Tubuloglomerular feedback in adenosine A₁ receptor-deficient mice

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“THE SUN WILL NOT RISE UNTIL after the first cup of coffee.” Who has not once required a mug of coffee to get going? Among the first things to do after draining the cup is to rebalance the body fluids. In fact, more volume is excreted than the amount of coffee consumed. Why is this so? Four members of our editorial team may have come a bit closer to answering this question (1, 6). The effects of caffeine may rely on their capability to inhibit adenosine receptors. Adenosine plays an important role in kidney function, as has been reported recently in this journal (3, 4, 7). Renin secretion is enhanced by adenosine, leading to larger quantities of ANG II, a potent vasoconstrictor. Moreover, adenosine may play the crucial role in mediating the tubuloglomerular feedback response. The tubuloglomerular feedback is one of the major mechanisms involved in autoregulating glomerular filtration and renal blood flow. The tubuloglomerular feedback mechanism enables the fine tuning of glomerular filtration. Excessive filtration leads to an increase in the distal tubular sodium chloride load. This is sensed by the macula densa, and then vasoconstriction of renal afferent arterioles occurs by a hitherto unknown substance. The enhanced preglomerular vascular resistance brings filtration back to normal levels. Previously it was held that renin played the decisive role in mediating the tubuloglomerular feedback. There is a clear relationship between early distal NaCl concentration and plasma renin levels (2). Accumulating evidence brought about by experiments using blockers of adenosine receptors indicates, however, that adenosine may have a more important role than previously believed. Indeed, adenosine is required to cause vasoconstriction of the renal afferent arterioles in the face of the distal tubular sodium chloride challenge. This has now been shown unequivocally in mice lacking functional adenosine A₁ receptors (1, 6). Microperfusion studies in these animals demonstrated the total absence of a tubuloglomerular feedback response. Currently, it seems that renin is only important for determining the pressure range and level of autoregulation (5). In the study published in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology (1), sodium excretion was more than twice as high in the A₁ receptor-deficient animals and mean arterial blood pressure was slightly elevated in the homozygous knockout mice. In the study by Sun et al. (6), however, the changes in these parameters did not reach statistical significance.

As pointed out by Brown and associates (1), the modest hypertension and natriuresis resemble the effects of caffeine at levels reached by normal coffee consumption habits. The authors therefore suggest that the A₁ receptor-deficient mouse could serve as a model for coffee drinkers! Because caffeine may block adenosine receptors unspecifically, it is not fully clear if this is the optimum model. However, their study has provided a crucial step for understanding the tubuloglomerular feedback.

REFERENCES