Delineating the contributions of \( \text{AT}_{1\alpha} \) and \( \text{AT}_{1\beta} \) receptor-mediated uptake of ANG II in kidneys and adrenals

Rudy M. Ortiz

Division of Natural Sciences, University of California, Merced, California

Inappropriately elevated angiotensin II (ANG II) levels induced by infusion of ANG II or overexpression of the renin-angiotensin system (RAS) commonly result in increased intrarenal and intra-adrenal ANG II content (8). Derangement of renal function due to inappropriate activation of intrarenal RAS or augmented intrarenal ANG II content induced by receptor-mediated sequestration impairs the kidney’s ability to maintain \( \text{Na}^+ \) balance, and thus contributes to different forms of hypertension (7). The consequences of increased intra-adrenal ANG II in cardiovascular and renal diseases are not well described but are most likely associated with the effects of elevated aldosterone. An appreciation of the mechanisms that regulate intraorgan ANG II content and its subsequent effects will enhance our understanding of the contributions of these target tissues in the regulation of blood pressure.

Intrarenal and intra-adrenal ANG II. Under conditions of ANG II infusion or overexpression of RAS, tissue levels of ANG II are much higher than in plasma, resulting from increased local production since many tissues contain all components of RAS and/or increased receptor-mediated sequestration. Local ANG II production is regulated by negative feedback of ANG II on renin, and thus intrarenal levels of ANG II would be expected to decrease during increased ANG II protocols (infusion or RAS overexpression). However, antagonism of the ANG II receptor with a receptor blocker (ARB), which can stimulate renin release and thus increase ANG II generation, during long-term ANG II infusion consistently prevents the uptake of extracellular ANG II, suggesting that the augmentation of intrarenal ANG II (and possibly other tissues as well) is predominately mediated by the angiotensin receptor (3, 11, 14, 15). Furthermore, in the transgenic rat model that contains an inducible extrarenal renin gene (TGR-Ren2) and that is characterized by increased systemic renin and plasma ANG II, and suppressed renal renin, treatment with an ARB completely prevented the augmentation of intrarenal ANG II (6) further suggesting that the augmentation of intrarenal ANG II during elevated ANG II conditions is predominantly receptor-mediated, and that local production is minimal. Cervenka et al. (1) demonstrated a 2.7-fold increase in plasma ANG II concentration associated with a 47% decrease in kidney ANG II (although not significant) in non-volume expanded ANG II receptor knockout mice (Agtr1a\(^{-/-}\)), but because the kidney ANG II levels were not significantly reduced, the authors suggested that plasma and kidney ANG II levels are regulated independently. To help clarify the interpretation of this nonsignificant decrease in kidney ANG II, Li et al. (3) recently showed that renal intracellar ANG II levels in the kidney were significantly reduced in Agtr1a\(^{-/-}\) compared with wild-type, suggesting that the tissue metabolism of ANG II contributes to the regulation of plasma levels of ANG II. Nonetheless, Li et al. (3) could not ascertain whether the reduced kidney levels were due to reduced intracellular ANG II production or reduced receptor-mediated uptake of extracellular ANG II. Thus the issue of the relative contributions of local ANG II production vs. receptor-mediated sequestration to augmented intrarenal (and intraorgan) ANG II levels remains to be resolved. Furthermore, the contribution of intraorgan ANG II metabolism to the circulating pool of available ANG II warrants further investigation.

Two isoforms of the ANG II receptor, \( \text{AT}_{1\alpha} \) and \( \text{AT}_{1\beta} \), are expressed in rodent kidneys and adrenal glands (1, 4, 12). It is not known which \( \text{AT}_{1\alpha} \) receptor plays a predominant role in mediating ANG II uptake in rodents, nor is it clear whether the \( \text{AT}_{1\beta} \) receptor would assume the role of the \( \text{AT}_{1\alpha} \) receptor when the former is absent. Previous studies in rats and pigs using \( \text{AT}_{1\alpha} \) receptor antagonists were unable to determine the precise role of \( \text{AT}_{1\alpha} \) and \( \text{AT}_{1\beta} \) receptors, because the antagonists used in those studies block both receptor subtypes with similar specificities and affinities (10, 13, 15). The markedly elevated plasma ANG II concentrations observed in the Agtr1a\(^{-/-}\) model due to systemic deletion of \( \text{AT}_{1\alpha} \) receptors may alter the kinetics of \( \text{AT}_{1\beta} \) receptor- or other non-receptor-mediated mechanisms of ANG II uptake in the kidney and other tissues. Nonetheless, the use of the Agtr1a\(^{-/-}\) model will prove to be highly beneficial in addressing a number of these unresolved issues.

For many years, the focal organ has been the kidney, so data on the effects of elevated ANG II on other tissues such as the adrenal and heart are scarce. Originally, it was shown that ANG II infusion in rats did not increase intra-adrenal and intracardiac ANG II content and that treatment with an ARB actually exacerbated the levels of ANG II in both tissues (15); however, intra-adrenal and intracardiac ANG II levels were increased in the pig and the increase was prevented by an ARB, suggesting that intraorgan accumulation of ANG II during ANG II infusion is receptor mediated (10). Furthermore, recently we showed that both ANG II infusion (9) and overexpression of RAS (8) in rats resulted in increased intra-adrenal ANG II. However, the paucity of data and incongruent results of ANG II accumulation in other tissues necessitate further examination of the mechanisms contributing to the tissue levels of ANG II during either infusion or overexpression of RAS.

\( \text{AT}_{1\alpha} \) vs. \( \text{AT}_{1\beta} \). Clearly, a number of questions remain to be resolved with respect to the mechanisms contributing to intraorgan accumulation of ANG II during either ANG II infusion or overexpression of RAS; however, the recent contribution by Li and Zhou (4) has further advanced our understanding of these mechanisms. Using the Agtr1a\(^{-/-}\) model, Li and Zhou were able to quantify the contributions of the \( \text{AT}_{1\alpha} \) (80%) and \( \text{AT}_{1\beta} \) (20%) receptors to intracellular uptake of ANG II during ANG II infusion, indicating that the \( \text{AT}_{1\alpha} \) receptor is largely
levels were cell surface receptor-bound ANG II, renal intracellular ANG II cold acid buffer to exclude the extracellular ANG II and the 13–15). However, after kidneys were perfusion-washed with a previous findings in rats and pigs that show that treatment with mice, which at first glance would appear to be at odds with implications.

mediated sequestration of tissue ANG II to the regulation of enhancement our understanding of the contributions of receptor-


ACKNOWLEDGMENTS
I thank Dr. L. G. Navar for discussion of and comments on this topic that greatly improved the presentation.

REFERENCES


