Insights from direct renal insulin infusion: a new hammer for an age-old nail

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Running Title

Kidney-restricted hormone delivery offers new insights

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In biology, and particularly in renal physiology, there is often a delay between observations of clinically relevant phenomena and elucidation of the underlying mechanisms, because the tools ("hammers") available to researchers are insufficient and require development of new and innovative techniques to overcome these hurdles. The role of insulin action in different tissues is one such phenomenon. Since the work of De Fronzo et al. (1), many investigators have tried to tease apart how and if insulin increases blood pressure due to enhanced renal sodium reabsorption and whether this is due to direct or indirect actions on the kidneys, nervous system, or vasculature. In this issue, Irsik et al. report on a technique to deliver insulin to the intact rat kidney in order to measure its direct effect on renal ion handling and blood pressure.

The central role of the kidney in determination of blood pressure has been appreciated since Guyton’s recognition of sodium excretion as a critical regulator of blood volume (2). Over the past several decades, many studies in humans have demonstrated strong associations between hypertension and conditions associated with insulin resistance and concomitant hyperinsulinemia (e.g. metabolic syndrome and type 2 diabetes mellitus). Several lines of evidence support the hypothesis that insulin may act in the kidney to increase blood pressure (9). Insulin infusion, dosed to mimic the hyperinsulinemia of insulin resistance, decreases sodium excretion in humans (1) and in many pre-clinical models, and serum insulin concentration associates with higher blood pressure in humans (7). However, efforts to determine the organ and cell types that may transduce insulin’s antinatriuretic and possible hypertensive effects have been challenging. To address this issue in rats, Irsik et al. deliver insulin to the kidney via a microcatheter placed into the renal artery of one kidney after contralateral nephrectomy. The authors demonstrate convincingly that there are negligible systemic effects of the insulin infusion and thus provide an elegant model of enhanced, kidney-restricted insulin
signaling without changes in blood glucose. These rats developed increasing blood pressure over one week of chronic infusion surprisingly, without an antecedent decrease in net sodium excretion.

This work by Irsik et. al. lays the groundwork for a critical next question: is insulin action in the renal vasculature sufficient to augment blood pressure? Thus far, the role of insulin signaling to augment blood pressure has mainly focused on insulin’s ability to augment sodium reabsorption in the nephron but the results have been incongruent. While, several sodium transporters and channels are upregulated in expression or activity with elevated insulin *in vivo, ex vivo, and in vitro* (7), Tiwari et. al.(10) showed that constitutive deletion of the renal tubular insulin receptors, presumably with intact receptors in the vasculature, develop hypertension. In light of the findings published by Irsik et. al., observed alterations in renal insulin signaling to increase oxidative stress, nitric oxide and thromboxane (5), may be of particular relevance for further studies of the renal vasculature. Irsik et. al. helps to narrow the wide range of putative mechanisms to study in rats, and its methodology could be applied in non-nephrectomized rats to study the renal molecular mechanisms of insulin-mediated increased blood pressure. Using unilateral renal hyperinsulinemia, the contralateral kidney would respond to any systemic effects, providing a control for indirect effects of renal insulin infusion (e.g. downregulation of distal sodium transporters or channels if insulin enhances proximal tubular sodium reabsorption).

It should be noted that these data contrast previous work in dogs (3), also by Brands and colleagues, in which intrarenal insulin infusion did not alter blood pressure. These data echo the disparate results across species (from mice to humans) which have confounded the field of renal insulin signaling (7). The reasons for these differences are
still unknown. Potential explanations include differences in insulin sensitivity, pharmacokinetics, or compensatory effects of contralateral nephrectomy.

An unresolved issue not directly addressed by this important work is the contribution of renal insulin signaling to blood pressure in disease or genetic models characterized by insulin resistance, such as metabolic syndrome and diabetes mellitus. Prior work by this same group have demonstrated that while chronic insulin did not reduce sodium excretion in healthy dogs, diabetic dogs, in response to insulinopenia, experience dramatic sodium excretion that is rescued with insulin treatment (6). In addition, there may be a significant distinction between insulin resistance-mediated compensatory hyperinsulinemia and insulin infusion. For example, our laboratory showed that an increase in epithelial sodium channel activity, measured in several insulin-sensitive mouse models with insulin treatment, was absent in insulin resistant, hyperinsulinemic mice (8). Using the advances in kidney-restricted hyperinsulinemia described in Irsik et al., this issue could now be addressed in rat models of insulin resistance and hypertension. Moreover, utilizing this technique in transgenic animals is now more tractable than in the aforementioned use of direct renal insulin infusion in dogs.

Another intriguing implication of this work is the potential action of insulin on renal insulin-like growth factor 1 (IGF-1) receptors. Although the experiments were conducted quite differently, Tiwari et al. (10) observed the opposite of Irsik et al., i.e. that constitutive insulin receptor deletion predisposed to higher blood pressure and sodium retention. However, insulin, at supraphysiologic doses, can bind IGF-1 receptors and increase sodium transport, and IGF-1, presumably through its own cognate receptor, can enhance sodium reabsorption and hypertension. Whether renal IGF-1 receptors could bind insulin at less than supraphysiologic doses in vivo is unknown (4).
Irsik *et. al.* have contributed to our understanding of the renal actions of insulin for blood pressure and have opened the door for further investigation. The authors are to be commended for the development of this new technique and the insights that this work has provided, and utilization of this technique in disease models will no doubt further elucidate the role of insulin signaling in the kidney. Direct renal infusion can also be adapted to address the actions of other extrarenal hormones with multiple renal and extrarenal sites of action, e.g. glucagon, glucagon-like peptide-1, etc. Perhaps soon this new hammer will find another nail to strike.
References


