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Novel therapies in type 2 diabetes: insulin resistance

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Key messages:

1. Obesity is an important contributor to the development of insulin resistance via multiple mechanisms, particularly ectopic fat deposition.
2. The increasing understanding of the pathogenesis of insulin resistance allowed the development of several agents targeting difference aspects of the pathogenesis of insulin resistance
3. The development of these agents has been relatively slow due to the complexity of insulin resistance pathogenesis and that many components of the insulin signalling pathway are involved in other pathways such as cell survival and apoptosis.
4. Lifestyle interventions and treating obesity remain the cornerstone of treating insulin resistance
5. Sleep-related disorders are an increasingly recognised treatment target for insulin resistance

Abstract

Insulin resistance play an important role in the pathogenesis of Type 2 diabetes and cardiovascular disease. Obesity is a major risk factor for the development of insulin resistance. Hence, treating obesity with lifestyle interventions is the cornerstone of managing insulin resistance. However, when lifestyle interventions fail to produce sustainable impact, then pharmacotherapy and/or bariatric surgery can produce significant improvements in weight, insulin resistance and glycaemic measures. Ectopic fat in the liver and muscle is one of the main mechanisms via which obesity impact on insulin sensitivity. Hence, there are currently multiple therapeutic interventions in development that aim to improve ectopic fat which. With better understanding of the insulin signalling pathways, multiple agents are under development targeting different components of this pathway from the level of insulin receptor to the level of protein kinase B activation and the translocation of glucose transporters. The development of these agents has been slow due to the complexity of the insulin signalling pathway, the multiple negative feedback signals and that the molecules involved in insulin signalling are also involved in other pathways such as cell survival and apoptosis. Sleep-related disorders are increasingly recognised as independent risk factor for the development of insulin resistance and Type 2 diabetes; targeting sleep-related disorders as a treatment strategy for insulin resistance is under evaluation. In this article, I will briefly review the future treatments of insulin resistance that are in the pipeline and I will also briefly review the role of bariatric surgery and sleep-related disorders in the treatment of insulin resistance.

Introduction

Type 2 diabetes (T2D) is characterised by chronic hyperglycaemia caused by reduction in insulin secretion as a result of β-cell dysfunction and impaired insulin action as a result of insulin resistance (IR)[1]. IR results in impaired glucose uptake in the muscle, liver and adipose tissue, reduced glycogen synthesis in the liver and muscle, increased hepatic gluconeogenesis and increased lipolysis and release of fatty acids (FA) and glycerol[2]. Glycerol and FA contribute to and worsen IR, gluconeogenesis and ectopic fat accumulation in the liver and the muscle[2]. IR also contributes to the development of cardiovascular disease as it is associated with hypertension, dyslipidaemia, hypercoagulability, sympathetic activation and reduced insulin-dependent nitric oxide production and increased endothelin-1[3-5]. Hence, IR is an important treatment-target in patients with T2D[6].

Metformin and pioglitazone are the main available pharmacological agents to improve insulin sensitivity in patients with T2D, both are associated with variety of adverse events, have multiple contradications and their efficacy is not sustainable on the long run[7]. Hence there is a need for more therapies targeting IR in line with the improvements in the understanding of IR pathogenesis. However, it must be emphasised that lifestyle interventions and weight loss remains the cornerstone of managing IR and T2D[8].

In this article, I will provide an overview of the pathogenesis of IR and how this is related to the development of new treatments. In addition, I will briefly highlight the importance of targeting obesity and more novel life style factors that can impact on IR such sleep-related disorders. A more detailed review of IR pathogenesis can be found in[2;9].

The pathogenesis of insulin resistance

In brief, insulin binding to the α-subunit of the insulin receptor results in the phosphorylation of the insulin receptor substrates1 and 2 (IRS-1 & -2) which leads, via several intermediary steps, to activation of protein kinase B (AKT)[8]. AKT activation results in the translocation of the glucose transporters (GLUTs) to the cell surface, allowing glucose entry, and the activation of glycogen synthase to stimulate the storage of glucose as glycogen[9]. IR can result from deficits in any part of the insulin signalling pathway resulting in inadequate response to insulin **(Figure 1)**[7].

IR results from complex and multifactorial interactions between the genes and the environment[10]; but obesity remains the major risk factor for development of IR and T2D[10]. Obesity contributes to the development of IR via several mechanisms **(Figure 2)** [2;9;10].

Ectopic fat and lipids accumulation in the liver (non-alcoholic fatty liver disease (NAFLD)) and skeletal muscle (intramyocellular lipid IMCL) plays an important role in the pathogenesis of IR[2;9]. IMCL has been shown to be a better predictor of IR than fat mass and several studies have shown that IMCL blocks glucose entry to the muscles in obese and lean individuals with and without T2D[2]. The impact of IMCL and NAFLD on IR is mediated via diacylglycerol (DAG) accumulation leading to protein kinase C (PKC) activation which impairs insulin-stimulated tyrosine phosphorylation of IRS-1 and the consequent activation of phosphatidylinositol 3-kinase (PI3K) resulting in reduction in AKT[2;11].

Ectopic fat accumulation is caused by increased supply of FA as a result of increased lipolysis caused by increased adipose tissue inflammation[11]. FA are esterified upon cellular entry to form acylglycerols or ceramides, which can reduce AKT activation[9;12] . In addition, the inflammation associated with obesity can activate JNK-1, that can bock the IRS-1, and IKK that can lead to increased ceramides[9].

Pharmacotherapy for Insulin resistance under development

Improving insulin sensitivity can be achieved by addressing the causes of IR (such as obesity, sedentary behaviour or more emerging factors such sleep disorders), or the mechanisms via which obesity impact on IR (such as ectopic fat, inflammation or adipokines) or the deficits in the insulin signalling pathway (such as activating the insulin receptor or potentiating the phosphorylation that occur following the insulin receptor activation). Currently available treatments for IR exert their impact by combinations of the above-mentioned mechanisms. For example, metformin increases the phosphorylation of the insulin receptor by increasing the β-subunit tyrosine kinase activity (TKA) and activation of adenosine 5'-monophosphate-activated protein kinase (AMPK), which inhibits tyrosine phosphatases that are responsible for the dephosphorylation of the insulin receptor[13;14]. In addition, AMPK activation results in decreased lipolysis in adipose tissue, decreased hepatic lipogenesis, increased fatty acid oxidation in the liver and muscle and increased glucose uptake[13]. Thiazolidinediones improve IR by reducing inflammation, increasing adiponectin production and increasing lipogenesis in the subcutaneous depots resulting in reduction in FA release and improvements in ectopic fat[14].

Targeting mechanisms linking obesity to insulin resistance

Targeting ectopic fat

Fibroblast growth factor 21 (FGF21) has been gaining much interest recently as a regulator for lipid and glucose metabolism that can reduce ectopic fat and as a result improve IR. Rodents studies have shown that FGF21 can reduce hepatic and peripheral IR and liver triglycerides in chow- and high-fat

fed wild-type mice[15]. These improvements in IR were associated with increased whole body energy expenditure and reduction in hepatocellular and myocellular DAG content and PKC activation in liver and skeletal muscle with no effect on ceramides[15]. LY2405319 is a FGF21 analogue that has reached clinical development. In a Phase Ib 28-day RCT, 47 obese patients with T2D (44% Whites, diabetes duration 7.4 years, age 57.7 years, BMI 32.1 kg/m^2, HbA1c 7.96%) were randomised to placebo vs. multiple doses of LY2405319[16]. The results of this RCT were consistent with the rodent studies and showed that LY2405319 (compared to placebo) reduced fasting glucose (by 0.4-0.6 mmol/l) and insulin levels and increase adiponectin levels[16]. In addition, LY2405319 resulted in modest decrease in weight (by 1.5-1.8 kg) and improved lipid profile (reduced LDL by 20-30% and triglycerides by 44-46% and increased HDL by 15-20%)[16]. In a more recent study using ob/ob mice and a methionine- and choline-deficient (MCD) diet to induce steatohepatitis, LY2405319 attenuated non-alcoholic steatohepatitis (NASH) progression and enhanced hepatic mitochondrial function[17].

Another therapeutic option to address NAFLD is the inhibition of Acetyl-CoA carboxylase (ACC). ACC catalyses the ATP-dependent carboxylation of Acetyl-CoA to malonyl-CoA, which is the rate-limiting step in FA synthesis and also plays a role in FA oxidation[18]. ACC has two isozymes; ACC1 which is a cytosolic enzyme present in the liver and adipose tissue, and ACC2 which is associated with the mitochondria and present in the liver, heart, and skeletal muscle[18]. In the liver, the malonyl-CoA formed in the cytoplasm by ACC1 is used primarily for FA synthesis while the malonyl-CoA formed at the mitochondrial surface by ACC2 regulate mitochondrial FA oxidation[18]. Several rodent studies have shown favourable impact of ACC inhibition on NAFLD and T2D[2]. ND-630, an ACC inhibitor, has been shown to reduce FA synthesis and stimulate FA oxidation in human hepatic HepG2 cells[18]. Chronic administration of ND-630 to rats with diet-induced obesity reduced hepatic fat and improved insulin sensitivity and lipids profile[18]. When ND-630 was administered to Zucker diabetic fatty rats, it reduced hepatic steatosis, and improved HbA1c by 0.9%[18].

Another novel therapeutic approach to improve hepatic steatosis is to increase hepatic mitochondrial uncoupling by promoting hepatic triglyceride oxidation, but older generations of these agents were associated with unaccepted adverse events profile including death but newer agents are showing better safety profile[19]. Controlled-release mitochondrial protonophore (CRMP), that produces mild hepatic mitochondrial uncoupling, reduced hypertriglyceridemia, insulin resistance, hepatic steatosis, and liver fibrosis[19]. Similarly, Niclosamide, which is FDA approved as an anthelmintic drug, has been shown to have favourable impact on IR and hepatic steatosis high-fat diet mice and it improved glycemic control in the db/db mice[20].

Adipokines

Adiponectin is an insulin sensitizing adipokine that improves insulin sensitivity by activating AMPK and Peroxisome proliferator-activated receptor (PPAR)-α[21]. AdipoRon, an orally active adiponectin receptors 1 and 2 agonist, improved IR and glucose levels in high-fat diet-fed (HFD) mice and ameliorated diabetes in db/db mice[22]. Apelin is another adipokine that also improves insulin sensitivity by AMPK activation[23]. Apelin administration in HFD obese mice for 4 weeks improved fat mass, glycaemia, and triglycerides and were protected from hyperinsulinemia compared with placebo[24].

Resveratrol:

Resveratrol is a phytophenol found in many plants, especially red grape and is a potent sirtuin 1 activator. Sirtulin 1 improves several processes that are involved in IR pathogenesis including inflammation and oxidative stress[25]. Resveratol has been shown to activate AMPK, increase PPAR-gamma coactivator (PGC-1α) levels, increase mitochondrial activity and respiration and to reduce intramyocellular and intrahepatic lipid content[26]. In addition, resveratol has been shown to reduce lipolysis and FA levels post prandially[26]. A meta-analysis of 11 RCTs showed that resveratrol had no effect on IR or glycaemic measures in people without diabetes but lowered HbA1c (average 0.8%) and IR in patients with T2D[27]. However, only 2 of these RCTs were in patients with T2D, the sample sizes were < 70 patients for these studies and the treatment duration was for 3 months. So more well-designed RCTs of larger sample size and adequate longer follow up are needed.

Inhibitor kappa-B kinase-beta (IKKB) inhibitors

Inflammatory cytokines activate IKKB which results in dephosphorylation of the Akt by increasing cermaides production[9]. Administration of IKKB inhibitor (IMD-0354) to KKAy mice receiving HFD improved hyperglycaemia, IR and iadiponectin levels after 7 days of treatment[28].

Targeting the insulin receptor

These compounds can generally be divided into agents that can stimulate the insulin receptor independently of insulin binding to the receptor and agents that can potentiate the insulin-initiated tyrosine phosphorylation of the insulin receptor β subunit and the IRS 1/2, or prevent their dephosphorylation[29]. Some of these agents can be given orally[7;8].

Demethylasterriquinone and its derivatives

Demethylasterriquinone (DMAQ) B1 (L-783,281 or compound 1) is a benzoquinone derivative derived from the fungus Pseudomassari[30]. It binds to the β subunit of the insulin receptor and initiate the insulin signalling pathways without the need of insulin[31]. However, this compound had a quinone moiety that when in contact with high energy that resulted in the production of free

radicals, which made it unsuitable for humans[13;32]. As a result, non-quinone DMAQ B1 derivatives were developed. One example is D-410639, which is 128 fold less cytotoxic than DMAQ B1 and was able to activate the recombinant human insulin receptor on the CHO cell line[30]. In addition, D-410639 inhibited epidermal growth factor receptor (EGF-R/ErbB1) which is involved in vascular dysfunction in patients with diabetes; which suggests that this compound might have vascular benefits[33]. Another promising compound is compound 5,8-diacetyloxy-2,3-dichloro-1,4-naphthoquinone which also binds to the kinase domain of the insulin receptor to trigger insulin action[34]. This oral compound improved glucose levels in wild-type C57BL/6J mice and db/db and ob/ob mice without evidence of toxicity[34].

XMetA

XMetA is a high affinity, allosteric, human monoclonal antibody to the insulin receptor that does not compete with insulin binding[35]. It activates the insulin receptor but not the IGF1 receptor and it mimics the glucoregulatory but not the mitogenic actions of insulin[35]. In diet-induced obese mice, XMetA normalised fasting glucose, corrected glucose tolerance and improved non-high density lipoprotein cholesterol with no weight gain or hypoglycaemia[35]. Similar results were found recently in a study in diabetic cynomolgus monkeys[36].

α-lipoic acid (ALA)

ALA (1, 2-dithiolane-3-pentanoic acid) is a naturally occurring compound synthesized in mitochondria from octanoic acid and is a cofactor for mitochondrial a-ketoacid dehydrogenases, and thus serves a critical role in mitochondrial energy metabolism[8]. In rat hepatocytes, ALA directly binds to and activates the tyrosine kinase domain of the insulin receptor resulting in activation of the insulin signalling pathway and increasing GLUT-4 translocation[37]. In a small RCT (n=107) of patients with T2D who were randomised to supplements including ALA vs. placebo for 3 months, ALA improved HbA1c by 0.6%, and lowered LDL and triglycerides and HOMA-IR without an effect on weight[38].

Protein tyrosine phosphatase 1B (PTP-1B) Inhibitors

PTP-1B terminates the insulin receptor activity by dephosphorylating the insulin receptor β-subunit, and the IRS1/2; hence inhibiting PTP-1B would potentiate insulin action when insulin is bound to the α-subunit[13]. Several studies using different compounds showed that PTP-1B inhibition increased insulin receptor and IRS phosphorylation, enhanced insulin actions, improved IR, and improved hyperglycaemia in rodent studies [8;39]. However, the clinical development of these agents proved to be challenging due to adverse events and lack of selectivity[29]. High selectivity is essential

as PTP1B and T-cell protein tyrosine phosphatase (TCPTP), which is abundantly expressed in hematopoietic cells, share more than 70% amino acid sequence identity in the catalytic domain[40].

PKC inhibitors:

As discussed above, PKC activation via increase DAG reduces insulin-mediated IRS and AKT phosphorylation and PI3K activation leading to IR[41]. Studies in obese and diabetic rodents showed that treatment with Ruboxistaurin (LY333531), a selective PKCβ inhibitor, improved insulin-stimulated Akt phosphorylation and IR and insulin stimulated vascular contraction[42].

Targeting post insulin receptor signalling

PTEN inhibitors:

The Phosphatase and tensin homolog (PTEN) dephosphorylates phosphatidylinositol (3,4,5)-trisphosphate (PIP3) to phosphatidylinositol 4,5-bisphosphate (PIP2) causing a reduction in AKT phosphorylation[43]. PTEN is a tumour suppresser protein[43]. Patients with Cowden syndrome, a rare cancer predisposing condition with PTEN loss of function mutation, were found to have increased AKT phosphorylation and better insulin sensitivity compared to age, sex and BMI matched healthy controls[44;45]. Similar results were found in rodent studies using PTEN inhibitors[46]. PTEN inhibitors need to be highly specific and only inhibit PTEN partially in order to have an acceptable safety profile.

Inositol phosphatases inhibitors

Type-II SH2-domain-containing inositol 5-phosphatase (SHIP2) is a member of the inositol polyphosphate 5-phosphatase family. SHIP 2 contributes to the conversion of PIP 3 to PIP 2 resulting in the inhibition of AKT phosphorylation[47]. Rodent studies showed that SHIP2 mutations are associated with improved insulin sensitivity and increased concentration of GLUT-4 [42;48]. Inhibiting SHIP2 using an antisense oligonucleotide has also been shown to improve IR and AKT phosphorylation[49]. Several studies in humans showed that polymorphisms in the SHIP 2 gene were associated with T2D[50].

Inositol derivatives

Myoinositol forms the structural basis for PIP2 and PIP3. Pinitol (3-O-methyl-chiroinositol), from the plant *Bougainvillea spectabili*, has been shown to improve IR and lower glucose levels in animal studies; these effects were inhibited by the presence of PI3K inhibition[51]. In humans, the results of RCTs were not consistent; while some studies showed no effect on hyperglycaemia or IR[52], others showed reduced HbA1c, and HOMA-IR as well as favourable impacts on LDL/HDL ratio and blood

pressure[53;54]. D-chiro-inositol and myo-inositol have been shown to improve IR in women with polycystic ovarian syndrome, although this has not translated into better clinical outcomes in terms of ovulation and fertility[55]. In a recent meta-analysis of 5 trials containing 513 participants, myo-inositol reduced the risk of gestational diabetes (risk ratio 0.29; 95% CI 0.19-0.44)[56].

Targeting the underlying causes of insulin resistance

Obesity

Obesity is a major risk factor for T2D, as a result interventions (lifestyle, pharmacotherapy, bariatric surgery) aimed at causing weight loss (from as little as 5%) and reduction in visceral fat result in significant improvements in T2D and/or IR[8;57]. More recently bariatric surgery became an important treatment option in patients with T2D resulting in long-term sustained weight loss with significant improvements in glycaemic parameters, IR and cardiovascular disease risk factors[8;58]. The impact of bariatric surgery in patients with T2D was superior to medical care in several RCTs[59-61]. The improvements in glycaemic control after bariatric surgery occurred in the context of reduction in the use of insulin and other glucose lowering agents. More details about the mechanism of action and impact of bariatric surgery in T2D can be found here [62;63].

Sleep-related disorders

An emerging important risk factor for the development of IR and T2D is sleep-related disorders. In a meta-analysis of 36 studies (including 1,061,555 participants) the pooled relative risks (RR, 95%CI) for developing diabetes were 1.48 (95%CI:1.25,1.76), 1.18 (1.10,1.26) and 1.36 (1.12,1.65) for sleeping ≤5 hours, 6 h, and ≥9 hours/day respectively. The RR (95%CI) for developing diabetes in patients with poor sleep quality, obstructive sleep apnoea (OSA) and shift work were 1.40 (1.21,1.63), 2.02 (1.57, 2.61) and 1.40 (1.18,1.66), respectively[64]. Another meta-analysis showed similar results in that short sleep duration was associated with increased risk of developing diabetes as well as increased risk of mortality, obesity and cardiovascular disease[65].

In patients with T2D, short and long sleep duration and poor sleep quality were associated with higher HbA1c as was shown in a recent meta-analysis (weighted mean difference: 0.23% (0.10-0.36); 0.13% (0.02-0.25), 0.35% (0.12-0.58) for short sleep, long sleep and poor sleep quality respectively[66]. Short sleep duration was also associated with higher HbA1c and higher IR in patients with Type 1 diabetes (based on hyperinsulinemic euglycemic clamp)[67]. In laboratory based studies, acute sleep restriction in healthy lean individuals resulted in IR and dysglycaemia[68].

Interventional studies assessing the impact of sleep duration manipulation on IR and glycaemic control are ongoing but a recent small study of 10 young adults with habitual sleep duration < 6.5 hours/night showed that extending sleep duration by 1.6 hours/night for 2 weeks in their home environment was associated with 14% decrease in overall appetite and a 62% decrease in desire for sweet and salty foods[69], suggesting that such interventions might have important metabolic effects.

OSA is very common in patients with T2D and is associated with IR and worse glycaemic control[70]. Several meta-analyses have shown that OSA treatment (continuous positive airway pressure (CPAP)) improves IR in patients with and without T2D[71]

Summary and conclusions

IR plays an important role in the pathogenesis of T2D and associated cardiovascular disease. Improving IR is an important treatment target in patients with T2D and pre-diabetes/the metabolic syndrome. As our understanding of the pathogenesis of IR improved, new pharmacological agents were developed. But many of these agents are in the pre-clinical phase and it remains unclear which will progress to clinical trials in humans. Developing new treatments for IR is challenging due to the complexity of IR pathogenesis and the presence of multiple feedback loops which makes it difficult to predict the consequences of a particular intervention[8]. For example, treatments that target deficits in proximal locations of the insulin signalling pathway might result in a broader spectrum of benefits compared to targeting distal locations; but the impact of the negative feedback exerted by distal signalling steps on earlier ones might lessen such benefits[7;13]. In addition, the insulin signalling pathway is involved in cell survival and other functions and hence any interventions need to be specific, partial and reversible [6;8;13]. Targeting obesity remains a major step in the management of patient with T2D and IR, but life style interventions are difficult to maintain on the long term. As a result, bariatric surgery is an important option to consider in some patients. Sleep-related disorders are also emerging as an important contributor to IR but interventional studies are awaited in relation to the impact of sleep duration manipulation on IR. The data about the impact of CPAP on IR in patients with OSA are encouraging but CPAP compliance is challenging in real life and the impact of CPAP on glycaemic control is controversial.

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