Chapter 1

Introduction
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Type 2 diabetes is the major cause for morbidity and mortality throughout the world. It has been estimated that over 200 million people will be afflicted with the disease by the end of this decade. Even after intense of research, the pathogenesis of type 2 diabetes is not understood in full detail, but it has become clear that acquired and non-genetic factors represent a critical link in the pathogenesis of type 2 diabetes (Leng et al., 2004; Saltiel et al., 2000). Insulin resistance is one of the salient features of type 2 diabetes and is also linked to hypertension, hyperlipidemia and polycystic ovarian disease (Pessin et al., 2000). Insulin resistance occurs when normal circulating concentrations of the hormone fails to regulate body glucose homeostasis. Insulin regulates glucose homeostasis mainly by increasing the transport of glucose into the skeletal muscle. Insulin binding to the α-subunit of its receptor triggers its intrinsic tyrosine kinase activity of the β-subunit. The auto-phosphorylated insulin receptor phosphorylates the tyrosine residues of insulin receptor substrate-1 (IRS-1). IRS-1 tyrosine phosphorylation promotes the transcriptional and mitogenic activities of the insulin through mitogen activated protein kinase (MAPK) cascade, while activation of phosphatidylinositol 3 kinase (PI3K) pathway is engaged with the hormone’s metabolic effects (Pessin et al., 1999). In muscle and fat cells, the glucose transport is mediated through the insulin-stimulated translocation of intracellular glucose transporter GLUT4 isoforms to the cell surface via PI3K activation.

Several defects in insulin signaling have been reported in insulin resistance. Previous studies have demonstrated decreased insulin stimulated PI3K activity and GLUT4 translocation in insulin resistance (Zierath et al., 1997). This suggests that defects in the proximal insulin signaling pathway as a common element in insulin
resistance. Although evidence for proximal defects in insulin signaling has been widely reported, studies have produced conflicting results. A decreased insulin receptor, IRS-1 levels and diminished insulin receptor tyrosine kinase activity associated with insulin resistance has been reported (Barnard et al., 1997; Han et al., 1997). But others have reported normal function of insulin receptor in insulin resistance (Youngren et al., 2001). Hansen et al (Hansen et al., 1998) reported a reduced insulin stimulated IRS-1 tyrosine phosphorylation in diet induced insulin resistant animals. Recent studies have linked the increased serine phosphorylation of insulin receptor and IRS-1 with insulin resistance in both invtro and invivo preparations (Anna et al., 2005; Roith et al., 2001; Sykiotis et al., 2001). Thus the early defects in insulin signaling pathway and the sequence of events responsible for the development of insulin resistance remains unclear.

There are convincing experimental and clinical evidence for the generation of increased reactive oxygen species (ROS) in both type 1 and type 2 diabetes (Ceriello, 2001; Rudich et al., 1997; Wittman et al., 1996). Oxidative stress refers to a situation of imbalance between the production of ROS and antioxidant defense, leading to potential tissue damage. Oxidative stress resulting from increased production of ROS plays a key role in the pathogenesis of late diabetic complications (Evans et al., 2002). Studies have linked the role of oxidative stress in the pathogenesis of insulin resistance (Ceriello et al., 2000; Paolisso et al., 1994 & 1996). Through invtro and animal models of insulin resistance, it has been found that antioxidants, especially α-lipoic acid, vitamin E and vitamin C improve insulin sensitivity (Evans et al., 2002; Jacob et al., 2000). When rat L6 muscle cells and mouse 3T3L1 adipocytes were exposed to oxidative stress, insulin stimulated glucose uptake was inhibited (Rudich et al., 1997&1999; Tirosh et al., 1999). Even though H2O2 induced insulin resistance is reported, it is generally accepted that
H$_2$O$_2$ exerts insulinomimetic effects (Goldstein et al., 2005; Kozlovsky., 1997). Studies have shown oxidation-sensitive step(s) within the insulin signaling machinery (Mahadev et al., 2001). Thus the role of oxidative stress on insulin action is not clear. Reactive oxygen species (ROS) can act as signaling molecules and activates a number of redox sensitive pathways. Studies have shown that the ROS induced activation of multiple stress sensitive serine kinase cascades and their role in the pathogenesis of insulin resistance (Adler et al., 1999; Cohen et al., 1996; Kyriakis et al., 1996). Such major intracellular serine kinase targets for oxidative stress are nuclear factor-kappa B (NF-kB), C-Jun-N-terminal kinase (JNK) and p38 mitogen activated protein kinase (p38MAPK) pathways. Activation of these pathways in various tissues under diabetic condition has been reported (Basu et al., 1998; Obata et al., 2000; Yuan et al., 2000). Thus, it is likely that the oxidative stress induced activation of redox sensitive serine kinase pathways are crucial mediators in the progression of insulin resistance. Even though, oxidative stress and stress sensitive serine kinase activities are reported in insulin resistance, their associated role in the pathogenesis of insulin resistance have not been studied together. Moreover, the precise components of insulin signaling pathway disturbed by these redox sensitive serine kinases have not been identified. Even though the beneficial effect of antioxidants in insulin resistance is documented, the molecular mechanism by which these antioxidants improve insulin sensitivity is not known. Elucidation of the link between oxidative stress and molecular events in insulin resistance is an important area of investigation. This may help in identifying pharmacological targets for the treatment and/or prevention of insulin resistance and its complications.

In view of the above, the present study was designed to investigate the role of oxidative stress and redox sensitive serine kinase pathways in insulin resistant subjects
(type 2 diabetes and rheumatoid arthritis), invitro (rat L6 muscle cells) and animal models (high fat fed rats) of insulin resistance.