A different vision of the osmolar regulation of renin secretion

William H. Beierwaltes
Hypertension and Vascular Research Division, Henry Ford Hospital, and Department of Physiology, Wayne State University School of Medicine, Detroit, Michigan

In this issue, the proverbial question of osmotic regulation of renin secretion is revisited by Kurtz and Schweda (9) with rather surprising, yet apparently definitive, results. Since the development of osmotic diuretics, there has been much interest in whether renin secretion by the kidney is somehow regulated by changes in osmolality, either in the plasma perfusing the kidney or in the microenvironment surrounding the renin-containing juxtaglomerular (JG) cells. However, early studies in whole animals using osmotic diuretics offered mixed and inconclusive results. In 1964, Vander and Miller (13) found that mannitol, urea, or sodium sulfate prevented renal baroreceptor-stimulated renin, and Birbari (1) reported that mannitol suppressed plasma renin activity (PRA) in dogs. Young and Rostorfer (14), also using dogs, reported that intravenous injection of either urea or dextrose increased PRA, whereas studies in rats (2) found that mannitol infusion decreased PRA. Kopp and DiBona (8) changed intrarenal plasma osmolality using graded levels of hypertonic saline and found no effect on renin secretion rate. The inability to control the complex interactions between different cell populations in these whole animal preparations, combined with the multiple signals such as changing distal NaCl concentrations (2, 8), no doubt obscured or undermined the quest for a consistent answer as to whether the JG cells can act as osmosensors to regulate renin secretion.

To circumvent the complexities of whole animal studies, a large number of in vitro studies have been performed using different renin-releasing preparations, including kidney slices (3), isolated glomeruli (5), isolated afferent arterioles (12), cultured isolated JG cells (4), and permeabilized JG cells (6, 7). Overall, these studies have shown that relatively minor changes in the osmolality of the bath surrounding renin-containing JG cells influenced renin release. In his definitive 1988 review of osmotic forces and renin, Skott (11) examined all of these results and concluded that “renin secretion changes inversely with the extracellular osmolality.” The question surrounding this conclusion was not whether relatively small increases in osmolality inhibited renin release and small decreases would stimulate it, but whether these were direct effects on swelling of the renin-containing granules as part of the signal that initiated fusion of the vesicles with the cell membrane, thereby facilitating release of active renin from the granule, or whether it was a more intrinsic sensitivity of the JG cell that would initiate a cascade either impairing or enhancing the signaling pathway that ultimately releases renin from the cell. This inverse relationship has been the established doctrine for the past 20 years, exemplified by a review of cellular control of renin secretion in 1999 by Kurtz and Wagner (10), in which they stated “renin secretion from JGE cells is sensitive to changes in extracellular osmolality, such that the rate of renin secretion is inversely related to the extracellular osmolality.”

So, just when we are beginning to feel that we have understood osmolar regulation of renin, the present studies of Kurtz and Schweda (9) challenge us to reconsider our thinking. Unlike the rather static in vitro preparations cited above, these authors have used an isolated, perfused kidney model. Notably, whereas many laboratories have abandoned this model due to results with high perfusate flows and low resistance, low filtration fraction, time-dependent deterioration of renal function, and loss of distal integrity, their Regensburg laboratories have continued to improve the model to overcome these problems and use it to address questions for which it is particularly well suited, such as dynamic regulation of renin. It simplifies the often-perplexing variables of classic in vivo studies while maintaining the anatomic integrity of the whole kidney and the important hemodynamic elements lost in most in vitro systems. Armed with this methodology, they report that in both rat and mouse kidneys, contrary to the results of the past 20 years, renal perfusion with different osmotic challenges establishes a direct relationship between increased osmolality and rapid and pronounced renin secretion. This response was concentration dependent and further amplified cAMP-mediated renin secretion induced by isoproterenol. The response to a hyperosmolar challenge was also amplified by manipulations designed to lower JG cell calcium and blunted by angiotensin. These results suggest that the renin response to an osmolar challenge is not due to direct changes in the second messengers of intracellular calcium or cAMP but acts in synergy with these mediating signals. They also observe that the magnitude of changes induced by osmotic challenge parallel the steady-state renin release before the challenge. Furthermore, their data suggest that renin secretion in response to the osmotic challenge is primarily sensitive to the changes in osmolality rather than a steady-state condition. Although they observe that osmotic challenges alter perfusion rate, they also dissociate these changes from the renin response, suggesting that it is not simply a flow-dependent artifact. Thus their data may contradict the long-held bias of the inverse relationship between osmolality and renin secretion. They argue that their results are independent of flow, and also of an interaction with the macula densa pathway, suggesting a direct effect of osmolality on the JG cells themselves. This would seem even more at odds with the abundant in vitro data where the direct effect of osmolality on JG cells results in an inverse relationship between osmolality and renin release. The resolution to these apparently diametrically opposed results derived from two solid data sets is not provided but would seem to lie within the characteristics of the different experimental models. All in vitro studies over the past 20 years have been static or involved minimal and constant perfusion, suggesting that those findings are the result of changes in a steady state of cell adaptation to changes in extracellular osmolality, such that the rate of renin secretion is inversely related to the extracellular osmolality.”

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different osmotic conditions. In contrast, the isolated, perfused kidneys in the present study provide dynamic and transient changes, which are reflected in the speed and reversibility of the renin responses they report. The controlled conditions of the isolated, perfused kidney allow the present authors to make these abrupt changes without the hemodynamic or systemic adaptations incurred in the older in vivo literature, in which results were inconsistent and inconclusive. While I appreciate and value the in vitro data for what they tell us about possible trafficking of renin-containing granules, my bias is that in all probability these novel dynamic data provided by Kurtz and Schweda (9) more realistically reflect the nature of the JG cell as an osmosensor, reacting to changes in the nature of the renal perfusion. Overall, the lesson I take from this scientific exercise is that I should never become complacent in thinking I understand renal physiology; for as soon as I do, someone less willing to accept established doctrine will provoke me with a new vision and perspective, as these authors have done.

REFERENCES