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Editorial

A brief history of insulin resistance: from the first insulin radioimmunoassay to selectively targeting protein kinase C pathways

The first description of insulin resistance goes, historically, back to 1960, shortly after the development of radioimmunoassays made the quantification of insulin in the serum possible and subsequently demonstrated that individuals with late-onset diabetes mellitus had high insulin levels [1,2]. Drs Yalow and Berson [1,2] defined *insulin resistance* as "a state in which a greater than normal amount of insulin is required to elicit a quantitatively normal response." The next landmark discovery in the history of insulin resistance was the discovery of the insulin receptor and the observation that hyperinsulinemia, secondary to insulin resistance, was associated with abnormal binding of insulin to its receptor in rodent models [3,4]. It was not until 1976 when the first evidence, that insulin receptor defects could be associated with insulin resistance in humans, provided translational evidence for the importance of insulin resistance in human pathophysiology [5]. Kahn et al [5] described 2 syndromes that where characterized by acanthosis nigricans, virilization, anovulation, hirsutism, acne, and defective binding of insulin on insulin receptor of circulating lymphocytes. The first syndrome was characterized as type A insulin resistance when the latter occurred in the absence of anti-insulin antibodies and the defect of the insulin receptor was primary, whereas it was characterized as type B when it was associated with clinical features of autoimmune diseases and it occurred in the presence of neutralizing anti-insulin antibodies [5]. The description of type A and type B syndrome was followed by the description of the hyperandrogenism, insulin resistance, and acanthosis nigricans syndrome; the Rabson-Mendenhall syndrome; leprechaunism; and lipodystrophy, all representing rare syndromes of extreme insulin resistance [6-8]. The description and subsequently the molecular understanding of these extremely rare syndromes not only played a vital role in our understanding of the mechanisms involved in insulin resistance but importantly opened the road for a better understanding of disease states associated with insulin resistance through the study of the molecular mechanisms underlying insulin resistance in these disease states.

Insulin resistance lies in the core pathophysiology of obesity, type 2 diabetes mellitus, the metabolic syndrome, and polycystic ovarian syndrome, which constitute disease states of major and increasing importance in terms of morbidity and mortality in modern society [9-11]. In addition, there is strong accumulating evidence that insulin resistance is an independent risk factor for several malignancies, such as colon [12,13], breast [14-16], endometrial cancer [17-19], melanoma [20], and lung cancer [21]. Insulin resistance is also tightly associated with increased cardiovascular morbidity and mortality [22], mostly by adversely modifying well-established cardiovascular risk factors such as dyslipidemia and hypertension [22-24] and by causing endothelial dysfunction [25].

One of the most well-established mechanisms through which insulin resistance contributes to the overall risk for coronary artery disease is the development of an unfavorable lipoprotein profile [26-28]. The latter is characterized by increased triglyceride (TG) and very low-density lipoprotein (VLDL) levels, decreased high-density lipoprotein levels, normal low-density lipoprotein (LDL) concentration, and high percentage of atherogenic small-dense LDL [29]. Insulin resistance is associated with postprandial hyperchylomicronemia and hyperlipidemia, mostly through impairment of the activating insulin action on lipoprotein lipase [30], which is responsible for chylomicron and VLDL catabolism in euglycemic individuals. In addition to the attenuation of lipoprotein lipase activity, insulin resistance in the liver causes downregulation of the LDL receptor and thus decreased LDL and remnant clearance [31]. Hypertriglyceridemia is caused by increased secretion of VLDL by the liver, secondary to increased free fatty acid flux from the adipose tissue, de novo hepatic lipogenesis, and decreased VLDL clearance, all of which are results of insulin resistance [29]. The enzyme cholesteryl ester (CE) transfer protein exchanges TGs of the VLDL particles with CEs of the LDL particles. In insulin-resistant states, there is a surplus of VLDL particles; and through the action of CE transfer protein, the LDL particles become highly enriched in TG and depleted of CE [32]. These particles are further processed by hormonal sensitive lipase, the action of which is increased by insulin resistance, to ultimately form the highly atherogenic small-dense LDL particles [29]. These mechanisms, in conjunction with defective lecithin-cholesterol acyltransferase (LCAT) activity, contribute to the dyslipidemia, including low high-density lipoprotein levels, seen in individuals with insulin resistance [29].

Importantly, it has also been described that insulin resistance leads to hypertension, even after taking into consideration obesity as a confounding factor [33], with elevated insulin levels preceding the development of systolic hypertension [34]. Interestingly, insulin resistance is highly prevalent in hypertensive patients, irrespective of whether they receive antihypertensive medication or not, and poses them to a higher risk for cardiovascular disease [35]. Although the association between hypertension and insulin resistance is well established, the underlying causal mechanisms remain largely unknown [23]. One of the most appealing proposed mechanisms is that insulin resistance attenuates the natriuretic response to sodium load, leading to a greater water and salt retention [36], while at the same time, insulin resistance causes endothelial dysfunction through impairment of the nitric oxide vasodilatory response [37].

At the molecular level, insulin signaling starts with the binding of insulin to insulin receptor, causing autophosphorylation of tyrosine residues in the intracellular side of the receptor [38]. The phosphorylated and thus activated insulin receptor phosphorylates insulin receptor substrates (IRSs) and particularly IRS1 and IRS2 [39,40]. Downstream signaling pathways that are activated by the phosphorylated forms of IRS1 and IRS2 include the IRS1/PI3K/Akt pathway that ultimately leads to activation of AS160 (GLUT-4 translocation to cell membrane and thus enhanced glucose uptake) and GSK-3 (glycogen synthesis) [41-44] as well as the IRS2/P3K/atypical protein kinase C (aPKC) pathway, ultimately leading to enhanced glucose uptake through GLUT-4 upregulation in the muscle and lipogenesis through SREBP-1C upregulation in the liver. Atypical PKC in the liver also has a proinflammatory effect by inhibiting IKK, which is the major inhibitor of IκB, and ultimately disinhibiting NFκB action and upregulating several proinflammatory cytokines [41-45]. Other signaling molecules that are downstream of the IRS pathway are the ERK1/2, the MAPK (cellular proliferation), and the JNK-p38 (response to cellular stress) pathways [46]. Studies of ex vivo–treated muscle have demonstrated that insulin-resistant subjects have impairment of the insulin signaling pathway at the level of IRS1/2-PI3K and aPKC, whereas overt diabetic patients exhibit impairment at the level of insulin receptor and Akt phosphorylation [46].

Among all signaling molecules described above, PKC is the one that has recently attracted most of the attention, especially because of its close association with insulin resistance and diabetes mellitus [47] as well as with complications of diabetes [48]. From a biochemical point of view, the members of PKC are serine/threonine kinases and are categorized in 3 subgroups: classic PKCs (α, β-I, β-II, and γ), novel PKCs (δ, ε, η, and θ), and atypical PKCs (ζ, λ, and ι) [47]. The difference between typical and novel PKCs is that the latter are not activated by calcium [48]. The "atypical" PKCs are named so because they are not regulated from diacylglycerol (DAG), phorbol-12-myristate-13-acetate, and calcium, which is a property "typical" for the classic PKCs [49]. Both typical and novel PKCs are activated by DAG that is increased intracellularly in hyperglycemic states [50]. In diabetes mellitus, intracellular DAG levels, and thus PKC activation, are increased in the aorta, retina, renal glomeruli, pericytes, and mesangial cells as well as in the skeletal and smooth muscle and the liver [48]. Animal models have demonstrated that PKC activation has been associated with both macrovascular and microvascular complications of diabetes and, specifically, medium-large vessel atherosclerosis (PKC-β), cardiomyopathy (PKC-α and -β), retinopathy (PKC-β and -δ), nephropathy (PKC-β), and neuropathy (PKC-α, -β, -γ, -δ, and -ε) [48]. There is strong evidence that aPKC plays a central role in fine-tuning glucose homeostasis (*a*) by increasing glucose uptake by skeletal muscle through promotion of GLUT-4 surface translocation [51] and (*b*) by phosphorylating serine/threonine residues of IRS-1 acting as a negative feedback autoregulatory loop in the insulin receptor signaling cascade [52-54]. In addition, there is accumulating evidence that exercise can increase aPKC phosphorylation levels, contributing to enhanced glucose uptake from the exercising muscle [55,56]. Atypical PKCs have also been demonstrated to regulate genes associated with β-cell function and insulin secretion from the pancreas [57].

Targeting the PKC pathway(s) has recently been the focus of research efforts in both academia and industry; the first selective PKC inhibitors have already reached phase II and III clinical trials. Ruboxistaurin (RBX), a selective PKC-β inhibitor, is the most studied PKC inhibitor to date [48]. Clinical trials in which RBX was used to treat diabetic retinopathy [58,59], nephropathy [60,61], and neuropathy [62] have yielded promising results in terms of efficacy and have shown a favorable adverse effect profile [63]. In addition, RBX reverses hyperglycemia-induced endothelial dysfunction [64] and restores femoral-mediated dilatation in diabetic patients [65]. Rottlerin is another novel inhibitor of PKC that was initially assumed to selectively inhibit PKC-δ; recent evidence however demonstrates that this is not an efficient PKC-δ inhibitor, whereas it interferes with the activity of many kinase and nonkinase mediators but also blocks potassium channels [66]. The latter was apparently the reason for the inability of this inhibitor to reach the stage of clinical trials. Other inhibitors of PKC-δ (KAI-9803) and -ε (KAI-1678, KCe-12, and KCe-16) have been evaluated in rodent models of myocardial infarction and insulin resistance, accordingly demonstrating an amelioration of the pathological conditions in each model [67]. Midostaurin, bryostatins (typical and novel PKC), enzastaurin (PKC-β), and aprinocarsen (PKC-α) are PKC inhibitors that had been developed as antineoplastic medications; but unfortunately, very promising results from in vitro and animal studies failed to be translated in humans [68]. Finally, none of the aPKC inhibitors has currently reached the stage of clinical trials.

In this issue of *Metabolism*, Sajan and colleagues [69] present marked improvements in obesity, hepatosteatosis, hyperlipidemia, insulin resistance, and glucose metabolism by treating a model of obese/type 2 diabetes mellitus mice with 2 isoform- and liver-specific inhibitors of PKC-λ/ι. The inhibitors that they used were 1H-imidazole-4-carboxamide, 5-amino-1-[2,3-dihydroxy-4-61 [(phosphonooxy)methyl] cyclopentyl-[1R-(1a,2b,3b,4a)], a molecule that binds to the substrate-binding site of PKC-λ/ι [70], and aurothiomalate, a molecule that interferes with PKC-λ/ι PB1-dependent scaffolding [71]. The investigators used a muscle-specific PKC-λ heterozygous knockout mouse model in which PKC-λ deficiency leads to impaired glucose uptake by the muscle and,

consequently, to hyperinsulinemia, obesity, and insulin resistance and activation of liver aPKC [44]. The authors demonstrate that treating these mice with either 1H-imidazole-4-carboxamide, 5-amino-1-[2,3-dihydroxy-4-61 [(phosphonooxy)methyl] cyclopentyl-[1R-(1a,2b,3b,4a)] or aurothiomalate reversed the metabolic syndrome phenotype (hyperglycemia, hypertriglyceridemia, hyperinsulinemia, hepatosteatosis, and abdominal obesity) through decreasing hepatic aPKC phosphorylation and thus decreasing aPKC activation. These findings are novel and have important translational potential not only in the area of de novo drug design but also because they may provide a deeper insight on the pathophysiological mechanisms that underlie insulin resistance, obesity, diabetes, and the metabolic syndrome.

The model used for testing these inhibitors was a Cre-Lox engineered mouse model, one of selective deactivation of PKC-λ in the muscle [44]. The latter resulted in a decrease of muscular glucose uptake by 80% in the homozygotes and 50% to 60% in the heterozygotes KO mice, which was attributed to decreased GLUT-4 membrane localization [44]. Metabolic syndrome phenotype also developed, particularly, insulin resistance with impaired glucose tolerance and islet β-cell hyperplasia, abdominal adiposity, hepatosteatosis, hypertriglyceridemia, and dyslipoproteinemia. This is an excellent model for testing the efficacy of potential therapeutic agents of this class, although it may not be as representative of garden-variety insulin resistance/obesity in humans as other models such as the diet-induced obese model [72,73] or the brown adipose tissue ablated model [74]. In the latter, animals develop remarkably decreased energy expenditure and hyperphagia that ultimately lead to obesity, severe insulin resistance, diabetes, and hyperlipidemia [74]. Replication of these results in other animal models of insulin resistance and obesity and particularly in the diet-induced obese model that most closely resembles the development of insulin resistance in humans will certainly have to follow before further development of these, or similar compounds, ensues. These compounds should also be tested in animal models of diabetes and cardiovascular disease before proceeding to further development and/or phase I and early proof-of-concept clinical trials. In any case, the data presented herein provide proof of concept in mice [69].

In summary, these data demonstrate that PKC is an emerging molecular target for the treatment of insulin resistance, obesity, diabetes mellitus, and the metabolic syndrome. Sajan and colleagues [69] demonstrate the pathogenic role of hepatic aPKC in the development of diabetes, obesity, and other features of the metabolic syndrome, providing for the first time evidence that novel, chemical agents can be used to selectively target hepatic aPKC isoforms and rapidly improve clinical abnormalities in these disorders. More data need to be collected; and results should be confirmed and extended using other obesity, diabetes, and cardiovascular disease animal models before testing these emerging agents in human studies. It is anticipated that, if results are positive, these experiments may have great impact in the therapeutics of several disease states associated with insulin resistance such as obesity, diabetes, and the metabolic syndrome, as well as the associated comorbidities.

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