Confirmation of the pivotal role of Gsα in renin release

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ARISTOTLE, in the 4th century BC, deduced that the earth was round from the circular shadow on the moon during a lunar eclipse. Using simple trigonometry, Eratosthenes, a 3rd century BC Greek mathematician, calculated the diameter of the earth, and in 1522 the Magellan expedition completed a circumnavigation. Yet even with all of the preexisting indirect evidence, the Apollo 8 photographs of the spherical earth floating in the black of space were profoundly satisfying in part because this was direct evidence of a round earth. Good job, Aristotle and NASA; case closed!

Like the Apollo 8 photographs, the data by Chen et al. (1) in this issue of the American Journal of Physiology-Renal Physiology are deeply gratifying, and for similar reasons. Before this article, much indirect evidence suggested that stimulation of adenyl cyclase by Gsα, if not the final common pathway for the stimulation of renin release, is at least a pivotal component of the signal transduction processes mediating renin release. A review in 1991 (3) proposed that all three physiological mechanisms of renin release, i.e., the intrarenal β-adrenoceptor mechanism, the intrarenal baroreceptor mechanism, and the macula densa mechanism, involve Gsα-induced activation of adenyl cyclase, leading to intracellular accumulation of cAMP and the exocytosis of renin. Perhaps there was never any doubt regarding the role of Gsα in the intrarenal β-adrenoceptor mechanism because of the overwhelming evidence that β-adrenoceptors couple predominantly to Gsα. On the other hand, the role of Gsα/adenyl cyclase in intrarenal baroreceptor-induced and macula densa-induced renin release was less certain and the evidence more circumstantial. Nonetheless, strong evidence was forthcoming in the 1980s (4, 5) and is continuing until today (2) that prostaglandins (particularly prostacyclin) participate in renin release responses to a reduction in renal perfusion pressure (i.e., the intrarenal baroreceptor mechanism) and to a decrease in sodium chloride delivery to the thick ascending limb (i.e., the macula densa mechanism). The facts that prostacyclin receptors stimulate adenyl cyclase via Gsα, that cell-permeant analogs of cAMP stimulate renin release, that direct activators of adenyl cyclase augment renin release, that inhibition of cAMP metabolism to AMP increases renin release, and that inhibition of adenyl cyclase attenuates prostacyclin-induced renin release further support the pivotal role of Gsα/adenyl cyclase in the physiological pathways to renin release. And yet all this indirect evidence, as convincing as it was, left a yearning for more.

Like the photographs from Apollo 8 removing all residual doubt about the geometry of the earth, the highly significant article by Chen et al. (1) has sponged away most, if not all, of the remaining doubt regarding the absolutely critical role of Gsα in the physiological mechanisms of renin release (as well as in basal renin production). The authors of this exploration approached the problem in an impressively creative fashion: by crossing mice that express Cre recombinase under the control of the endogenous renin promoter with mice in which exon 1 of the gene for Gsα (Gnas) was flanked by loxP sites to generate mice with preferential and nearly total abolition of Gsα expression in juxtaglomerular cells. And what was the phenotype? In addition to reduced basal levels of renin expression and plasma renin concentration, these mice had markedly attenuated renin release responses to furosemide (activates macula densa), hydralazine (activates intrarenal baroreceptors), and isoproterenol (activates intrarenal β-adrenoceptors). Moreover, when juxtaglomerular cells from these mice were placed in primary culture, renin release responses induced by a β-adrenoceptor agonist (isoproterenol) or by a prostaglandin (PGE2) were abolished. Consistent with the impaired ability to release renin in response to physiological stimuli, these engineered mice also were hypotensive and demonstrated reduced levels of aldosterone. Case closed? It would seem so!

REFERENCES

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