

# Letter to the Editor

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## **Response to Aliskiren Therapy Will Have Minimal Effect on Intracellular Renin of Renin-Producing Cells**

We appreciate Campbell's<sup>1</sup> thoughtful comments on our recently published cell culture data.<sup>2</sup> From our results, we deduced that the intracellular aliskiren concentrations are  $\approx 1\%$  of the extracellular levels. Given the in vivo plasma concentrations of aliskiren at therapeutic doses, combined with its putative high plasma protein binding ( $\approx 95\%$ ), he concluded that the "free" plasma concentrations of aliskiren would be  $< 10$  nmol/L, ie, too low to allow meaningful cellular accumulation of aliskiren. In fact, according to this concept, tissue aliskiren levels, being dependent on free plasma aliskiren, would never exceed plasma aliskiren levels. Yet, after a 2-week treatment of Sprague-Dawley rats with either a low or a high dose of aliskiren, extensive partitioning of aliskiren was observed in the kidney, its renal tissue levels being  $\leq 63.7$  times those in plasma.<sup>3</sup> The cell type in which aliskiren was localized could not be determined in this study. Given the virtual absence of renal clearance of aliskiren ( $< 1\%$ ),<sup>4</sup> it is, however, unlikely that such accumulation relates to clearance mechanisms. Furthermore, in a comparable study in double-transgenic rats harboring the human genes for renin and angiotensinogen, at 3 weeks after stopping aliskiren treatment (when the drug could no longer be detected in blood plasma), the renal tissue aliskiren levels were still in the range of its  $IC_{50}$ .<sup>5</sup> Similarly, in hypertensive patients, both blood pressure and plasma renin activity remained suppressed for several weeks after stopping aliskiren treatment.<sup>6</sup> This is too long to be attributed to the in vivo half life of aliskiren ( $\approx 40$  hours<sup>3</sup>) and, thus, may also point to an aliskiren reservoir outside the blood compartment. Finally, the high plasma protein-binding percentage reported by Campbell<sup>1</sup> needs to be interpreted with care, because it was calculated on the basis of data from 3 different laboratories, each applying their own specific assay conditions. In fact, a considerably lower percentage ( $\approx 50\%$ ) was reported by

Vaidyanathan et al.<sup>4</sup> Therefore, significant (renal) tissue accumulation of aliskiren appears to be possible, and future studies should now determine its precise cellular accumulation site(s), as well as the mechanism of such accumulation, particularly in view of the possibility that  $\geq 50\%$  of aliskiren in blood plasma is protein bound.

## **Disclosures**

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