Diabetes is a growing epidemic worldwide, a rise of 250 million diabetics is expected by the year 2010 globally [1].

The perplexing feature of this end organ disease is its polygenicity. Diverse and complex mechanisms are involved at molecular level in the evolution of this endocrine disorder.

Insulin resistance 10-20 years prior to actual manifestation of the disease has been postulated [2, 3].

The insulin receptor is tyrosine kinase enzyme in essence, involved in autophosphorylation and mediating a series of phosphorylation reactions

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culminating in insulin action. The receptor consists of 2 alpha subunits and two beta subunits. The alpha subunits are extracellular domains of the receptor complex and bind to insulin. The later, beta subunits constitute transmembranous and intracellular components of the receptor complex. The beta subunits are linked by disulphide linkages.

On binding of insulin to the alpha subunit, the beta subunit undergoes auto phosphorylation leading to activation of a cascade of phosphorylation.

IRS -1 and IRS -2 are the substrate proteins at the insulin receptor which on being phosphorylated at their tyrosine residue sites set of a cascade of phosphorylating reactions including activation PI3K culminating in physiological effects of insulin. IRS -1 is involved in gene regulation and cell mitogenesis and has a contribution towards insulin/IGF related glucose transport into cells.

However mice which were deficient in both IRS 1 alleles exhibited only mild insulin resistance. This led to discovery of IRS- 2 [Isolated from the myeloid progenitor cells], hence termed due to its resemblance to IRS -1 [4].

The IRS -1 is the essential substrate for insulin/IGF-1 on being phosphorylated or activated it phosphorylates phosphatidylinositol kinase, Grb 2 and several other proteins with SH2 domains. It was noted that IRS 1 gene ablation led to growth retardation, impaired glucose tolerance and obtunded PI3K activity. The mice with IRS 1 gene ablation were 50% smaller compared to controls and had increase beta cell mass to compensate for the insulin resistance.

Cellular mechanisms of insulin resistance

Source: Journal of Clinical Investigation
In contrast IRS-2 gene ablation showed profound effects in the affected mice so much so that they phenotypically were diabetic and had peripheral insulin resistance along with dysfunctional beta cell mass with a 50% decrease in the mass.

Studies bear increasing evidence that elevated serum fatty acids induce insulin resistance in both human and animal models. Studies done at University of Alabama cite that exposure if adipocytes to 1mmol palmitate, myristate and separate resulted in abating glucose transport to around 50%.

It is an interesting correlation to note that palmitate concentration found in diabetics is around 0.3Mm which is in fact the required concentration to achieve insulin resistance. Insulin resistance has been primarily attributed to GLUT 4 mediated transports. The resistance does not have any paramount relation GLUT 4 translocation to cell membrane surface or insulin mediated incorporation of glucose into glycogen [5].

Randle et al proposed fatty acids induced insulin resistance is due to a negative feed back mechanism by citrate on the enzyme phosphofructokinase, which led to increased levels of glucose 6 phosphate which in turn lead to inhibition of hexokinase enzyme. He attributed to increased levels of fatty acids being converted NADH+ and acetyl coA and subsequently being converted to citrate, which exerted its effect on the enzyme phosphofructokinase.

Randle et al postulated that the mechanism by which fatty acids induced insulin resistance is by their by their metabolites namely diacylglycerol, fatty acyl coA, ceramides, these metabolites lead to activation serine and threonine kinases which in turn phosphorylating serine and threonine residues on IRS-1 and IRS-2 substrates. The consequence of such phosphorylation is hampering of PHOSPHO INOSITOL 3 KINASE ENZYME which is essential in phosphorylating cascade of downstream molecules for mediating insulin s action [6].

To elucidate the mechanism involved in fatty acids induced insulin resistance a study was carried out by the department of medicine at the University of Yale. The study involved nine healthy individuals in whom skeletal muscle glycogen content and glucose 6 phosphate levels were measured using nuclear magnetic resonance spectroscopy every 15 min. These measurements were carried out with subjects being on high and low lipid infusions in both euglycaemic and hyperinsulinaemic clamps.

It was noted during the first three and a half hours, that glucose uptake per se was not hampered and lipid infusion ad no deleterious effect on the same. However after 6 hour period interesting facts surfaced. It was noted that glucose uptake was obtunded by 46% in comparison to control values.

The muscle glycogen synthesis was obtunded by fifty % as a consequence of approximately 40% reduction in glucose oxidation leading to a reduction in glucose 6 phosphate levels.

The reduced glucose 6 phosphate levels led to reduced glucose incorporation as glycogen. This theory however is contrary to Randle et al
theory where increase glucose 6 phosphate levels have been linked to hexokinase inhibition leading to insulin resistance. The above study postulates that insulin resistance due to obtund glucose transport at molecular levels at cell membrane surface. [7]
The lipid induced insulin resistance is influenced by three determinant features abated action of IRS-1 activation of phospho inositol 3 kinase activity which in turn can be linked to blunted IRS -1 activation at its tyrosine residues and increase in protein kinase theta activity which is predominantly involved in phosphorylation of serine residues on IRS molecules and hence causing a hindrance along the PI3K activation cascade.[8]

In a study conducted at Yale university fat devoid transgenic mice were created by targeting a negative protein gene A-ZIP/F-1. On conducting hyperinsulinaemic and euglycaemic clamps in these mice interesting facts surfaced, these fat devoid mice were in fact discovered to be insulin resistant due to deficient PI3K activity which is activated via phosphorylated IRS 1 and IRS 2 substrates.

However upon transplantation of adipocytes into these transgenic mice insulin resistance was abated restoring insulin's activity suggesting increased levels of triglycerides around vital organs like liver visceral adiposity and raised triglycerides around muscles with disproportnate fat distribution was the underlying pathology.[9]

REFERENCES:


