In both humans and animals, heart failure is associated with sympathoexcitation and increased activity of the renin–angiotensin system. Studies in animals have shown that in heart failure, there is increased expression of angiotensin type 1 (AT$_1$) receptors in key brain regions regulating sympathetic activity, such as the nucleus of the solitary tract, rostral ventrolateral medulla (RVLM), and the hypothalamic paraventricular nucleus (PVN), as well as in the area postrema and subfornical organ (SFO), both of which are circumventricular organs that are accessible to circulating angiotensin II (Ang II). It has long been known that Ang II in the RVLM, PVN, and SFO can increase blood pressure and sympathetic activity, and there is good evidence in rats and rabbits that upregulation of the brain renin-angiotensin system contributes to increased sympathetic activity.

The mechanism by which increased expression of AT$_1$ receptors occurs in heart failure has been the subject of much recent attention. It is known that Ang II can upregulate its own receptor, and a recent study by Chan et al showed that in the RVLM, Ang II triggers via AT$_1$ receptors increased intracellular production of superoxide and phosphorylation of the mitogen-activated protein kinase (MAPK) extracellular signal-regulated protein kinase, which is also known as p44/42 MAPK. Furthermore, microinjection into the RVLM of an antisense oligonucleotide that suppressed p44/42 activation also significantly reduced the pressor effect as well as increased AT$_1$ receptor expression in the RVLM by a 1-week ICV infusion of Ang II. Thus, these observations indicate that in the RVLM, p44/42 MAPK plays a critical role in mediating both the increased AT$_1$ receptor expression and sympathoexcitation induced by chronic central administration of Ang II.

In the study by Wei et al published in this issue of Hypertension, the authors tested the hypothesis that in heart failure, Ang II can increase AT$_1$ receptor expression by inducing an increase in MAPK activity. In their study, they focused on the PVN and SFO, which lie within and outside, respectively, the blood–brain barrier. Thus, the PVN is influenced by Ang II that is either synthesized locally or released from the terminals of neurons that project to the PVN, whereas the SFO is influenced by circulating Ang II. In addition to p44/42 MAPK, the authors also examined p38 MAPK and c-Jun N-terminal kinase (JNK), which are the other 2 major MAPK family members.

The authors found that in rats with heart failure, there is increased phosphorylation of all 3 of these MAPK family members in the PVN and SFO. ICV infusion of losartan (an AT$_1$ receptor antagonist) decreased the phosphorylation of all of them and also decreased AT$_1$ receptor expression in both the PVN and SFO. More important, ICV infusion of inhibitors of p44/42 MAPK or JNK for 4 weeks, or even for 3 hours, reduced the AT$_1$ receptor expression in the SFO and PVN in heart failure rats back to levels measured in normal control rats. However, ICV infusion of an inhibitor of p38 had no effect on AT$_1$ receptor expression. Finally, hemodynamic measurements indicated that the 4-week ICV infusion of losartan and inhibitors of p44/42 MAPK or JNK improved cardiac function in heart failure rats, although there was not complete restoration of function.

These exciting observations should be considered in light of previous studies by this group of investigators as well as others. First, the observations expand on a previous study by Liu et al, who found that in rabbits with heart failure or infused ICV with Ang II, there is upregulation of AT$_1$ receptors in the RVLM associated with increased JNK expression. Consistent with the findings of Wei et al, Liu et al also found that in neuronal cell cultures, Ang II–induced expression of AT$_1$ receptors was reduced by a JNK inhibitor but not by an inhibitor of p38 MAPK. However, in contrast with the findings of Wei et al, an inhibitor of p44/42 MAPK did not block Ang II–induced AT$_1$ receptor expression in neuronal cell cultures. The reason for this discrepancy between effects in vivo and in vitro is not clear at this time.

In another very recent study, Wei et al showed that infusion of losartan or inhibitors of p44/42 MAPK, but not of JNK, reduced mean arterial pressure, heart rate, and renal sympathetic nerve activity in rats with heart failure but not in normal rats. Thus, although the overexpression of AT$_1$ receptors in the PVN and SFO of rats with heart failure is dependent on activation of AT$_1$ receptors and on the p44/42 MAPK and JNK signaling pathways, a reduction in this overexpression does not invariably lead to a reduction in sympathetic activity. This, in turn, indicates that the effect of blockers of AT$_1$ receptors or inhibitors of p44/42 MAPK in reducing sympathetic activity is independent of their effect in increasing AT$_1$ receptor expression, as shown schematically in the Figure. For example, an intracellular pathway that includes p44/42 MAPK as a critical element may alter...
neuronal excitability by modulating potassium or calcium ion channels.

The PVN projects to the spinal sympathetic output both directly and via premotor neurons in the RVLM. Although in normal rats, AT₁ receptors have not been located on PVN neurons that project to the spinal cord or RVLM, the study by Wei et al. reported that in heart failure rats, AT₁ receptors have a much more diffuse distribution in the PVN than in normal rats. This suggests that in heart failure, AT₁ receptors are expressed in PVN neurons regulating the sympathetic outflow, and that activation of those AT₁ receptors then leads to sympathetic excitation.

Although this study demonstrates the importance of AT₁ receptors and downstream MAPK signaling pathways in the upregulation of AT₁ receptors in heart failure, it does not address the question as to how heart failure triggers this sequence of events. One possible contributing factor is the increase in circulating Ang II in heart failure, which then activates AT₁ receptors on angiotensinergic neurons in the SFO that project to the PVN, leading to release of Ang II within the PVN (Figure). Other factors such as aldosterone or proinflammatory cytokines or inputs from cardiac receptors may also increase the level of local Ang II within the PVN or else activate intracellular signaling pathways by other mechanisms, leading to upregulation of AT₁ receptors. Nevertheless, although many questions remain unanswered, the study by Wei et al. is an important step forward in our understanding of the intracellular mechanisms that mediate the physiological responses to heart failure.

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References
Brain Angiotensin and Heart Failure: Further Evidence for a Critical Role of Mitogen-Activated Protein Kinases

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