OF THE MANY PHYSIOLOGICAL effects exerted by atrial natriuretic peptide (ANP), its direct influence on vascular tone seems to be the most puzzling. In the peripheral circulation, ANP binds to the extracellular ligand binding domain of the membrane-bound guanylyl cyclase isoform A (GC-A), which is widely expressed in vascular smooth muscle, to increase intracellular levels of cGMP (11). Activation of intracellular cGMP signaling will ultimately reduce the intracellular concentration of free Ca$^{2+}$, resulting in profound smooth muscle relaxation (5). Confirming a vasodilator function of ANP, isolated aortic segments display an endothelium-independent relaxation along with increases in levels of cGMP in response to ANP (4, 12).

In contrast to what might be expected, however, in vivo studies showed that acute increases of ANP cause vasoconstriction rather than vasorelaxation in a wide variety of vascular beds from different species (6–8, 10, 13, 14). The vasoconstriction was not caused by an activation of sympathetic nerve activity or of the renin-angiotensin system. The cellular signaling pathways involved in this paradoxical vascular response to ANP remained unclear.

In a recent study, Sultanian et al. (10) found that ANP-induced increases in postcapillary resistance in the rat spleen can be blocked competitively with the GC-A selective peptide antagonist A71915, suggesting that a stimulation of GC-A may be a necessary step involved in the vasoconstrictor action of ANP. In this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Andrew and Kaufmann (2) describe experiments in which this hypothesis is tested directly. The authors compare the effects of increasing doses of ANP on isolated splenic vessels from mice lacking GC-A (3) with those from wild-type control animals. They find that vessels from wild-type mice respond to the addition of ANP with a dose-dependent vasoconstriction, which is further enhanced when the endothelium is removed. The vasoconstrictor response to ANP is entirely absent in splenic vessels from GC-A-deficient mice, whereas the vasoconstriction induced by phenylephrine is preserved.

These results strongly support the conclusion that ANP activates GC-A to induce vasoconstriction in murine splenic vessels. This concept raises several interesting questions. In an earlier study, Lopez et al. (4) demonstrated that ANP potently relaxes precontracted aortic rings from wild-type mice, but failed to affect contraction in GC-A-deficient mice. Thus ANP appears to induce either relaxation or contraction of smooth muscle by activating the same membrane receptor isoform, which implies that the intracellular downstream signaling of GC-A may significantly differ between individual vascular beds. Such differences in intracellular signaling may underlie opposite vascular responses to ANP in the pulmonary and gastrointestinal vasculature (2, 15). Moreover, a stimulation of cGMP signaling by nitric oxide effectively relaxes the murine splenic vasculature (1). Since nitric oxide binds to the soluble guanylyl cyclase isoform (sGC) to increase intracellular cGMP (5), the discrepancy between the effects of ANP and NO on splenic smooth muscle tone may indicate that the physiological consequences of an elevation of cGMP may depend on its subcellular location. A possible compartmentalization of cGMP changes is supported by the observation that activation of CG-A, but not of sGC, induces a sharp increase of the release of cGMP from the cell (9). Addressing these and other questions will undoubtedly pave the way for a better understanding of the still largely ignored phenomenon of ANP-induced vasoconstriction and may offer new insights into the control of vascular tone in general.

REFERENCES


