Insulin Mediators, NIDDM and PCOS

Insulin mediators are glucosamine- or galactosamine-derivatives of myo-inositol, D-chiro-inositol, or D-pinitol (1D-3-O-methyl-chiro-inositol). The structures of putative insulin mediators have not been reported in detail. One putative insulin mediator of particular interest in relation to Non-Insulin Dependent Diabetes Mellitus (NIDDM) (Larner and Huang, 1999) and PolyCystic Ovary Syndrome (PCOS) (Nestler et al., 1998, 1999, 2000) is a putative insulin mediator (pH 2.0 type) preparation isolated from rat liver that contains an unusual combination of galactosamine and D-chiro-inositol (Larner et al., 1988). The best guess as to the structure of the galactosamine D-chiro-inositol putative insulin mediator from rat liver comes from the chemical synthesis of a compound with the structure

![Putative Insulin Mediator](image)

O-α-D-(2-amino-2-deoxy)-galactopyranosyl-(1→3)-D-chiro-inositol (Berlin et al., 1990) (CAS Registry No. 129568-93-0) and related to the rat liver putative insulin mediator (Berlin et al., 1990). The choice of the (1→3) linkage in this structure was based on making a corresponding D-chiro-inositol compound related to a glycan from T. bruci with a possible putative insulin mediator structure of 4-O-glycosyl-myo-inositol-1-phosphate.

Of particular interest is the similarity in structure between this synthetic “putative insulin mediator” (pH 2.0 type) and the structure of fagopyritol A1

![Fagopyritol A1](image)

O-α-D-galactopyranosyl-(1→3)-D-chiro-inositol as determined unambiguously by NMR techniques (Obendorf et al., 2000). Chemical Abstracts Service has given fagopyritol A1 the CAS Registry No. 2092287-65-0. Other fagopyritols in this unique series are fagopyritol A2 (α-D-galactopyranosyl-(1→6)-α-D-galactopyranosyl-(1→3)-1D-chiro-inositol) (CAS Registry No. 209287-66-1) and fagopyritol A3 (α-D-galactopyranosyl-(1→6)-α-D-galactopyranosyl-(1→3)-1D-chiro-inositol) (CAS
Members of the fagopyritol B series include fagopyritol B1 (α-D-galactopyranosyl-(1→2)-1D-chiro-inositol) (CAS Registry No. 79-39-04-1), fagopyritol B2 (α-D-galactopyranosyl-(1→6)-α-D-galactopyranosyl-(1→2)-1D-chiro-inositol) (CAS Registry No. 116261-02-0), and fagopyritol B3 (α-D-galactopyranosyl-(1→6)-α-D-galactopyranosyl-(1→2)-1D-chiro-inositol) (CAS Registry No. 208708-11-6) (Horbowicz et al., 1998; Szczeciński et al., 1998; Obendorf et al., 2000; Steadman et al., 2001c).

Berlin et al. (1991) synthesized additional structures related to insulin mediators. These structures are O-(2-amino-2-deoxy)-α-D-glucopyranosyl-(1→4)-D-myoinositol-1-phosphate (pH 1.3; type A) or O-(2-amino-2-deoxy)-α-D-glucopyranosyl-(1→4)-D-myoinositol (pH 1.3; type A) and O-(2-amino-2-deoxy)-α-D-galactopyranosyl-(1→4)-D-chiro-inositol-1-phosphate (pH 2.0) or O-(2-amino-2-deoxy)-α-D-galactopyranosyl-(1→4)-D-chiro-inositol (pH 2.0) (CAS Registry No. 129568-93-0) (Berlin et al., 1991), and various chemical derivatives of these structures.

Non-Insulin Dependent Diabetes Mellitus (NIDDM)

Non-insulin dependent diabetes mellitus (NIDDM) or Type II diabetes (also referred to as adult onset diabetes) is an insulin response disorder. Subjects with NIDDM have abnormal D-chiro-inositol metabolism, are deficient in a specific insulin mediator containing galactosamine and D-chiro-inositol, have decreased glycogen synthase, and high blood glucose (Larner and Huang, 1999).

Polycystic Ovary Syndrome (PCOS)

Polycystic ovary syndrome (PCOS) also is an insulin response disorder that affects about 10% of women of reproductive age. Subjects with PCOS have greatly enlarged ovaries with many cysts, have decreased responsiveness to insulin (insulin resistant) that inhibits ovulation, stimulates ovarian testosterone, and results in impaired glucose tolerance (many develop NIDDM with age) and increased blood pressure (Nestler et al., 1998, 1999, 2000).

D-chiro-inositol, Insulin Mediators, and NIDDM / PCOS

Oral intake of D-chiro-inositol by subjects with NIDDM lowers blood glucose and increases insulin response (Larner and Huang, 1999). The effect is enhanced by manganese (Fonteles et al., 2000). Buckwheat is a good source of manganese (Steadman et al., 2001b) and a good source of fagopyritols (Horbowicz et al., 1998; Steadman et al., 2000). Dietary consumption of buckwheat as flour or biscuits made from buckwheat flour has been demonstrated to have hypoglycemic effects in patients with diabetes resulting in lowered blood sugar and urine sugar (Lu et al., 1992; Wang et al., 1992).

Oral intake of D-chiro-inositol by subjects with PCOS improves ovulatory function, improves glucose tolerance, lowers blood pressure, lowers plasma triglycerides, and
increases insulin response (Nestler et al., 1999, 2000). Clinical studies using buckwheat products containing fagopyritols as dietary treatments for PCOS and NIDDM are being conducted at well-known institutions in the United States.

Insulin has a multitude of effects. Some of these effects as related to diabetes, in particular non-insulin dependent diabetes mellitus (NIDDM) or Type II diabetes, involve the release of specific putative insulin mediators from specific phosphatidyl inositol glycan components similar to membrane-protein anchors on the outer surface of the cell (Alverez et al., 1988; Berlin et al., 1991; Brodbeck, 1998; Hanson and Ortmeyer, 1996; Jones and Varela-Nieto, 1998) and arranged in caveolae microdomains of the plasmalemma, special signalling compartments where glucose transporters accumulate (Müller et al., 1998; Strålfors, 1997). Phosphatidylinositol glycans involved in insulin mediated signal transduction may have different carbohydrate cores than those of membrane-protein anchors (Brodbeck, 1998; Jones and Varela-Nieto, 1998). The insulin mediators are released with insulin from membranes (Kilgour et al., 1992; Romaro et al., 1988) and released into muscle tissue (Kennington et al., 1990) and into circulation (Shashkin et al., 1997). Extracts from human liver (Caro et al., 1997), rat liver (Larner et al., 1988), and bovine liver (Fonteles et al., 1996; Huang et al., 1999; Larner et al., 1997) each contain two major subtypes of insulin mediators based on differences in molecular weight, isoelectric point, and biological activity (Cheng and Larner, 1985). A pH 1.3 (type A) putative insulin mediator contains myo-inositol-phosphate, glucosamine, and mannose (Larner et al., 1988). A pH 2.0 putative insulin mediator contains galactosamine linked to D-chiro-inositol (Larner et al. 1988). Type II diabetic subjects (NIDDM; human or animal) usually have abnormal D-chiro-inositol metabolism (Craig et al., 1994; Hanson and Ortmeyer, 1996; Kennington, et al., 1990; Larner and Craig, 1996; Ortmeyer et al., 1993a; Ostlund et al., 1993; Suzuki et al., 1994), a deficiency in D-chiro-inositol synthesis (Pak et al., 1992; 1998), and reduced levels of a pH 2.0 type putative insulin mediator (Asplin et al., 1993; Hanson and Ortmeyer, 1996; Sánchez-Gutiérrez et al., 1994; Shashkin et al., 1997). In healthy men, the bioactivity of a pH 2.0 type putative insulin mediator was stimulated by glucose ingestion whereas activity of the pH 1.3 (type A) mediator was unaltered; there was no change in either pH 2.0 or pH 1.3 mediators in insulin resistant (NIDDM) men suggesting that inadequate generation or release of pH 2.0 mediator is associated with insulin resistance (Shashkin et al., 1997). Oral or intravenous administration of D-chiro-inositol lowers blood glucose in subjects with NIDDM (Hanson and Ortmeyer, 1996; Ortmeyer et al., 1993b; 1994; 1995; Ostlund and Sherman, 1998). Intravenous administration of insulin mediators into laboratory animals also stimulates glycogen synthesis and lowers blood glucose (Huang et al., 1993). Oral intake of a mixture of D-chiro-inositol and D-pinitol (4.15 mg/kg daily for 3 days) by non-insulin dependent type II (NIDDM) human diabetics results in increased plasma levels of both D-chiro-inositol and D-pinitol and a reduction in plasma insulin and glucose levels (Ostlund and Sherman, 1998). Manganese enhances D-chiro-inositol and D-pinitol effect (Fonteles et al., 2000).

A myo-inositol phosphoglycan containing a cyclic 1,2-phosphate was partially purified from normal human plasma, found to increase in type II diabetic plasma, and shown to inhibit a type P (pH 2.0) putative insulin mediator (Galasko et al., 1995; 1996). Recent studies with a model system suggest that pH 1.3 and pH 2.0 insulin mediators may act synergistically to control the dephosphorylation of regulators of activities in the pathway
of action of insulin (Huang et al., 1999). Frick et al. (1998a,b) suggest the early signalling step(s) used by phosphatidyglycans (the putative insulin mediators) may represent a target for the treatment of insulin resistant states (NIDDM).

Information on the structures of the pH 1.3 (type A) putative insulin mediator may be obtained from the chemical synthesis of homologs of insulin mimetics (Jaramillo et al., 1994; Zapata et al., 1994). The glucosamine myo-inositol phosphate structures and glucosamine d-chiro-inositol phosphate structure synthesized by Jaramillo et al. (1994) and Zapata et al. (1994) are:

1D-4-O-(2-amino-2-deoxy-α-D-glucopyranosyl)-myo-inositol 1-phosphate
1D-6-O-(2-amino-2-deoxy-α-D-glucopyranosyl)-myo-inositol 1-phosphate
1D-6-O-(2-amino-2-deoxy-α-D-glucopyranosyl)-myo-inositol 1,2-(cyclic phosphate)

1D-6-O-(2-amino-2-deoxy-α-D-glucopyranosyl)-chiro-inositol 1-phosphate

Of these four synthetic pH 1.3 (type A) putative insulin mimetic compounds, only the third (glucosamine myo-inositol cyclic-phosphate) displays promotive effects on the early developing inner ear of the chick embryo (Zapata et al., 1994). None contain galactosamine, and none have been tested for effects on NIDDM.

Other researchers are attempting to chemically synthesize the entire structure of a membrane-protein anchor (Thailler et al., 1999). However, the carbohydrate core of a membrane-protein anchor phosphatidylinositol may differ from that of phosphatidylinosits for signal transduction (Brodbeck, 1998; Jones and Varela-Nieto, 1998).

D-Pinitol insulin mediator:

Several insulin mediators have been isolated from beef liver (Fonteles et al., 1996; Huang et al., 1999; Larner et al., 1997). One of these appears to be a galactosamine D-pinitol (pH 2.0; type P) putative insulin mediator (Fonteles et al., 1996; Huang et al., 1997; Larner et al., 1997). O-(2-deoxy-2-amino)-β-D-galactopyranosyl-(1→3)-4-O-methyl-D-chiro-inositol (CAS Reg. No. 179069-37-5), and several derivatives of this structure, were synthetically prepared as putative insulin mediators (Larner et al., 1995; 1998). Of interest is that the pH 2.0 (type P) putative insulin mediator from beef liver contains D-pinitol and the galactosamine linkage is a β-linkage instead of an α-linkage to D-chiro-inositol as in the rat liver pH 2.0 putative insulin mediator.
D-Pinitol Putative Insulin Mediator:

L-Pinitol insulin mediator:

O-(2-deoxy-2-amino)-β-D-galactopyranosyl-(1→3)-4-O-methyl-L-chiro-inositol (CAS Reg. No. 214404-47-4) is a stereoisomer of the above structure (Frick et al., 1998a).

References


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