors are located in key brain nuclei (including the RVLM) that are known to regulate cardiovascular function and fluid homeostasis (3, 7). Third, more recently it was discovered that ANG II can trigger the production of reactive oxygen species (ROS) via activation of the enzyme NADPH oxidase (5) and that, in the brain, excessive production of ROS contributes to ANG II-dependent hypertension (9). For example, in rats with renovascular hypertension, there is an increased level of ROS in the RVLM, and microinjection of a ROS scavenger into the RVLM in the RVLM leads to a decrease in blood pressure and in renal sympathetic nerve activity (8).

Because most studies have been performed in male animals, it is not always fully appreciated that there are some major sex-related differences in central cardiovascular regulatory mechanisms. For example, chronic ANG II infusion in mice leads to a much greater increase in blood pressure in males compared with females, apparently due to a greater degree of sympathetic activation (14). Similarly, the magnitude of the blood pressure increase in other animal models of hypertension, including spontaneously hypertensive, Dahl salt-sensitive and deoxycorticosterone-salt hypertensive rats, is greater in male than in female animals (10). Unraveling the factors that may be responsible for these sex-related differences in animal models of hypertension would clearly be of great interest, in view of their likely relevance to understanding the causes of similar sex-related differences in human hypertension.

The study by Wang et al. (13) produced a number of interesting and unexpected findings. First, the authors found that immunoreactivity for ANG type 1 (AT1) receptors on catecholamine neurons in the RVLM was higher in female than male rats, whereas immunoreactivity for pregnancy-related AT1 receptors, which were actually decreased. Second, direct application of ANG II caused an increase in ROS production in dissociated bulbospinal neurons in the RVLM, but not in nonbulbospinal neurons. This effect was dependent on both AT1 receptors and NADPH, and was of similar magnitude in male and female rats. As the authors state, these observations suggest that the increased density of AT1 receptors on RVLM bulbospinal neurons in female rats is counterbalanced by a reduced level of NADPH oxidase activity, such that the final effect on ROS production is not changed.

The authors also found, however, that ANG II evoked increases in L-type Ca\(^{2+}\) currents in dissociated RVLM bulbospinal neurons, which were larger in female than male rats. Because, as mentioned above, ANG II-evoked ROS production was similar in male and female rats, this increased response must be due to a mechanism that is independent of the AT1 receptor-ROS pathway. In fact, the authors also found that after blockade of this pathway (by means of the AT1 receptor antagonist losartan), application of a L-type Ca\(^{2+}\) channel activator evoked a greater response in RVLM neurons from female rats compared with those from male rats. Thus, the difference in the overall Ca\(^{2+}\) current response between males and females could be accounted for by a difference in the number and/or sensitivity of L-type Ca\(^{2+}\) channels in the two sexes.

These findings are important because they establish that there are several marked sex-related differences in the ANG signaling pathway in putative sympathoexcitatory neurons in the RVLM. At the same time, as the authors acknowledge, the study also raises a number of important questions. In particular, it is not clear if the overall effect of these differences is likely to increase or decrease the neuronal excitability of RVLM sympathoexcitatory neurons. A previous study by the same group (12) has shown that application of 17β-estradiol to RVLM bulbospinal neurons decreases L-type Ca\(^{2+}\) currents, leading to the suggestion that this underlies the previously demonstrated sympathoinhibitory effect of 17β-estradiol in the RVLM (11). If that were the case, then this suggests that the acute ANG II-evoked increase in L-type Ca\(^{2+}\) currents as observed in the present study by Wang et al. (13) would result in an increase in neuronal excitability of RVLM sympathoexcitatory neurons in female rats. As the authors point out, however, L-type Ca\(^{2+}\) channels also modulate K\(^{-}\) channels, and so the effect of the ANG II-evoked increase in L-type Ca\(^{2+}\)
currents on the activity of RVLM sympathoexcitatory neurons will depend on which particular channels are activated.

For technical reasons, the neurophysiological experiments reported in the paper by Wang et al. (13) could only be performed in juvenile rats. Therefore, it is not known whether the ANG II-evoked effects observed reflect those that occur in mature rats. Perhaps more importantly, the sex-related differences in AT1 receptor and NADPH oxidase expression, and in L-type Ca2+ channels in the RVLM may lead to changes in gene expression, which will have major sustained effects on the activity of sympathoexcitatory neurons. As the authors recognize, these questions will need to be addressed in future studies. The findings of the present study, however, suggest that differences in ANG signaling is one of the key factors underlying the different central cardiovascular control mechanisms in male and female animals.

GRANTS
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