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REVIEW

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Involvement of sulfatide in beta cells and type 1 and type 2 diabetes

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Abstract Mammalian tissues express β-isoforms of glycosphingolipids and, among these, sulfatide (sulphated galactosylceramide) is present in the beta cells, and it is here that the short fatty acid chain (C16) isoform is predominately found. In vitro studies have shown that sulfatide preserves insulin crystals and facilitates insulin monomerisation under certain biochemical conditions. It also activates beta cell potassium channels and moderates insulin secretion. Anti-sulfatide antibodies are seen in type 1 diabetes, and immunological presentation of glycosphingolipids by the non-classical CD1 molecules has recently been reported. It is via this mechanism that α-galactosylceramide and sulfatide are able to influence the innate immune system and inhibit autoimmunity, possibly through regulatory natural killer T cells. Administration of sulfatide substantially reduces the incidence of diabetes in non-obese diabetic mice and prevents antigen-induced experimental autoimmune encephalomyelitis in wild-type mice. Sulfatide has specific anti-inflammatory properties, increasing the number of $CD3^+CD25^+$ regulatory T cells and reducing production of several cytokines, including TNF-α. Patients with type 2 diabetes have low serum concentrations of sulfatide, and some animal models of type 2 diabetes have low pancreatic expression of C16:0 sulfatide; administration of this increases insulin secretion and improves first-phase insulin response in Zucker fatty rats. Glycosphingolipids in general, and sulfatide in particular, appear relevant to both type 1 and type 2 diabetes.

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Abbreviations CGT: UDP-galactosyl:ceramide galactosyltransferase · CST: ceramide galactosyl sulfotransferase · GalCer: galactosylceramide · MIP-1α: macrophage inflammatory protein-1α · NKT cell: natural killer T cell · NOD: non-obese diabetic · SulphLacCer: sulphated lactosylceramide

Introduction

Sulfatide is a glycosphingolipid, originally identified in neural tissue [1] and later in the islets of Langerhans [2]. It is also found in the kidneys, retina and associated with lipoproteins in the blood [3]. Sulfatide is an amphiphilic molecule composed of ceramide, galactose and sulphate (Fig. 1); the sulphate group has a negative charge and acidic properties. The molecular weight (800–900 Da) of each glycosphingolipid varies according to the composition of the hydrophobic moiety; in humans, this is primarily related to the length of the fatty acid chain, which generally consists of 16–24 carbon atoms. The names of the different isoforms are designated according to the length and extent of saturation of the fatty acid chain, e.g. the saturated isoform with 16 carbon atoms is denoted as C16:0 sulfatide. In the brain, long-chain forms are most frequent, whereas the pancreas contains considerable amounts of the short-chain variety (C16:0); in the pancreas of some species, 50% of sulfatide is found in this form [4]. Variations in fatty acid chain length influence the physical chemical properties of the sulfatide molecule.

Sulfatide is a derivative of galactosylceramide (GalCer), a glycosphingolipid produced by the addition of galactose to ceramide by the enzyme UDP-galactose:ceramide galactosyltransferase (CGT) [5]. Ceramide galactosyl sulfotransferase (CST) synthesises sulfatide through the addition of a sulphate group to GalCer [6]. Both CGT and CST have been

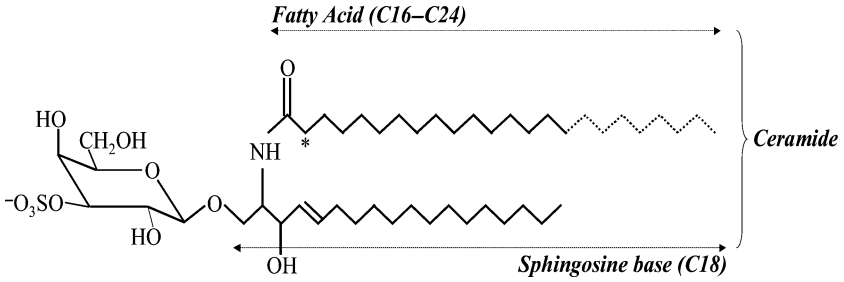


Fig. 1 Chemical structure of sulfatide. Sulfatide consists of a sulphated galactose group attached to ceramide. The ceramide moiety is composed of a sphingosine base (dihydroxy sphingosine, d18:1) and a fatty acid with a chain length of 16–24 carbon atoms. *Possible position of hydroxylation of the fatty acid chain

cloned and knock-out mice generated [7, 8]; both types of genetically modified mice have serious neurological disorders and are unable to breed. CST also catalyses the synthesis of seminolipid and sulphated lactosylceramide (SulphLacCer).

Sulfatide and beta cells

Using the monoclonal antibody Sulph I [9], secretory granules containing insulin crystals were found to be stained in beta cells examined by electron microscopy [10] (Fig. 2 and Text box: Physiological functions of sulfatide in beta cells).

Physiological functions of sulfatide in beta cells

1. Sulfatide is present in the islets [2, 10].
2. Sulfatide recycles in the beta cells and it is here that the C16:0 isoform is predominately found [4].
3. Sulfatide interacts with insulin [13].
4. Sulfatide facilitates the exocytosis of insulin secretory granules, activates potassium channels and induces beta cell rest [18].

Thin layer chromatography revealed the antigen to be sulfatide [2, 10], and FACS sorting has indicated sulfatide attachment to the cell membrane [11]. Sulfatide is primarily produced by a recycling pathway in beta cells [4]. Desulphation takes place in lysosomes and is catalysed by arylsulphatase [12]; the GalCer formed is transported to the Golgi apparatus, where new sulphation by CST takes place [4]. Thus, like proinsulin, sulfatide is formed in the Golgi apparatus, and may even facilitate proinsulin folding [13]. Sulfatide also seems to be involved in the preservation of insulin crystals. In the absence of sulfatide these crystals are broken down after a couple of days, even under optimal in vitro conditions, whereas in its presence the crystals have a lifespan of up to 3 weeks [13]. Interestingly, insulin crystals are preserved by the C16:0 fatty acid isoform of sulfatide [14] which is found in the pancreas, but neither the long-chain isoform nor GalCer have this effect [13, 14]. Finally, there are strong indications that sulfatide facilitates the instant monomerisation of insulin, which takes place during the secretion of this hormone from the beta cells [13]. Thus, sulfatide seems to serve as a molecular chaperone for insulin—one of the first examples of a non-protein chaperone effect [15].

Beta cells secrete insulin in a chain reaction, each succeeding the next in terms of secretion and subsequent rest. Regulation of this succession is unknown but each individual beta cell presumably requires a period of rest before its next first-phase insulin response. Insulin stimulates its own secretion via positive feedback [16], whereas C-peptide inhibits insulin secretion [17]. Sulfatide inhibits insulin release from glucose-activated islets in vitro in a similar fashion, activating potassium channels which subsequently close calcium channels, thereby mediating beta cell rest [18]. Use of diazoxide, or other pharmacological compounds that activate ATP-sensitive potassium channels in a manner similar to sulfatide, has been considered for the treatment of pre-type 1 [19] and type 2 diabetes [20] patients.

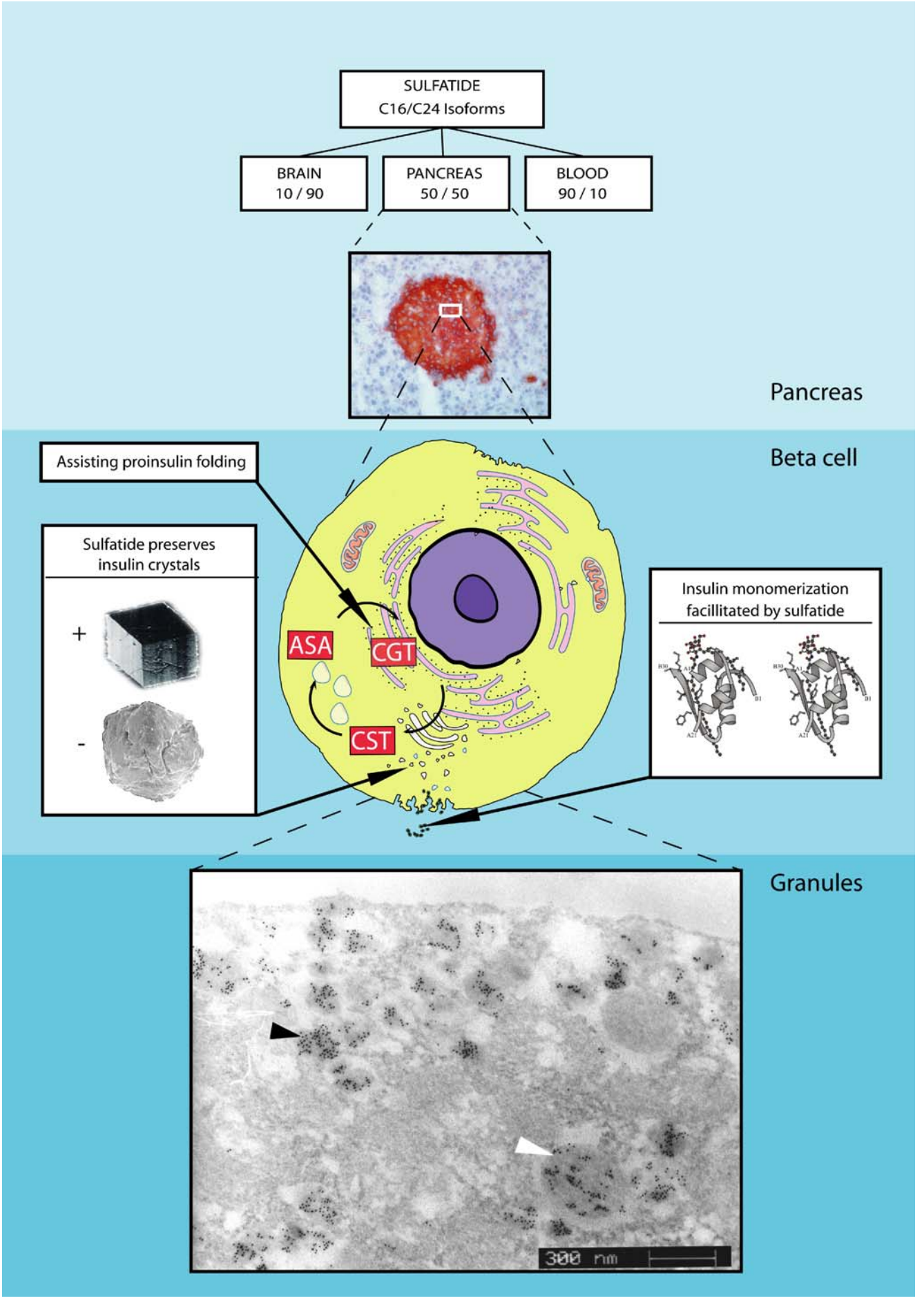
Sulfatide and type 1 diabetes

Sulfatide has been linked to type 1 diabetes (Text box: Sulfatide and type 1 diabetes).

Sulfatide and type 1 diabetes

1. Anti-sulfatide antibodies are present in type 1 diabetes [2].
2. Anti-sulfatide antibodies can be detected by ELISA [21].
3. Sulfatide inhibits the development of type 1 diabetes in NOD mice [23].
4. Sulfatide inhibits cytokine production [25, 26].
5. Sulfatide is a ligand for P- and L-selectin [28].
6. Sulfatide binds to CD1a, b, and c and stimulates the production of regulatory $CD3^{+}CD25^{+}$ T cells [34].
7. Sulfatide binds to CD1d [36].

Fig. 2 Interactions of sulfatide in beta cells. The upper panel shows ▶ the ratio of the predominant sulfatide isoforms (C16:0 and C24:0) in the brain, pancreas and serum. The presence of sulfatide in the islets is demonstrated by staining with the monoclonal anti-sulfatide antibody Sulph I. The majority of sulfatide in the beta cells is synthesised via a recycling process [4] that involves several enzymatic steps: CGT adds galactose to the ceramide moiety, giving rise to GalCer, which is then sulphated by CST to form sulfatide. Sulphation takes place in the trans-Golgi apparatus, and sulfatide follows insulin trafficking into the secretory granules, as shown in the electron micrograph of human islets (beta cells) (*lower panel*, indicated by the *black arrow*). Sulfatide is either secreted together with insulin or transported to lysosomal structures (*lower panel*, indicated by the *white arrow*). In the lysosomes, sulfatide is degraded to GalCer by arylsulphatase A (ASA) and recycled to the *cis*-Golgi apparatus to serve as a sulfatide precursor [4]. Sulfatide assists proinsulin folding in the Golgi compartment and preserves insulin crystals in the secretory granules, as shown by the scanning electron micrographs (*middle panel*, *left-hand insert*). The micrographs show insulin crystals maintained at pH conditions comparable to those of secretory granules in the presence (*top*) or absence (*bottom*) of sulfatide. A model of insulin-sulfatide interactions at the level of secretion (where crystals first disintegrate into insulin hexamers, and then into the biologically active insulin monomer) has been proposed (*middle panel*, *right-hand insert*) [13]


SULFATIDE
C16/C24 Isoforms
BRAIN
10 / 90
PANCREAS
50 / 50
BLOOD
90 / 10
Pancreas
Beta cell
Assisting proinsulin folding
Sulfatide preserves
insulin crystals
+
-
ASA
CGT
CST
Insulin monomerization
facillitated by sulfatide
Granules
300 nm

Anti-sulfatide antibodies, detected using a conventional ELISA [21] are frequently present at diagnosis [2] and before the onset of diabetes [21]. Although antibodies to GAD, insulin and insulinoma-associated antigen-2 are well-established screening tests for diabetes [22], anti-sulfatide antibodies may also have prognostic value, and further refinement of analytical methods to achieve high through put screening should enhance our understanding of their value in this respect. Anti-sulfatide antibodies are also found in neurological diseases such as Guillain–Barré syndrome [2], but those observed in patients with type 1 diabetes have a different specificity; seminolipid and SulphLacCer are labelled by anti-sulfatide antibodies from those with Guillain–Barré but not from those with diabetes (Fredman et al., unpublished observations). Furthermore, anti-sulfatide antibodies associated with type 1 diabetes inhibit insulin secretion and exocytosis from beta cells, whereas those from Guillain–Barré patients do not [18].

Treatment of non-obese diabetic (NOD) mice with sulfatide reduced the incidence of diabetes to 35%, as compared with 85% for the control animals [23]. Although many different treatments prevent diabetes in NOD mice, including numerous immunosuppressive agents, the few beta cell-related molecules that are effective in suppressing disease development [24] include GAD and insulin; sulfatide has a comparable effect of the same order of magnitude [23].

The T cell-dependent immune system is implicated in the development of type 1 diabetes, and it is therefore of interest that beta cells produce a peptide-based hormone, insulin, which is potentially immunogenic and an autoantigen in type 1 diabetes. Other endocrine cells that are not protected by the blood–brain barrier, as in the pituitary, produce hormones of low molecular weight that are not (or are only slightly) immunogenic. Beta cells require anti-inflammatory mechanisms for protection against accidental immune reactions; it may, therefore, be important that sulfatide has anti-inflammatory properties (Text box: Sulfatide and type 1 diabetes). T cell clones against beta cell epitopes and insulitis have been demonstrated in various animal models and in humans, and cytokines are involved in the maintenance of insulitis and may also cause direct beta cell damage. Sulfatide interferes with a number of these processes, as discussed below.

The role of sulfatide in cytokine production was investigated using unselected white blood cells from healthy donors. Sulfatide inhibits the production of IL-1, IL-6, IL-10 and TNF-α, whereas GalCer increases the secretion of IL-1, IL-6 and TNF-α [25, 26]. Similar changes were observed at the mRNA level [26]. In terms of isoforms, the C16:0 isoform of sulfatide was able to reduce the production of IL-1, IL-6, TNF-α and the chemokines MIP-1α and IL-8 by approximately 50%, whereas the C24:0 isoform was less effective at decreasing cytokine production [27].

Sulfatide has other anti-inflammatory properties. It binds to P- and L-selectin and, being a ligand of these molecules, it inhibits the adhesion of inflammatory blood cells and thereby impairs the migration of these cells from the blood [28]. This might be important with regard to the pathogenesis of type 1 diabetes, as blockade of L-selectin inhibits insulitis and prevents diabetes in NOD mice [29]. The selectin-mediated anti-inflammatory effect of sulfatide has been demonstrated in other inflammatory conditions, namely experimentally induced liver inflammation [30] and experimentally induced acute lung injuries [31].

Glycosphingolipid molecules cannot be presented by the MHC complex, which only binds peptides. However, given that some T cells recognise glycosphingolipids, these molecules must be presented somehow. It has now been established that presentation is achieved through the MHC-like CD1 molecules [32]. The CD1 molecule contains a groove with two large hydrophobic pockets that are able to anchor the lipid tails of a glycosphingolipid [33]. Human antigen-presenting cells, such as dendritic cells, can express five kinds of CD1 molecules. These are divided into two groups: group 1 includes CD1a, b, c and e, and group 2 comprises CD1d only. It has been demonstrated that CD1a, b and c are able to load sulfatide on the cell surface without proteasome processing, and prime T helper type 1 and T helper type 2 responses [34]. Sulfatide-stimulated T cells include $CD3^+$ $CD25^+$ cells, which have regulatory properties [34]. The crystal structure of the CD1a-sulfatide complex has been determined [35].

Treatment of mice with sulfatide prevents antigen-induced experimental autoimmune encephalomyelitis, an animal model of human multiple sclerosis [36]. The mechanism seemed to involve an increase in the number of regulatory T cells, many of which express NK1.1. Interestingly, sulfatide had no effect in CD1d-deficient mice, indicating that the protective effect of sulfatide involved binding to this CD1 variant [36].

Only a few other ligands of CD1d are known, one of which is the mammalian, non-antigenic (β-) GalCer [37]. The most investigated ligand is α-GalCer, which is isolated from marine sponges [38]. When presented by dendritic cells, α-GalCer stimulates natural killer T (NKT) cells. NKT cells are CD1d-restricted T cells, which in humans express Vα24Jα Q in their T cell receptor [39]; they are thought to play a regulatory role in autoimmune responses in vivo [40]. Both SJL and NOD mice, animal models of autoimmune diseases, have defects in NKT cell development and/or function [41, 42].

NKT cell numbers are reduced in humans with autoimmune diseases [43]. Studies using NK1.1 markers found decreased number of NKT cells in patients with type 1 diabetes [44]. Conversely, detection of NKT cells by tetramer CD1d/α-GalCer indicated no systemic reduction in cell numbers [45]. However, this does not exclude a relative deficiency of NKT cells within the relevant organ in situ, as α-GalCer-specific activation of NKT cells protects against diabetes in NOD mice [46, 47], providing strong evidence that CD1d-reactive NKT cells suppress autoreactive T cells. Similarly, overexpression of NKT cells protects Vα14Jα281 transgenic NOD mice against diabetes [48], whereas a shortage of NKT cells in CD1d knock-out mice leads to exacerbation of type 1 diabetes [49]. Finally, upregulation of CD1d expression within the beta cells restores the immunoregulatory function of NKT cells and prevents dia-

betes in NOD mice [50]. In the latter study the authors speculate as to the nature of the endogenous ligand that was loaded in the CD1d receptor. This might indeed have been sulfatide, which is present in the islet [4], can act as a ligand for CD1d [36], and inhibits (as with α-GalCer) diabetes development in the NOD mouse model [23].

Sulfatide and type 2 diabetes

Sulfatide might also be involved in type 2 diabetes (Text box: Sulfatide and type 2 diabetes).

Sulfatide and type 2 diabetes

1. Type 2 diabetes animal models lack C16:0 sulfatide [14].
2. Sulfatide mediates beta cell rest [18].
3. Sulfatide reduces the production of TNF-α [25].
4. Low serum concentrations of sulfatide and the presence of SulphLacCer are associated with insulin resistance and type 2 diabetes [51].
5. Treatment with sulfatide increases insulin secretion in Zucker fatty rats [54].

Insulin resistance is associated with low serum levels of sulfatide and/or the presence of another sulphated glycosphingolipid, SulphLacCer [51]. In this study, sera from 270 type 2 diabetic patients were analysed for sulfatide and SulphLacCer and compared with sera from a similar number of healthy controls, who were matched in terms of sex and age (mean age 65 years). For individuals in the lowest serum sulfatide tertile the odds ratio for type 2 diabetes was approximately 2.2 for both sexes, and for individuals with SulphLacCer in their serum (which is not usually present) the odds ratios were 1.7 and 7.6 for men and women, respectively [51]. These associations of type 2 diabetes with sulfatide and SulphLacCer were independent of each other and of other known classical diabetes risk factors.

Although the effect of sulfatide on insulin resistance [51] has not been explained, it could be partly mediated through inhibition of TNF-α [27], which is known to be present at elevated concentrations in type 2 diabetic patients and is associated with increased insulin resistance [52]. TNF-α is produced in fat cells and other tissues, and preliminary in vitro studies of human adipocytes have shown that sulfatide inhibits secretion of TNF-α and IL-6 by up to 40%, which is reflected by a corresponding decrease in levels of TNF-α mRNA.

At the beta cell level, sulfatide might suppress type 2 diabetes through activation of potassium channels, an effect mainly attributable to the C16:0 isoform of sulfatide [18]. The C16:0 isoform of sulfatide is present in substantial amounts in the pancreas of Lewis rats [4], BALB/c mice and humans [53], but *ob/ob* mice and *db/db* mice selectively lack this specific isoform of sulphatide [14]. In the Zucker rat, an animal model of type 2 diabetes, treatment with C16:0 sulfatide intraperitoneally twice a week almost doubled insulin secretion and improved the first-phase insulin response, as detected in a glucose tolerance test [54]. This is consistent with the effects of diazoxide and pharmacological potassium-channel openers, which improve insulin secretory responsiveness by mediating beta cell rest [20].

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