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Resistance to insulin and kidney disease in the cardiorenal metabolic syndrome; role for angiotensin II ☆

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ABSTRACT

The presence of insulin resistance is increasingly recognized as an important contributor to early stage kidney disease independent of the contribution of diabetes. Important in this relationship is the strong correlation between hyperinsulinemia and low levels of albuminuria (e.g. microalbuminuria). Recent work highlight mechanisms for glomerular/tubulointerstitial injury with excess insulin and emerging evidence identifies a unique role for insulin metabolic signaling and altered handling of salt reabsorption at the level of the proximal tubule. Evidence is also emerging for the role of insulin signaling in the glomerulus both epithelial and endothelial. Central to the mechanism of injury is inappropriate activation of the RAAS.

1. Introduction

The presence of insulin resistance is central to the cardiorenal metabolic syndrome and is increasingly recognized as a risk factor for both kidney and cardiovascular disease independent of overt diabetes (Pulakat et al., 2011; Sowers, 2004; Alberti and Zimmet, 1998; NCEP-ATEP III, 2006; Grundy et al., 2006; Manhiani et al., 2012; Shepard and Kahn, 1999). The presence of insulin resistance implies an impaired biological and physiological response to insulin-dependent metabolic signaling in traditional insulin sensitive tissues such as skeletal muscle, liver, adipose tissue and pancreas as well as non-traditional cardiovascular tissue such as the heart and kidney (Pulakat et al., 2011; Sowers, 2004; Grundy et al., 2006). Much of the work on insulin responses in cardiovascular tissue has focused on NO bioavailability in endothelial function, contractility in vascular smooth muscle cells and relaxation of cardiomyocytes, and regulation of sodium excretion in the kidney as unifying concepts in insulin resistance and cardiovascular disease. In this context, work done in humans and animal models of insulin resistance that display compensatory increases in circulating insulin (e.g. hyperinsulinemia) either through endogenous increases in insulin production, through exogenous infusion, or genetic receptor deletion support a direct correlation with endothelial dysfunction, hypertension and kidney disease (DeFronzo et al., 1975; Gesek and Schoolwerth, 1991; Catena et al., 2003; Shepard and Kahn, 1999; Stenvinkel et al., 1992). Although, a large body of work supported acute insulin-mediated sodium retention, chronic insulin infusion failed to retain sodium in dogs sparking a hot debate over the chronic effects of insulin on sodium retention. Recently, chronic insulin infusion over 6 days during the acute phase of alloxan induced diabetes has shown that prevention of hypoinsulinemia in a hyperglycemic setting can offset natriuresis and diuresis, thereby raising the possibility that insulin is indeed sodium retaining (Manhiani et al., 2012).

Recent work by our group and others implicate inappropriate activation of the renin–angiotensin–aldosterone system (RAAS) with subsequent elevations in angiotensin (Ang) II and aldosterone to alterations in insulin signaling pathways, reactive oxygen species formation and endothelial dysfunction in heart and kidney disease (Manhiani et al., 2012; Shepard and Kahn, 1999; Whaley-Connell et al., 2011; Sherajee et al., 2012; Hitomi et al., 2011; Wei et al., 2007; Ketsawatsomkron et al., 2010). Furthermore, all of the above features of insulin resistance correlate well with proteinuria in kidney disease and diastolic dysfunction in the heart, thereby, suggesting a critical role for insulin resistance/hyperinsulinemia as a potential unifying mechanism in the cardiorenal metabolic syndrome. Herein, we review emerging data on the critical role for insulin metabolic signaling, the RAAS, and kidney disease.

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2. The link between insulin resistance and chronic kidney disease (CKD) in the cardiorenal metabolic syndrome

There exists a strong association between insulin resistance and CKD documented through numerous population studies. Data from cohorts such as the national health and nutrition examination survey (NHANES) and the National Kidney Foundation's Kidney Early Evaluation Program (KEEP), reveal a concurrent increase in prevalence of obesity, the presence of insulin resistance, and incident end-stage renal disease (ESRD) suggesting that insulin resistance independent of diabetes is one of the leading contributors to the recent expansion of CKD persons (USRDS, 2006; Ejerblad et al., 2006; Iseki et al., 2004; Yamagata et al., 2007; Hsu et al., 2006; Saab et al,, 2001; Gelber et al., 2005). In this regard, it becomes paramount to distinguish the risk for CKD between earlier stages in the prediabetic population (e.g. those with insulin resistance) and overt diabetes with the potential for complications such as progression to ESRD. In this context, data from Kaiser Permanente and the US Renal Data System (USRDS) utilizing more than 320,000 individuals suggest this relationship between insulin resistance and CKD extends beyond early stages of CKD and that after controlling for the presence of diabetes, individuals that are insulin resistant are at an increased risk for progression to ESRD (Fox et al., 2004).

To extend this notion into prospective evaluation of insulin sensitivity and kidney function, recent work supports a linear correlation with insulin resistance and decline in renal function using clearance rather than estimating equations for glomerular filtration rate (Kobayashi et al., 2005; Emoto et al., 1997; Chen et al., 2003a, 2004a,b). In one study, investigators explored glucose disposal in relation to creatinine clearance (Kobayashi et al., 2005). Healthy participants had a higher glucose disposal rate (GDR) compared to patients with CKD. Additionally, this study reported a positive correlation between GDR and creatinine clearance and negative association between GDR and serum creatinine (Cr) level. This holds true in more advanced CKD, a cohort with proteinuria and serum Cr > 2.0 mg/dL, demonstrated lower insulin sensitivity than individuals that were normo-albuminuric (Emoto et al., 1997). Following adjustments, increased BMI was an independent contributor to insulin sensitivity in those with CKD. Another analysis of NHANES in non-diabetic participants supports a direct correlation between increasing serum insulin and serum C-peptide levels with CKD.

In order to discern the risk with insulin resistance and earlier stages in the evolution of CKD, investigators have sought to establish correlates with the presence of microalbuminuria. Data from the NHANES and the KEEP support an association between elements of the cardiorenal metabolic syndrome (aka metabolic syndrome) and the respective risks for CKD and microalbuminuria (Chen et al., 2003a; Chen et al., 2004a,b; Whaley-Connell et al., 2010). From these studies each component correlates with microalbuminuria. Data from these same studies also suggest there exists a graded relationship between the number of components present and a corresponding increase in the prevalence of microalbuminuria. Data from the Insulin Resistance in Atherosclerosis Study (IRAS) extend this relationship, when adjusted for age and sex there is a decreasing prevalence of microalbuminuria with increasing insulin sensitivity (Mykkanen et al., 1998).

It is clear from population based studies that there exists a strong relationship between insulin resistance and hyperinsulinemia and the presence of early stage CKD in those with microalbuminuria.

3. Normal insulin signaling in the kidney

In order to understand the concept of how hyperinsulinemia/insulin resistance can be associated with microalbuminuria one would need to understand how insulin talks to cells in the kidney (Tiwari et al., 2007). Insulin has been shown to bind to both the insulin receptor and insulin-like growth factor receptor to promote its effects in the kidney (Nakamura et al., 1983; Tiwari et al., 2007) (Fig. 1). Generally in any tissue, binding to the insulin receptor triggers tyrosine kinase autophosphorylation that then leads to a cascade of events including recruitment of insulin receptor substrate (IRS1/2) which then engages phosphoinositol 3-kinase (PI3-K) to the plasma membrane (Gual and Le Marchand-Brustel, 2005; Tiwari et al., 2007). Docking of PI3-K requires tyrosine phosphorylation of IRS-1 at positions 608 and 628 (rat IRS-1 nomenclature) (Gual and Le Marchand-Brustel, 2005). PI3-K catalyzes PIP2 to PIP3 that then activates PDK1 that in turn recruits and activates Akt via Ser308 and Thr473 phosphorylation. It should be noted that PI3-K and Akt activation are not insulin specific and can be mediated by multiple pathways including RAS via GPCR activation (angiotensin II, Ang II) (Fig. 1). Activation of Akt is central to insulin signaling in the cells and depending on the context can lead to activation of metabolic pathways such as uptake of glucose via translocation of GLUT4 to the plasma membrane and glycogen synthesis via glycogen synthase kinase (GSK3β) phosphorylation and inhibition. In addition, other pathways such as growth/mitogenic (MAPK/ERK1/2, mTORC1/S6K), NO production (eNOS), cell cycle (overcome G1/G2 arrest), survival (Bcl2, NF-κB), autophagy (ATG, ULK), actin cytoskeleton remodeling (S6K1) are also activated by insulin signaling. How, activation/repression of these pathways leads to albuminuria is the topic of much debate and current work.

4. Abnormal insulin signaling: activation of serine/threonine kinases

Our knowledge about the specifics of insulin signaling derangements in the kidney is obviously limited due to limitations in the understanding of normal insulin signaling. However, some details are likely common and overlap with insulin signaling in other organ systems and cell types (Fig. 1). In this section, we will discuss some of the mechanisms by which cells become resistant to the actions of insulin. Broadly, the major players are the insulin receptor, IRS1/2 and Akt while the processes involved are serine/threonine phosphorylation, tyrosine phosphorylation, interaction with SOCS, regulation of expression, cellular localization and degradation (Gual and Le Marchand-Brustel, 2005).

In the context of resistance to insulin-dependent activation of metabolic signaling pathways, stimulation by factors such as TNF-α, free fatty acids, cellular stress, amino acids, hyperinsulinemia, Ang II, endothelin-1 leads to increased serine and decreased tyrosine phosphorylation of IRS-1. For example, phosphorylation at ser^{307} promotes separation of IRS-1 from insulin receptor, decreases tyrosine phosphorylation and promotes proteasomal degradation (Gual and Le Marchand-Brustel, 2005). Phosphorylation at ser^{612} and ser^{632} decreases the docking ability for PI3-K, thereby leading to decreased insulin metabolic signaling and glucose uptake (Gual and Le Marchand-Brustel, 2005). In contrast, phosphorylation at ser302 may promote increased activation of IRS-1 by insulin in vitro. Recent work highlights serine kinases that are redox sensitive in promotion of this excessive serine phosphorylation (Pulakat et al., 2011; Sowers, 2004; Gual and Le Marchand-Brustel, 2005) and may include known redox-sensitive serine kinases such as JUN NH_2-terminal kinase (JNK, ser^{307}), protein kinase C (PKC-θ, ser^{307} and ser^{1101}), extracellular receptor kinase (ERK, ser^{612} and ser^{632}), and recently the mammalian target of rapamycin (mTOR, ser^{612} and ser^{632}) pathway (Pulakat et al., 2011; Sowers, 2004; Marmy-Conus et al., 2002; Bhandari et al., 2001). It is thought excess activation of the RAAS with elevations in both Ang II and aldosterone promote activation of these redox-sensitive