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?

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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 p47, a key NADPH oxidase subunit, was actually decreased. Second, direct application of ANG II caused an increase in ROS production in dissociated bulbospinal neurons in the RVLM, but not in nondissociated 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 an 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 17\(\beta\)estradiol to RVLM bulbospinal neurons decreases L-type Ca\(^{2+}\) currents, leading to the suggestion that this underlies the previously demonstrated sympathoinhibitory effect of 17\(\beta\)-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 ROS production is not changed.
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 Ca\(^{2+}\) 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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**REFERENCES**