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Review Article

Role of Protein Tyrosine Phosphatase-1B Inhibitors in Type 2 Diabetes Mellitus

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Abstract

Diabetes emerged as major health care burden disease in US and other industrialized countries, among which type 2 diabetes is the most common. Insulin resistant is the main culprit of the patients of type 2 diabetes. Type II diabetes is most common form of diabetes in 85-90% of the diabetic patients. Type II diabetes (insulin independent diabetes mellitus) patients are unable to respond to insulin and it can be treated by dietary changes, regular exercise and drug treatment. Insulin resistance has been established as a key defect in progression to and maintenance of Type II diabetes. Major current treatment for Type II diabetes includes thiazolidinediones, gliptins (Dipeptidyl peptidase-4 inhibitors), sulfonylureas, metformin and liragutide (Glucagon-like peptide-1 agonist). Tyrosine phosphorylation is important for signaling pathways which are regulated by insulin and leptin. Insulin on binding to its receptor induces activation of the insulin receptor kinase through autophosphorylation. Drugs which can inhibit the negative regulator of the signaling pathways are expected to actuate the action of insulin and leptin. Hence, it can be beneficial for the treatment of diabetes (type 2) and obesity. In addition, various evidences suggest that insulin and leptin action can be exaggerated by the inhibition of Protein-tyrosine phosphatase 1B. Hence, Protein-tyrosine phosphatase 1B inhibition could be a new therapeutic option for treatment of patients with at risk type 2 diabetes mellitus and obesity.

Keywords: Type 2 diabetes, Obesity, Insulin, Leptin, Protein-tyrosine phosphatase 1B

1.Introduction

Diabetes and obesity have increased dramatically in recent decades worldwide. Diabetes mainly emerged as major health care burden disease in both US and other industrialized countries, among which type 2 diabetes is the most common. Insulin-resistant is the main feature which is distinguishes the patients of type 2 diabetes [1]. The morbidity and mortality associated with secondary complications of the disease such as retinopathy, nephropathy and cardiovascular disease have also elevated significantly [2]. Studies conducted in India highlighted that the prevalence of diabetes is much and that it is increasing rapidly in the urban and rural population. This study estimated that approximately 33 million adults with diabetes in India and it likely to increase up to 57.2 million by the year 2025 [3]. Type I diabetes (insulin dependent) is caused due to lack of functional beta cells insulin insufficiency occurs. Patients suffering from Type 1 diabetes are therefore totally dependent on external source of insulin while patients suffering from Type II diabetes (insulin independent diabetes mellitus) are unable to respond to insulin, which can be treated with dietary changes, exercise and medication. Type II diabetes (T2D) is the more common form of diabetes constituting 90% of the diabetic population. Insulin resistance has been established as a key defect in progression to and maintenance of T2D. Major current pharmacotherapies for T2D include thiazolidinediones [4], gliptins (Dipeptidyl peptidase-4 inhibitors), sulfonylureas, metformin, and liragutide (Glucagon-like peptide-1 agonist) etc. Medicinal plants like Allium sativum, Eugenia jambolana, Momordica charantia Ocimum sanctum,Phyllanthus amarus, Pterocarpus marsupium, Tinospora cordifolia, Trigonella foenum graecum and Withania somnifera has showed beneficial effects and can be used in treatment of diabetes [5]. There are also some limitations with these pharmacotherapies with respect to their efficacy or side effects like nausea, diarrhea, hypoglycemia, weight gain, fluid retention and cardiovascular complications [6].

2.Protein-tyrosine phosphatase 1B an active player in T2D

Protein-tyrosine phosphatase 1B is a unique enzyme that is included in the protein tyrosine phosphatase (PTP) family. It is encoded by the (Tyrosine-protein phosphatase non-receptor type 1) PTPN1 gene in humans. Protein-tyrosine phosphatase 1B is a negative regulator of the insulin signaling pathway and it is considered to be an important therapeutic target for treatment of type 2 diabetes mellitus. In physiologic condition, for long-term energy storage two hormones are crucial: insulin and leptin. Insulin controls the pathways responsible for lipogenesis and glucose uptake and leptin regulates peripheral energy expenditure and food intake [7]. T2DM is a common metabolic disorder. Chronic hyperglycemia and dyslipidemia are its characteristics which are resulting from insulin resistance of the peripheral tissues and impaired insulin secretion from the pancreas [8]. Resistance to insulin and leptin is the hallmark in common for type 2 diabetes mellitus and obesity. It has also been hypothesized that insulin resistance observed in Type II diabetes is because of disequilibrium in enzyme activity between the IR and PTP [9, 10]. Relieving insulin resistance has been considered as a primary strategy to improve metabolic control in T2DM subjects [11]. In type 2 diabetes, insulin receptor autophosphorylation and tyrosine kinase activity are impaired in skeletal muscle, fat and liver [12, 13]. The phosphorylation state of the insulin receptor (IR) is controlled by a balance between cellular protein tyrosine phoshatases (PTPs) and relative activities of the insulin receptor kinase [13]. In cell signal transduction reversible phosphorylation of tyrosyl residues in proteins plays an important role. Protein tyrosine phosphorylation is controlled by the combined actions of protein tyrosine kinases and protein tyrosine phosphatases (PTPs) [14-16]. PTPs have been involved to regulate many cellular events such as cell growth, motility, proliferation and differentiation [17]. Hence, in the signaling pathways the biological consequences controlled by PTKs and PTPs are important. On the other hand, the PTPs can also potentiate the action of Receptor tyrosine kinases (RTK). Therefore, deregulation of the PTP activity can lead to impaired signaling that can responsible to the development of various diseases in human such as autoimmunity, infectious diseases, cancer, diabetes and inflammation [18-20].

2.1.Structure of PTP1B

PTPs are characterized by a conserved active site sequence (H/V) C(X) 5R(S/T), called the PTP signature motif, in which the cysteine residue functions as a nucleophile and is essential for catalysis. A recent survey of the human genome revealed 107 PTP genes of which 81 encoded as active phosphatases [21]. PTP1B was the first PTP enzyme to be purified to homogeneity from human placental tissue among all PTP enzymes [22]. PTP1B is a widely expressed 50 kDa monomeric enzyme that is localized mainly in the endoplasmic reticulum (ER) via a cleavable proline-rich C-terminal segment. This monomeric enzyme contains 435 amino Acid residues [23]. The main structural feature are the catalytic loop containing the catalytic residue WPD (tryptophan, proline, aspartic acid) loop, Cys215 and the secondary Aryl phosphatase binding site (Fig.1).

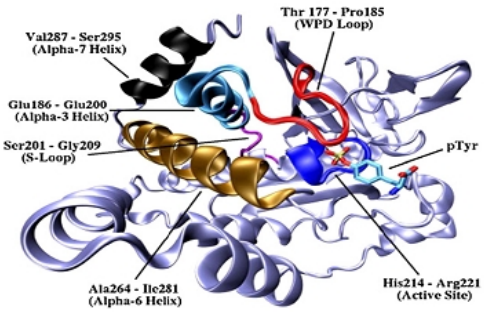

Fig.1: Structure of PTP1B enzyme

The active site His214–Arg221 lies within the pTyr substrate binding region. The essential reduced Cys-215 lies within this sequence. Three dimensional views is the WPD (tryptophan, proline, aspartic acid) loop (Thr177–Pro185). The WPD loop is flexible region which is in 'open' conformation in the absence of any substrate and closes when the pTyr substrate binds with the region. Closure is essential for catalysis, and hydrogen bond forms between the amino acids Trp179 in the WPD loop and Arg 221 in the active site. Inhibitors which reduce the WPD loop mobility may block substrate binding and/or decrease catalytic activity. The S-loop, Ser201–Gly209 also influences WPD loop mobility and itself also be inhibited by inhibitor binding. (Reproduced from Kamerlin et al (2007, Biochemical and Biophysical Research Communications 356: 1011–1016) with permission.)

In figure 1 another features involved in phosphatase selectivity are the YRD (tyrosine. arginine, aspartic acid) motif and gateway residue, glycine (Gly) 259 Cys 215. The N-terminal domain (amino acids 1–298) includes the catalytic domain which contains two aryl phosphate-binding sites: First site is a high-affinity catalytic site (containing the nucleophile cysteine residue, Cys215) and another site is a low-affinity non-catalytic site (demarcated by Arg24 and Arg254 residues) [24]. The C-terminal domain of PTP-1B (amino acids 299–435) is rich in proline residues, whereas the hydrophobic amino acid residues 400–435 contribute to location of the enzyme at the cytoplasmic face of the endoplasmic reticulum [25]. The C-terminal domain influences the N-terminal domain by causing a global conformational change of PTP-1B molecule that allows formation of direct contacts between the catalytic domain and the phosphorylated substrates [26].

2.2 PTP-1B in insulin resistance

2.2.1. Type 2 diabetes disease states: Mainly obesity combined with a genetically changes, produces insulin resistance and impaired glucose tolerance. Hyperinsulinaemia, glucotoxicity and lipotoxicity affect the pancreatic-islet β-cells and it results into failure in maintainence of sufficient insulin levels for compensating the insulin resistance which leads to elevated glucose levels and diabetes. Microvascular complications become apparent as the time proceeds. In addition, Leptin resistance might have a crucial role in the connection between obesity and insulin resistance.

2.2.2. Protein tyrosine phosphatase 1B (PTP1B) and negative regulation of the insulin and leptin metabolic signal transduction pathways:

Insulin after binding to receptor, insulin induces activation of the insulin-receptor kinase (IRK) through autophosphorylation. Insulin receptor substrate (IRS) proteins recruitment actuates activation of phosphatidylinositol-3-kinase (PI3K) through binding of the p85 subunit and activation of the catalytic p110 subunit. PI3K activation induces downstream effectors such as phosphatidylinositol dependent kinase 1 (PDK1) and protein kinase B (PKB), leading to translocation of glucose transporter 4 (GLUT4) and glucose uptake in muscle and inactivation of glycogen-synthase kinase 3 (GSK3). IR activation also actuates the c-Cbl-associated protein (CAP) and mitogen-activated protein kinase (MAPK) pathways. The binding of leptin to ObR receptor leads to phosphorylation of Janus kinase 2 (JAK2) and thereby activating the JAK/signal transducer and activator of transcription (STAT) pathway and conceivably the PI3K pathway. Activation of STAT3 through JAK2 phosphorylation induces translocation of STAT3 to the nucleus. STAT3 induces gene responses that reduce transcription of acetyl coenzyme A carboxylase (ACC), reducing malonyl CoA and fatty-acid synthesis, while increasing fatty-acid oxidation. Cytosolic and endoplasmic reticulum bound PTP1B responsible for dephosphorylates membrane bound or endocytosed insulin receptors and leptin receptors and result into their deactivation. PTP1B substrates such as IRS1 and PTP1B, can down regulate IRK activity by forming a complex with growth factor receptor bound protein 2 (GRB2).

2.3.Regulation of signaling pathway by PTP1B

PTP-1B localizes to the endoplasmic reticulum with its phosphatase domain which is directed towards the cytoplasm, whereas the IR is located in the plasma membrane. As given in some research possible explanation would be that some PTP-1B is associated with the plasma membrane, bringing PTP-1B into close proximity with the IR. As per the research once insulin binds to the receptor, the activated receptor is internalized quickly into endosomes from the endosomes the receptors can be degraded or recycled by delivery to secondary lysosomes. These recycled receptors are dephosphorylated prior to their return to the plasma membrane [27]. Hence, it is possible that IR is brought into contact with PTP-1B during internalization and its transit inside the cell. Further investigation shows that insulin signaling is mediated by highly integrated network beginning with insulin binding to its cell-surface receptor (Fig.2) [28].

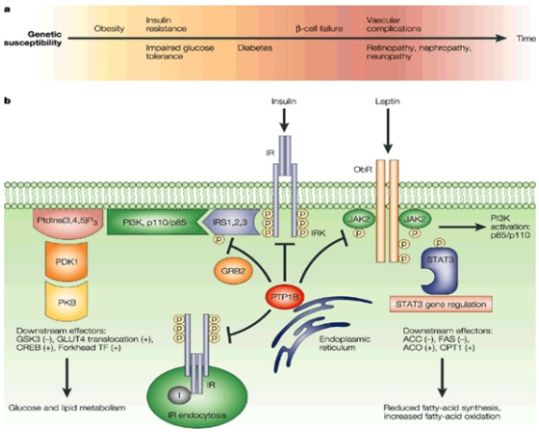

Fig. 2. Type 2 diabetes disease states and PTP1B regulated leptin and insulin signalling pathways

I: insulin, IR: insulin receptor, CREB: cyclic AMP response element binding protein, CPT1: carnitine palmitoyl transferase, ACO: acyl coenzyme-A oxidase, PtdIns (3,4,5) P3: phosphatidylinositol-3,4,5-trisphosphate), Forkhead TF: forkhead transcription factor .

The insulin receptor (IR) is a subclass of a large family of protein tyrosine kinases (PTKs). It is a transmembrane protein made up of two extracellular a-subunits and two transmembrane b-subunits. Metabolic insulin signal transduction occurs when IR bind to the insulin, the IR undergoes autophosphorylation on several tyrosine residues located in the insulin receptor activation loop of b subunits [29, 30]. Autophosphorylation enhances IR kinase activity and it also triggers downstream signaling events including IR substrate (IRS) proteins (IRS 1-4) tyrosyl phosphorylation of and followed by activation of other adaptor molecules (e.g. Grb2 and Shc) that are linked to the activation of two main signaling pathways: the phosphatidylinositol 3-kinase (PI3K) and downstream protein kinase B (PKB) pathway (PKB; also known as AKT), and translocation of the glucose transporter GLUT4, stimulation of glycogen synthesis) [31, 32], which is responsible for metabolic actions of insulin, another pathway is the Ras–mitogen-activated protein kinase (MAPK) pathway, which involve in the regulation of the expression of some genes and cooperates with the PI3K pathway for the control cell growth and differentiation [28, 30]. There are several mechanisms involve in the negative regulation of the IR: By protein tyrosine phosphatases dephosphorylation of Tyr residues, serine phosphorylation occurs by various Ser/Thr kinases, binding of various inhibitory proteins and ligand-induced down-regulation (degradation) [28]. Several ptps like rptp LAR (Leukocyte antigen related protein), SHP2 and PTP1b have been involved in insulin signal transduction [33]. PTP1B is act as a negative regulator of insulin and leptin signal transduction pathways.

2.4. PTP1B involved in Diabetes

Recent epidemiological studies stats that, North America Region has the highest prevalence of diabetes in the world, with 21.4 million people or 7.8% of the adult population. The impaired regulation of insulin secretion or signaling through the IR is responsible to the development of diabetes [33]. DM2 is characterized by a resistance of insulin in the insulin sensitive tissues like muscle, liver, and fat to insulin action [34-38]. Mechanism of the insulin resistance is tightly associated with obesity. Approximately ¾ of obese individuals will develop DM2. In DM2, as the expression of PTP-1B increased, the amount of IR tyrosine phosphorylation decreased [39]. These observations also have been done in various cell lines in which PTP 1B was over expressed [40]. In animal studies, mice deficient in the G-protein subunit Gia2 have a phenotype of insulin resistance that just like DM2, which is affected by increased levels of PTP-1B expression and PTP activity in adipose tissue, liver, and muscle [41]. In animal models of DM2, expression levels of PTP-1B and other PTPs as well as PTP activity have been measured in various mice like ob/ob and db/db mice and fa/fa Zucker rats, but with conflicting results. In ob/ob mice the liver cytosol and particulate fractions, PTP activity have been measured by dephosphorylation of the 32P labeled insulin receptor peptide 1142–1153.which is shown PTP activity decrease in one study [42], in contrast to another study where this activity increase was observed (43). Similar conflicting results have been observed for skeletal muscle PTP activity in Zucker (fa/fa) rats [44, 45]. This has been the case for chemically induced diabetes in animals using streptozotocin [46-48], goldthioglucose [49] and alloxan [50]. In human studies, PTP activity, PTP-1B and other PTP protein levels have been measured in muscle and adipose tissue of insulin-resistant obese nondiabetic and obese DM2 subjects, biopsies from both subjects, muscle of insulin-resistant obese non-diabetic individuals, two reports have shown that both PTP activity and PTP-1B protein levels are increased [51]. Decreased PTP activity and PTP-1B levels, have also been reported, again contradictory results have been observed [52]. The results from in obese DM2 individuals carried out the study and the results seem to be a bit more consistent in that they all individuals show a decrease in PTP activity either in soluble muscle fractions and decreased PTP-1B protein expression [51–53]. In adipose tissue of obese non-diabetic subjects, protein levels of PTP-1B, PTPs LAR and found to be elevated [54]. A role for PTPs in insulin signaling regulation and diabetes came from studies using vanadium compounds that normalized blood glucose levels in type 1 and type 2 diabetes mellitus in animal models [55, 56].

Vanadium compounds both in vitro and in vivo possess substantial insulin mimetic activity. In type 1 diabetic rats consequently, oral administration of vanadate normalizes blood glucose levels through stimulation of glucose uptake [57]. Hepatic cytosolic PTP activity was increased in those rats, which was reduced by administration of insulin and vanadate, and normalized blood glucose levels [58]. McGuire et al was first reported the Measurement of the PTP activity in muscle tissue from obese insulin-resistant non-diabetic patients and lean insulin-sensitive controls [59]. They found that in insulin-resistant subjects, PTP activity was 33% lesser than in controls from that this increased PTP activity could be contributing to the insulin resistance which is observed in these patients. This was followed by a study in which PTP activity in muscle from lean controls, obese insulin-resistant non-diabetics and obese NIDDM diabetics [60]. In contrast to the first report, compare to lean controls, the obese insulin-resistant non-diabetic individuals were found to have a 21% decrease in PTP activity in the particulate muscle sample. The reason for the discrepancy between these two reports is unclear, may be due to differences in the patient population used for each study the results are different. In muscle of obese NIDDM subjects was also measured, in this group PTP activity was decreased 22%, also compared to non-diabetic subjects there was a 38% decrease in the amount of PTP- 1 B protein observed in the diabetic. In a more recent study, Ahmad et al. measured PTP activity in muscle from lean controls, insulin resistant non-diabetic individuals and obese diabetic individuals. Compared to the controls, in the obese NIDDM subjects, PTP-1B and LAR protein levels were decreased in the particulate fraction. Finally, Worm et al. have measured PTP activities in the particulate fraction from muscle of type 2 diabetic patients and controls and found no significant difference although soluble PTP activity was found to be significantly decreased [61].Combining the results from these studies, we finds that the majority of obese non-diabetic insulin-resistant individuals have an increased particulate PTP activity in muscle. In one of the studies, this increased PTP activity relates with increased levels of PTP-1B and LAR protein whereas in the obese NIDDM group, particulate and soluble PTP activity decreases, and in two studies this correlates with a decrease in PTP-1B levels, where LAR is also affected. It has been reported that obese non-diabetic insulin-resistant subjects, PTP activity as well as PTP-1B and LAR protein levels are also increased [62]. Although there seem to be conflicting observations between the studies on PTP activities in diabetes and obesity (may be because of limited number of subjects in these studies), it appears that PTP activities may be affected in obesity and diabetes. The first evidence for PTP1B involve in the regulation of IR tyrosine phosphorylation was obtained by microinjection of PTP1B protein given into Xenopus oocytes [63]. These studies were supported by Ahmad et al. where tyrosine phosphorylation of the IR was markedly decreased [64]. In primary culture of rat adipose cells, transient over expression of PTP1B WT reduced glucose uptake and GLUT4 translocation to the cell surface [65]. Seely et al. using the substrate trapping method demonstrated a direct association between the IR and PTP1B [66]. The direct association between IR and PTP1B was independently demonstrated in intact cells over expressing the C215S trapping mutant of PTP1B [67]. In genetic Evidence Recently, in muscle of mice transgenic over expression of human PTP1B led to impaired activity of the PI3- Kinase and insulin receptor, followed by insulin stimulation. It also decreased muscle glucose uptake and whole body glucose disposal and [68]. Re-expression of PTP1B by adenoviruses injection given in the liver of PTP1B null mice reduced insulin sensitivity, again relating with decreased insulin-stimulated IR tyrosine phosphorylation [69, 70].

Together, these findings shown that in humans and rodents, over expression of PTP1B in muscle may involved in insulin resistance. Furthermore, this all research conform that liver and muscle are important sites for the PTP1B action in the regulation of insulin signaling and glucose homeostasis. Recent evidence suggest that PTP1B by inhibiting phosphorylation of JAK2, involved in negative regulation of leptin signaling, which attenuates leptin signaling in vivo [70]. Studies from two independent groups have shown that mice that lack the PTP1B gene shown more sensitive to insulin with resistance to weight gain also reduced plasma glucose on a high fat diet [71]. Over the past several years, from all the above researches and many efforts has been put in discovering PTP1B inhibitors proved beneficial effect in T2D and obesity patients [72].

3. Recent findings and future aspects

The marine-derived fungus Cosmospora sp. SF-5060, aquastatin A was isolated as a protein tyrosine phosphatase 1B (PTP1B) inhibitory component produced by the fungus which showed modest but selective inhibitory activity toward PTP1B over other protein tyrosine phosphatases [73]. Series of maslinic acid derivatives have been synthesized by introducing various fused heterocyclic rings at C-2 and C-3 positions having inhibitory effects on PTP1B,TCPTP and related PTPs are evaluated (74). As per one recent studies, a MeOH extract of the stem barks of Sorbus commixta Hedl. (Rosaceae) showed strong PTP1B inhibitory activity [75]. Several groups reported that ursolic acid, oleanolic acid, maslinic acid and other triterpenoid having in vitro inhibitory activity against protein tyrosine phosphatase 1B (PTP-1B) [76].

4.Conclusion

PTPases have active role in various diseases and PTP-1B appears to be an important therapeutic target. In last decade, much evidence has been provided to define the role of PTP1B in metabolism. As inhibition of PTP1B enzyme activity is of great promise for alleviating insulin and leptin resistance, hence drugs that inhibit PTP-1B activity have the potential for the treatment of type 2 diabetes mellitus and other metabolic disorders. Various human studies suggest that PTP activity increases in the insulin-resistant state and with increased levels of PTP-1B protein. PTP-1B-deficient mice are resistant to both diabetes and obesity. Thus, the beneficial role of PTP1B in the treatment of insulin resistance, obesity and diabetes is accepted and the search for effective and safe orally available compounds is currently ongoing.

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Conflicts of interest: The author declares no competing interests.

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