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REVIEW ARTICLE

AN OVERVIEW OF PATHOPHYSIOLOGY AND TREATMENT OF INSULIN RESISTANCE

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Abstract : Insulin resistance has emerged out as a concept linking diabetes mellitus and hypertension. Clinically it is characterized by hyperinsulinemia, hypertension, central obesity, abnormal lipid profile and cardiovascular complications. Insulin resistance is often associated with presence of anti-insulin antibodies and absent or dysfunctional insulin receptors. At molecular level insulin resistance appears to occur at the level of G-protein, kinase activation, glucose carriers (GLUT) and gene expression. Although with advent or research, the molecular mechanisms of insulin resistance are becoming more clear and there is development of new therapeutic agents like insulin sensitizers (thizolidinediones), in clinical practice, as of today, a patient with insulin resistance is looked upon as hypertensive or having diabetes mellitus. Accordingly he is taking either antihypertensives or antidiabetic drugs or both. It is thus essential to look into effects of these agents on insulin sensitivity. In recent years some scattered studies have been conducted to evaluate the effect of various antihypertensives and antidiabetics on insulin sensitivity. An antihypertensive or antidiabetic drug should directly benefit the cardiovascular risk profile of these patients. Although various newer approaches are explored to have a therapeutic benefit in insulin resistance, it is still a long way in the research, when a suitable pharmacological agent with least untoward effects will be available for the treatment of insulin residence.

Key words : non-insulin dependent diabetes mellitus
insulin resistance hyperinsulinemia

INTRODUCTION

The presence of higher plasma insulin levels in patients as compared normotensive individuals was first demonstrated in 1966 by Welhorn and coworkers (1). however, little attention was paid towards the relationship between hyperinsulinemia and hypertension over the next two decades. It has long been known that both hypertension and type 2 (non-insulin-dependent) diabetes mellitus are associated with overweight and that hypertension is more prevalent among diabetic then non-diabetic individuals (2–4).

Nankaervis et al (1985) reported that patients with insulinoma, who experience recurrent episodes of hypoglycemia may protect them from excessive lowering of plasma glucose level (5). Hyperlipidemia is also reported to be more common in both diabetic and hypertensive patients (6, 70). Reaven et al (8) reported a role of insulin in endogenous hypertriglyceridemia. Substantial evidence has been accumulated that indicates that there occurs resistance to insulin stimulated glucose uptake, increase in plasma insulin concentration, VLDL-triglyceride secretion rate and plasma triglyceride concentration in healthy subjects and in patients with of these metabolic abnormalities producing obesity (10), type 2 diabetes mellitus (11–13) and hypertension (14).

All these observations suggested the role of "insulin" resistance in the underlying cause of these metabolic abnormalities (10, 15, 16). In due course insulin resistance started emerging out as a concept linking diabetes mellitus, hypertension and other metabolic disorders. Reaven (1988) proposed that insulin resistance is primary defect of *Syndrome-X:* the combination of hyperinsulinemia, glucose intolerance, abnormal lipid profile and hypertension (17). Insulin resistance is now defined as a physiological stage in which insulin in its action produces a less-then-normal response (that is a setting of decreased insulin sensitivity) to a substrate regulated by insulin to various degrees (18). In this article we have reviewed the state of the art of pathophysiology and trends in the treatment of insulin resistance.

Clinical characteristics, complications and pathophysiology of insulin resistance

As mentioned above there are several characteristics observed in insulin resistance such as increase in central obesity, hypertension, hyperinsulinemia, abnormal lipid profile etc. These features can be observed clinically as mentioned in Table I.

TABLE I: Clinical and metabolic characteristics of the insulin resistant group and their percent differences from the control group.

	Mean ± SEM in insulin resistant population	*Percent difference from control (non-insulin resistant) population*
Waist hip ratio	0.932±0.012	+15%
Fasting glucose (mmol/l)	5.53±0.05	+5%
2-h glucose (mmol/l)	7.80±0.11	+20%
Fasting insulin (pmol/l)	129±3	+36%
2-h insulin (pmol/l)	787±18	+37%
Triglycerides (mmol/l)	2.01±0.03	+50%
Total cholesterol (mmol/l)	5.33±0.03	+10%
HDL cholesterol (mmol/l)	1.14±0.01	–8%
Systolic blood pressure (mm Hg)	123±0.4	+4%
Diastolic blood pressure (mm hg)	74±0.2	+4%

The comparison with the control group is made after adjusting for age, sex, ethnicity, and body mass index (BMI), and calculated at the mean population age (43 years) and BMI (27.9 kg/m^2) for a male Mexican-American subject.
(Adapted from Diabetologia 1991; 34: 416)

Insulin resistance may take place as a consequence of physiology of necessity. During prolonged fasting state, a decrease in insulin sensitivity may occur to mobilize other energy substrates form peripheral tissues so that metabolic function can be maintained (18). Similarly, insulin resistance is seen in patients with insulinoma, who experience recurrent episodes of hypoglycemia. Insulin resistance in such patients protects them from excessive lowering of plasma glucose levels (5, 19). Insulin resistance is one of the common characteristics in individuals with obesity (11–16, 17) and non-insulin dependent diabetes mellitus (NIDDM) (12-14). Besides these, there are several other clinical states where insulin resistance can observed (Table II). In subjects who retain insulin secretary function, particularly non-diabetics, a relatively linear relation is found between measures of insulin resistance and plasma concentration, i.e. more the insulin resistance, greater is the magnitude of hyperinsulinemia.

TABLE II : Clinical presentation of insulin resistant states.

Obesity (Especially upper body obesity): >130–140% of ideal body weight
Age
Non–insulin–dependent diabetes mellitus
Insulin dependent diabetes (IDDM), requiring large daily amounts insulin (e.g 200U/day)
Gestational diabetes (glucose intolerance with onset during pregnancy)
Non–diabetic, non–obese hypertrigiyceridemia
Acanthosis nigricans
Familial dylipidemic hypertension
Polycystic ovary syndrome
Lipodystrophy (partial or generalized)
Ataxia telanglectasia
Leprechaunism
Rabson-Mendenhall syndrome
Werner's syndrome
Alstom syndrome
Pineal hyperplasia syndrome
Hormonal disorders (excess counterinsulin hormones, e.g. pheochromocytoma, acromegali, Cushing's syndrome)
Anti-insulin-antibodies (Prereceptor resistance)
Absent or dysfunctional insulin receptor (Type A syndrome)
Anti-insulin-receptor antibodies (Type B syndrome)
Abnormal or mutated insulin molecule
Incomplete conversion of proinsulin to insulin
Drug induced (e.g. thiazide diuretics, glucocorticoids
Smoking

Adapted from Drugs 1993; 41(3): 387)

Insulin resistance and hyperinsulinemia are more severe and closely associated with hypertension in obese patients then in non- obese patients. Hyperinsulinemia is also a consequence of insulin resistance that stimulates the sympathetic nervous system increasing sympathetically mediated thermogenesis and reestablishing the energy balance. The increase in sympathetic nervous system activity, however also affects kidneys (14, 20). Hyperinsulinemia has been identified as a primary risk factor for coronary artery disease (CAD). Variety of direct effects of insulin at cellular level and the role played by it in the regulation of lipoprotein metabolism makes insulin as one of the primary risk factors of CAD (21). As mentioned earlier the resistance to insulin stimulated glucose uptake and compensatory hyperinsulinemia that occurs is responsible for hypertriglyceridemia in patients with high blood pressure. It has now been emphasized that the combination of a high plasma triglyceride and low high density lipoprotein (HDL) cholesterol concentration are the consequences of insulin resistance responsible for the increasing risk of CAD (22). Fig. 1 summarizes the sequel of clinical and pathophysiological events leading to the insulin resistance.

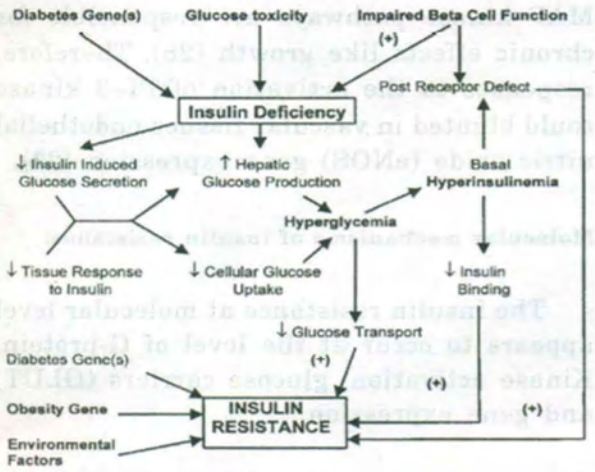

Fig. 1 : Pathogenesis sequence of events leading to development of glucose intolerance, insulin resistance, and impaired insulin secretion in non-insulin dependent diabetes mellitus. (+) shows positive feedback loops, the results in self perpetuation of primary defects. Adapted from Diabetes Care 1992; 15(3): 352.

Endothelial dysfunction in important capillary bead has also been suggested as the principal explanation for the development of the insulin resistance syndrome in parallel with large artery atherosclerosis (23). The endothelium is a monolayer of flat cells strategically located between circulating blood and vascular smooth muscle. They are the source of substances that profoundly affect the vascular tone, growth, platelet function, coagulation and monocyte function. The endothelium releases both contracting and relaxing factors. The contracting factors are endothelins, angiotensin II, thromboxane, and prostaglandins. The relaxing factors include nitric oxide (NO), Prostacyclin PGI_2) and endothelium derived hyperpolarizing factor (EDHF). Alteration in the release of substances such as nitric oxide, prostaglandins and endothelin-1 may not only mimic the hemodynamic alterations seen in hypertension, but may also involved in the development of cardiovascular complications such as myocardial infarction, renal failure and stroke (24).

Insulin resistance and vascular tissue

Both insulin resistance and possibly hyperinsulinemia have been suggested as risk factors for the development of cardiovascular complications in diabetes. In hyperglycemia the increased amounts of glucose can also be transported intracellularly and metabolized to increase flux through sorbitol pathway, change the redox potential or alter signal transduction pathways, such as the activation of the diacylglycerol (DAG) and protein kinase C (PKC) levels (Fig. 2). The activation of DAG-kinase pathway causes increased expression of transforming growth factor-b (TGF-b) which has been implicated in the development of mesangial expansion and basement membrane thickening in diabetes. The increased PKC and cytosolic phospholipase A_2 ($cPLA_2$) activities result in increases of arachidonic acid release,

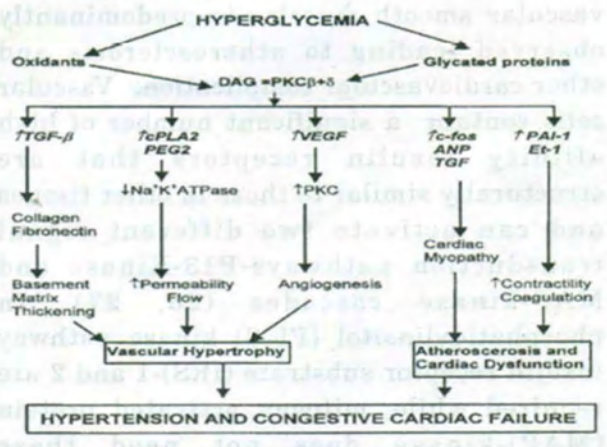

Fig. 2 : Schematic diagram of the adverse effects of hyperglycemia in vascular cells. Adapted from Diabetes Care 1999; 22(3): C33.

prostaglandin E_2 (PGE_2) production and decreases in Na^+-K^+ ATPase activity. PKC activation can also regulate vascular endothelial growth factor (VEGF). Similarly, the PKC activation also causes the expressions of plasminogen activator inhibitor-1 (PAI-1) and endothelin-1 (Et-1) leading to increased contractility and coagulation respectively. Thus, activation of the PKC pathway can, in vascular cells, regulate permeability, contractility, extracellular matrix, cell growth, angiogenesis, cytokine actions, and leukocyte adhesions, all of which are abnormal in diabetes (25).

In vascular cells insulin has two types of actions- anti-atherogenic and atherogenic. An example of insulin anti-atherogenic action is the ability to increase nitrous acid production that can cause vasodilatation and retard migration and growth of arterial smooth muscle cells. On the other hand insulin is known to promote proliferation of aortic or arterial smooth muscle cell cultures. But in hyperinsulinemia or insulin resistance 'Growth' action of insulin on vascular smooth muscles is predominantly observed leading to atherosclerosis and other cardiovascular complications. Vascular cells contain a significant number of high affinity insulin receptors that are structurally similar to those in other tissues and can activate two different signal transduction pathways-P13-Kinase and MAP-kinase cascades (26, 27). In phosphatidylinsitol (PI–3) kinase pathway insulin receptor substrate (IRS)-1 and 2 are required while, mitogen activated protein (MAP)-kinase does not need these substrates. It has been shown that activation of PI–3 kinase, and activation of MAP kinase pathways are responsible for chronic effects like growth (28). Therefore, responses to the activation of PI–3 kinase could blunted in vascular tissues endothelial nitric oxide (eNOS) gene expression (25).

Molecular mechanisms of insulin resistance:

The insulin resistance at molecular level appears to occur at the level of G-protein, Kinase activation, glucose carriers (GLUT) and gene expression.

G-proteins and their role in insulin resistance:

Insulin binds to insulin receptor dimers activating tyrosine kinase and large trimeric $\alpha\beta\gamma$ G proteins. Tyrosine phosphorylated IR β-subunits bind several docking proteins via SH2 domains, IRS is shown as one example. Large G proteins, in turn activate small G proteins by as yet unknown mechanisms, which in turn activate membrane phospholipases c and/or D to cleave glycosyl phophatidylinositol lipid (GPI)s to water soluble inositol phosphoglycan (IPG)s on the outer membrane surface. IPGs enter cell of origin or neighboring cells by an autocrine-paracrine mechanism and active IRS tyrosine phosphorylation by a cellular tyrosine such as Src recruited to the membrane by the dissociated bg subunits of the large G proteins. Tyrosine phosphorylation of IRS mediated by IPGs then constitutes a mechanism of cross-talk with the direct insulin receptor-initiated tyrosine kinase cascade (28). The inhibition of insulin signalling by pretreatment with rat adipocytes (30), hepatocytes (31), and BC3 H1 (32) myocytes with pertussis has been well documented indicating the

involvement of Gi or Go proteins in defective insulin signalling. All these reports suggest the possibility of abnormal functioning of G-proteins in the insulin resistant state.

Kinases and their role in insulin resistance:

Insulin receptor is a ligand-activated tyrosine protein kinase. Binding of insulin to the alpha subunits of the heterotertrameric insulin receptor leads to the rapid intramolecular autophosphorylation of several tyrosine residues in the beta subunits. In the intact cells, the insulin receptor is also phosphorylated on the serine and threonine residues presumably by protein kinase C or cyclic AMP dependent protein kinase. Such phosphorylation inhibits tyrosine kinase activity of the insulin receptor. The tyrosine kinase activity is required for the signal transducton. The activated receptor kinase initiates a cascade of events first by phosphorylating a protein called insulin receptor substrate-1 (IRS-1). Phosphorylated IRS-1 severs as a docking protein for the other proteins that contain so called Src homology 2 (SH2) domains. One of such SH2 domain proteins is phosphoinositide PI-3-kinase. PI3 kinase catalyzes the addition of phosphates to phosphoinositides on the 3-position of the D-myoinositol ring and this compound is one of the most potent mitogens. Ras has been Liked to the insulin action pathway because it is known to activate the cascade of the mitogen activate protein (MAP) kinases. MAP kinases are among the many of such kinases that are known to be activated by insulin. Insulin also activates of serine/threonine phosphorylation cascades. Serine kinases have a dual function in the insulin signalling pathway i.e. further transduction of the insulin signal and activation of glycogen synthase or MAP kinase activation (33). Fig. 3 summarizes some of the intracelluar protein kinase cascades after binding of insulin to its receptor. Insulin resistance seems to involve specifically the MAP-kinase and PI-3 kinase activation.

MAP-Kinase activation:

Insulin stimulation is known to activate components of the MAP-kinase cascade by phosphorylation, including MAP-kinase itself. Change et al (34) measured the activation of map kinase in the muscles of the lean and obese mice. They found that insulin could cause the activation of MAP kinase only in lean mice and not in the obese mice. It was concluded that the lack MAP kinase response to insulin could be one of the elements of insulin resistance in the obese animals (34).

P13-Activation:

As mentioned earlier P13-kinase activation following insulin stimulation is one of the critical steps in the insulin signalling cascade (35). It appears to increase the translocation of GLUT4 glucose transporter translocation to the plasma membrane, allowing glucose uptake to proceed (36, 37). PI3-kinase activity is reported to be lower in the obese animals as compared to the lean animals when insulin-simulated PI3-kinase activation in the incubated soleus muscle of the lean and obese mice. The magnitude of this defect suggests that there is impairment of PI3-kinase activity in the insulin resistant obese mice (38). Evidence suggests that

PI3-kinase impairment develops much before the emergence of overt insulin resistance. In adipocytes from young obese mice that were not insulin resistant, insulin receptor autophosphorylation and pp60 phosphorylation were found to occur normally, but there was a marked defect in IRS-1 tyrosine phosphorylation. In order obese mice however, all the three protein groups were less phosphorylated than in lean controls (39).

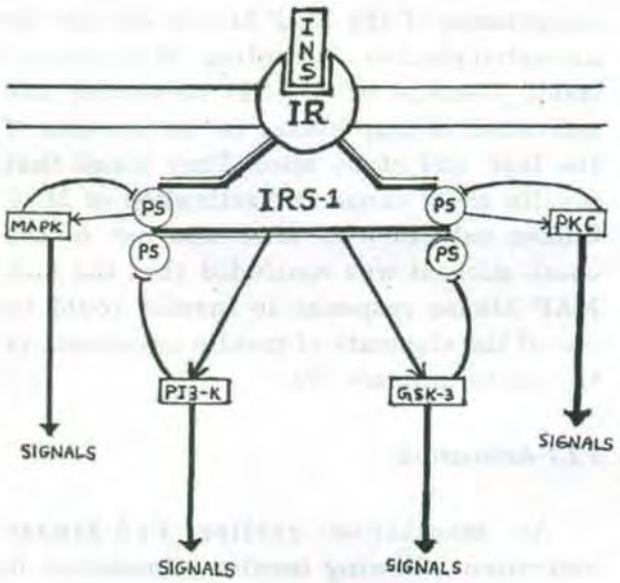

Fig. 3 : Different possible routes for phosphorylation cascade, abnormal functioning of these may lead to insulin resistance.
INS: Insulin
IR: Insulin Receptor
IRS–1: Insulin Receptor Substrate–1
PI3–K: Phosphatidylinositol 3–Kinase
MAPK: Mitogen activated protein kinase
GSK3: Glycogen synthase kinase 3
PKC: Protein kinase C
Adapted from *Exp Ciln Endocrinol Diabetes* 1999; 107: 103.

The capacity of platelet-derived growth factor (PDGF) to alter the ability of insulin to phosphorylate IRS-1 on tyrosine residues in cultured adipocytes is recently demonstrated. Short treatment with PDGF causes IRS-1 serine/threonine phosphorylation through a PI3-kinase dependent pathway and this prevents phosphorylation of tyrosine residues on IRS-1 (40).

Insulin like Growth Factor (IGF)-1 is as efficient as insulin in promoting glucose uptake. Its action is mediated through a PI3-kinase dependent pathway since, like insulin stimulated glucose uptake, it is completely inhibited by PI3-kinase inhibitor wortmannin (41). It is reported that IGF-1 signaling is defective in obese mice as compared to lean animals and that this is due to post receptor defects only (42).

Glucose transporters and their role in insulin resistance:

Glucose transport in skeletal muscle and adipose uptake tissue is insulin sensitive and is normally considered to be rate limiting for glucose uptake and utilization. Therefore, reduction in the number of glucose carriers could be another possible reason for the interruption of the signal flow (43). In NIDDM, the protein content of adipose tissue GLUT 4 (a major glucose transporter) is reduced and its translocation from intracellular stores in response to insulin stimulation is impaired. In skeletal muscle GLUT 4 expression is normal, but its translocation is impaired and insulin signaling is probably defective (44). Recently it has been reported that a mutation in the GLUT-2 glucose transporter gene of a diabetic patient abolishes transport activity. The presence of this mutation in a diabetic patient suggests that defect in GLUT-2 expression may by causally involved in the pathogenesis of insulin resistance (45).

Role of gene expression in insulin resistance:

Alterations in the various enzymes and proteins mentioned above are mediated through a change in rate of mRNA synthesis from specific genes. Various mutations have been detected in the insulin receptor gene in patients with genetic syndromes of extreme insulin resistance. A mutation in the structural gene coding for the transacting factor that impairs its ability to bind DNA or that effects the rate of transacting factors may be involved e.g. unrestricted gluconeogenesis is the primary source of the excessive overproduction of glucose in NIDDM. Because phosphoenol private carboxykinase (PEPCK) catalyzes the rate-limiting stop in gluconeogenesis. It is possible that faulty regulation of the PEPCK gene could be involved in insulin resistance (46).

Drug treatment in patients with insulin resistance

Although with advent of research the molecular mechanisms of insulin resistance are becoming better understood and there is development of new therapeutic agents like insulin sensitizers (thizolidinediones), in clinical practice, as of today, a patient with insulin resistance is looked upon as hypertensive or having diabetes mellitus. Accordingly he is taking other antihypertensives or antidiabetic drugs (sulfonylureas, biguanides or insulin) or both. It is thus essential to look into the effects of these agents on insulin sensitivity. In recent years some scattered studies have been conducted to evaluate the effect of various anthypertensives and antidiabetics on insulin sensitivity.

The antihypertensive drugs often used clinically have been reported not to affect glucose metabolism and insulin sensitivity favorably. Thiazide diuretic promote the development of glucose intolerance (48–50) and have been shown to increase the insulin resistance (51). Beta blockers are reported to worson glucose tolerance, especially in combination with diuretics (48). They are also found to worsen hypertriglyceridemia (52). However, there are exceptions too. Alpha-adrenoceptor blocker prazosin has been reported to improve insulin sensitivity (53). The newer antihypertesives used clinically viz, the ACE inhibitors and calcium channel blockers are better than the beta blockers and diuretics as far as their effect on insulin sensitivity is concerned. ACE inhibitors do not raise serum insulin levels and captopril has been reported to reduce insulin resistance (53–55). Calcium channel blockers also improve insulin sensitivity (53, 56, 57).

Hyperglycemia rarely occurs in isolation, and other conditions pertaining to the insulin resistance syndrome are usually in evidence. Thus, it is important that new antidiabetic agents should not impede and preferably directly benefit the cardiovascular risk profile of these patients.

Newer therapeutic agents as insulin sensitizers

There are several groups of pharmacological agents with immense potential for therapeutic use in insulin resistance associated with the above conditions. They can be classified depending on the mechanism of action.

I. Insulin sensitizing agents:

Thiazolidinedione derivatives have emerged out as a new class of antidiabetics. They include ciglitazone, pioglitazone, troglitazone and englitazone. The hypoglycemic action of these agents has been reported in various animal models of NIDDM and insulin resistance including obese Zuckar rats, ob/ob mice, and KKA mice (58, 59). Thiazolidinediones increase glucose oxidation (via stimulation of pyruvate dehydrogenase) in adipose tissue and muscle, increase glycogen and lipid synthesis from glucose and decrease glycogenolysis (60–62). Treatment of insulin resistant obese KKA mice with pioglitazone corrects the deficiencies in the glucose transport and GLUT 4 mRNA and protein abundance in both skeletal muscle and adipose tissue, and this increase in transporter number and function has a strict dependence on the presence of circulation insulin (44). Because thiazolidinediones enhance certain actions of insulin via the peroxisome proliferator-activated receptor γ (PPAR-γ) other types of PPAR-γ agonists are being sought (63).

Dichloroacetate has been shown to increase oxidative glucose metabolism via stimulation of pyruvate dehydrogenase in the in vitro studies. It also decreases free fatty acid oxidation resulting in inhibition of hepatic gluconeogenesis (64).

Vanadate has been reported to mimic most of the metabolic effects of insulin. In STZ-treated rats vanadate increased glucose uptake and oxidation in muscle (65). The impaired glycogen synthase activity and glycogen reserves returned to normal in diabetic rats (66).

II. Inhibitors of fatty acid oxidation:

Increase in free fatty acid (FFA) levels leads to insulin resistance in skeletal muscle (67). This may be a result of decrease in glucose utilization by inhibiting glucose oxidation via inhibition of pyruvate dehydrogenase and reduction in glucose uptake by inhibiting hexokinase (68). A decrease in FFA oxidation in patients with NIDDM should therefore have a favorable effect not only on hepatic glucose overproduction, but also on peripheral glucose disposal. Carnitine palmitoyl translocase-1 (CPT-1) is responsible for the transport of activated long chain fatty acids across the mitochondrial membrane in hepatocytes. Drugs that inhibit this enzyme could thus prevent the intramitochondrial oxidation of FFA to acetyl CoA, ketone bodies and nicotinamide adenine dinucleotide (NADH). CPT-1 inhibitors include clomoxir, etomoxir, TDGA. TDGA has been reported to decrease glucose levels in IDDM and NIDDM subjects (69). Etomoxir has been reported to produce a 33% increase in insulin mediated glucose uptake (70). It also produces a decrease in hepatic glucose production in obese NIDDM patients (71). However, there have been incidences of cardiac hypertrophy in long term animal toxicology studies with both TDGA and etomoxir (72).

III. Beta$_3$ adrenoceptor agonists:

These agents could be particularly useful in insulin resistance associated with obesity

as the $beta_3$ adrenoceptor has been reported to induce lipolysis and thermogensesis in skeletal muscle and adipose tissue (73). BRL37344, an active metabolite of BRL35135, is a potent $beta_3$ adrenoceptor agonist. It produces a dose dependent increase in energy expenditure, weight loss, post glucose load hyperinsulinemia and an improvement in glucose tolerance in otherwise healthy obese patients. BRL 35135 is reported to increase insulin sensitivity in obese patients with NIDDM (74). Long term clinical trials with beta adrenoceptor agonists is the need of the hour. These agents could be effective in the treatment of diabetic as well as non-diabetic obese patients.

IV. Inhibitors of gluconeogenesis:

Hepatic insulin resistance causes gluconeogensis and thus the inhibition of enzyme pyruvate carboxylase leading inhibition of gluconeogenesis could prove beneficial. Phenylalkanoic acid derivatives inhibit gluconegoensis in hepatocytes at concentrations that do not inhibit cell metabolism (75). Though there have been no human studies with these agents, a little success has been achieved in animal models.

V. Inhibitors of lipolysis:

Adenosine inhibits through its action on adipocytes. This action is probably mediated via the alpha receptor subtype (76). GR79239 is an analogue of adenosine and specific receptor for alpha receptor subtype. This compound inhibits lipolysis in human abdominal wall adipocytes and decreases plasma non-esterified free fatty acids (77). However, this is the only evidence for the association of these changes with significant reduction in plasma glucose levels. Nicotinic acid and its derivative acipimox have shown to have antilipolytic and hypoglycemic actions (78). However, these agents have a short duration of action and the hypoglycemic response is variable.

VI. Aldose reductase inhibitors:

The use of aldose reductase inhibitors to enhance insulin sensitivity in diabetes mellitus has been reported. These agents probably act by restoring and preserving intracellular reduced glutathione levels, thereby enhancing formation of insulin receptor mixed disulphide bonds (79). Tolrestat, Statil Sorbinil are a few aldose reductase inhibitors.

VII. Alpha-glucosidase inhibitors:

Another class of drugs that is reported to be effective in the treatment of hyperinsulinemia is alpha-glucosidase inhibitor. These agents reduce gastrointestinal breakdown and absorption of carbohydrates. They lower palsma glucose concentration and tend to cause weight loss. Acarbose belongs to this class of drugs and is reported to lower insulin levels and gastrointestinal peptide (GIP) levels (80). This however would potentiate glucose mediated insulin secretion. In addition, acarbose has other effects on gastrointestinal hormones. Alpha-glucosidase inhibitors might be of value in obese diabetic patients but they can not be useful in normal weight diabetics because of their effects on nutrition.

VIII. Alpha-2 antagonists and imidazolines:

Insulin secretion is normally subjected to tonic suppression via α-$_2$ adrenoceptors The possibility of relieving this suppression with selective α-$_2$ antagonists such as imidaglizole and MK-912 has been considered (81). While this approach has been shown to raise insulin concentrations and improve glycemic control in type 2 patients, it has proved difficult to achieve potency with sufficient selectivity to avoid pressor responses (82).

Imidazoline compounds like efaroxan can stimulate insulin secretion independently of an α-$_2$ blockade. There is evidence that this may occur via closure of K^+-ATP channels and possibly other K^+ channels as well as effects at more distal steps in the control of exocytosis (83, 84).

Gene therapy for reducing insulin resistance in type-2 diabetes:

There are two approaches for the treatment of insulin resistance in type-2 diabetes:

1. Transferring genes that are important in insulin transduction pathways and

2. Delivering hormones or soluble factors that can decrease insulin resistance.

The goal for gene therapy for type-2 diabetes is to increase peripheral glucose uptake, primarily in muscle and fat, and to decrease hepatic glucose output. Strepozotocin-treated diabetic mice show decreased glucokinase expression and activity, resulting ineffecient conversion of glucose to glucose-6-phosphate, inhibition of glycolysis experiments aimed at reducing from adipocytes and gastric mucosal cells, is a major regulator of body weight by modulating food intake and energy metabolism. Transfer of leptin receptor Ob-Ob to islets from ZDF rats, in which the receptor is mutated, resulted in BCL-2-mediated protection of the islets from the toxic effects mediated by triglyceride accumulation. Thus treatment with leptin may protect pancreatic islets against apoptosis induced by obesity and insulin resistance. Patients with obesity and type-2 diabetes often exhibit elevated plasma leptin levels and leptin resistance, rather than leptin deficiency. Leptin gene therapy using adenoviral vectors in ob/ob and lean mice resulted in dramatic reductions in both food intake and body weight, well as normalization of serum insulin levels and glucose tolerance. Overall, gene therapy for diabetes will likely require the transfer of multiple genes. It is still unclear which combination of genes and cell will be required to achieve lone term physiologic regulation of blood glucose without graft rejection or recurrent autoimmunity (85).

CONCLUSIONS

With the newer approaches to the therapeutic benefit in insulin resistance related disorders, a lot remains to be studied and scrutinized. Although it is long way in the research, the day does not seem to be far when suitable pharmacological agents with least untoward effects will be available for the treatment of insulin resistance.

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