The Load-Bearing Lipid

Ceramide in the healthy brain and in Alzheimer's disease — function, dysfunction, and the four coordinates that decide whether a measurement of this lipid means anything at all

Sphingolipids · Sulfatide · Myelin · Sphingomyelinase · Ceramide synthase · Sphingosine-1-phosphate · Extracellular vesicles

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Ceramide is described in this disease almost entirely as a poison, and the inference drawn is that it should be lowered. But the brain is the most sphingolipid-dependent organ in the body, myelin is built out of this lipid, and the inherited human diseases of ceramide insufficiency are themselves neurodegenerative. The pathway has a floor as well as a ceiling — and the largest, earliest lipid change in Alzheimer's disease is a loss, not an excess.

Contents

Abstract

Ceramide is discussed in Alzheimer's disease almost exclusively as a poison. It rises in vulnerable brain tissue, in cerebrospinal fluid and in plasma; it is found within senile plaques; it drives oxidative injury, permeabilises mitochondria, and packages the vesicles that carry pathological tau from one neuron to the next. The therapeutic inference drawn from this literature is that ceramide should be lowered. This paper argues that the inference is correct in direction and dangerous in its unqualified form, because it rests on a description of ceramide that omits half of what the lipid does.

Ceramide is not an intruder in the nervous system. It is the obligatory metabolic hub through which every complex sphingolipid the brain builds must pass, and the brain is the most sphingolipid-dependent organ in the body. Galactosylceramide and its sulfated derivative sulfatide are structural constituents of myelin; the very-long-chain ceramides made by ceramide synthase 2 are required for the myelin sheath to hold; the C18 ceramide made by ceramide synthase 1 is the neuron's characteristic species; ceramide-dependent membrane budding generates the extracellular vesicles by which brain cells communicate; and ceramide-dependent signalling participates in autophagy, in synaptic vesicle release, and in the elimination of damaged mitochondria. The human genetics confirms the point in the most direct way available: inherited lesions that impair ceramide synthesis, desaturation, or degradation — in *SPTLC1*, *CERS1*, *DEGS1*, *ASAH1*, *SMPD1* — produce progressive myoclonic epilepsy, hypomyelinating leukodystrophy, motor neuron disease, and neurodegeneration with intellectual disability. Too little ceramide, or ceramide of the wrong species, is as neurodegenerative as too much.

The paper therefore reconstructs the Alzheimer literature on a two-sided foundation. Part I sets out ceramide's chemistry, its synthetic and degradative apparatus, its molecular effectors, and its established physiological offices in the nervous system, closing with the evidence from human deficiency states. Part II sets out the dysfunction: what changes in Alzheimer tissue, cerebrospinal fluid and plasma; which enzymes move and in which direction; and the mechanisms through which the change is thought to injure — membrane geometry and secretase activity, mitochondrial permeabilisation, lysosomal and autophagic failure, vesicular propagation of tau, glial activation, myelin loss, and insulin resistance. Part III assesses the evidence.

Two conclusions are advanced. The first is that most of the apparent contradiction in this literature dissolves once four coordinates are specified for every measurement: which ceramide species, in which subcellular compartment, in which cell type, and at which point in the disease. A bulk ceramide number collapses all four and can move in either direction for reasons that have nothing to do with the mechanism under test. The second is that the sphingolipid pathway has a floor as well as a ceiling. The most reproducible lipid abnormality in early Alzheimer's disease is not an excess but a loss — of sulfatide, of sphingosine-1-phosphate, of glycosphingolipid synthesis — and a therapy that suppresses ceramide production without regard to species or cell type is as

likely to deepen that loss as to correct the excess. The strength of every major claim is graded explicitly, one foundational and still widely cited paper is identified as withdrawn by its journal, and a set of conditions is stated under which the account offered here should be abandoned.

Keywords: ceramide; sphingolipids; sulfatide; sphingomyelinase; ceramide synthase; sphingosine-1-phosphate; myelin; extracellular vesicles; lipid rafts; Alzheimer's disease.

Part I — The Lipid the Brain Is Built From

1. Introduction: A Lipid With No Off Position

A pharmacologist approaching a disease mechanism usually begins by asking what the target does when things are going well. For most Alzheimer targets this question has an answer, however partial. The amyloid precursor protein has physiological functions; tau stabilises microtubules; the secretases have substrates other than the one that made them famous. For ceramide the question is rarely asked at all. Three decades of literature describe what ceramide does to a sick neuron, and the description is consistent and alarming: it accumulates, it oxidises membranes, it opens the mitochondrion, it kills. The physiological entry — what ceramide is for — is usually compressed into a single sentence about it being "a bioactive sphingolipid" before the argument moves on to the pathology.

This omission is not merely a stylistic defect. It produces a specific and consequential error of reasoning, which is to treat ceramide as though it had an off position. Almost every therapeutic proposal in this field is a proposal to lower ceramide, or to inhibit one of the enzymes that make it, and the implicit model behind such a proposal is that of a toxin: something the healthy brain does without, which appears in disease, and whose removal returns the system to baseline. Ceramide is not that kind of molecule. It is the central intermediate of sphingolipid metabolism, the compound through which the cell must pass to build sphingomyelin, to build glucosylceramide and the gangliosides, to build galactosylceramide and sulfatide, and through which it must pass again to dismantle any of them (Merrill, 2011; Hannun & Obeid, 2018). A cell with no ceramide is a cell with no sphingolipids, and in the central nervous system that is not a viable state. It is not even a survivable one: the inherited human diseases of ceramide *insufficiency* are neurodegenerative, and they are catalogued in Section 6.

The nervous system makes this general point with unusual force, because the brain is the most sphingolipid-dependent organ in the body. Myelin, which occupies a large fraction of the brain's dry mass, is a lipid-dominated structure whose defining constituents include galactosylceramide and its sulfated derivative sulfatide — both of them ceramide with a head group attached (Chrast et al., 2011). The oligodendrocyte that wraps an axon eighty times is, in metabolic terms, largely a sphingolipid factory. A therapeutic strategy that lowers ceramide indiscriminately is a strategy aimed at the supply line of the brain's largest structural investment.

There is, besides, a plain empirical difficulty with the toxin model. The single largest lipid change reported in early Alzheimer's disease is not an accumulation but a depletion. In brain tissue

from subjects at the earliest clinically recognisable stage of the disease, sulfatide was reduced by as much as ninety-three per cent in grey matter and fifty-eight per cent in white matter, while other major lipid classes were essentially unchanged (Han et al., 2002). Transcriptional profiling across seventeen brain regions found the enzymes of de novo ceramide synthesis upregulated and the enzymes of glycosphingolipid synthesis downregulated as early as mild dementia (Katsel et al., 2007). Sphingosine-1-phosphate, the pro-survival lipid made downstream of ceramide, falls with advancing neurofibrillary stage (Couttas et al., 2014). The early Alzheimer brain is not simply a brain with more ceramide in it. It is a brain in which the traffic through the ceramide hub has been redirected: more entering by synthesis, less leaving toward the complex sphingolipids the tissue is structurally built from, less leaving toward the survival signal. Ceramide rises as a *consequence of a re-routing*, and the re-routing, not the level, is the phenomenon that requires explanation.

This paper is written to supply the missing half of the description and then to re-read the pathology in its light. Part I is a physiology: the chemistry of the molecule and what it does to a membrane (Section 2); the enzymatic apparatus that makes, moves, and disposes of it (Section 3); the small set of proteins it actually binds and regulates (Section 4); its established offices in the nervous system, from myelin to the synapse (Section 5); and the evidence from human and mouse deficiency states, which fixes a floor beneath any therapeutic strategy (Section 6). Part II is the pathology: what changes in the Alzheimer brain, cerebrospinal fluid and blood (Section 7); which enzymes move (Section 8); the mechanisms by which the change is proposed to injure (Section 9); the interaction with *APOE* and the conspicuous absence of ceramide enzymes from genome-wide association results (Section 10); and the question of when in the disease the change occurs (Section 11). Part III weighs the evidence: the four coordinates that determine whether a ceramide measurement means anything (Section 12); a graded assessment of each major claim (Section 13); the conditions under which this account should be abandoned (Section 14); the therapeutic consequences, including the floor (Section 15); the limitations of the synthesis (Section 16); and a conclusion.

A note on what this paper is and is not. It advances no primary data. It is a critical synthesis of the published record, and where a claim rests on a single study, or on cell culture, or on a mouse, that is stated rather than smoothed over. Two specific obligations of accuracy are discharged in the text rather than in footnotes. The first is that a foundational and still heavily cited experiment in this field — the report that ceramide stabilises the β-secretase BACE1 — was withdrawn by the journal that published it, and no part of the argument here depends upon it (Section 9.1). The second is that where two competent groups have reported opposite results, both are given, and the disagreement is left standing rather than resolved by selection.

2. The Molecule and the Membrane

2.1 A Small Head and a Waxy Tail

Ceramide is chemically simple. A sphingoid base — most commonly sphingosine, an eighteen-carbon amino alcohol carrying a *trans* double bond between carbons four and five — bears a fatty acid attached through an amide bond at the second carbon. That amide is the defining feature; the family name comes from *cera*, wax, and the description is apt, because ceramide is intensely hydrophobic and has essentially no polar head group at all, only two hydroxyls and the amide nitrogen (Merrill, 2011).

Two consequences follow, and between them they account for most of ceramide's biology.

The first is that ceramide is an exceptionally poor solvent for itself in a phospholipid bilayer. Membrane phospholipids carry bulky charged head groups that hold them apart; ceramide has almost nothing to hold it apart from its neighbours, and its amide and hydroxyl groups form an unusually strong intermolecular hydrogen-bonding network. It therefore self-associates. At concentrations of a few mole per cent, ceramide segregates laterally into rigid, tightly packed, gel-like domains within an otherwise fluid membrane, and it does so with a strong preference for the ordered, sphingomyelin- and cholesterol-rich regions from which it is usually generated (Goñi & Alonso, 2009). Ceramide does not dissolve into a membrane; it restructures it.

The second consequence is geometric. A lipid with a large head group and narrow tails is cone-shaped and favours positive membrane curvature; ceramide, with a negligible head group and two long saturated or monounsaturated chains, is an inverted cone and favours *negative* curvature — the curvature of a membrane bending away from the cytosol, which is precisely the geometry required for a vesicle to bud inwards into the lumen of an endosome. This is not an abstract point; it is the accepted physical explanation for ceramide's role in generating the intraluminal vesicles that become exosomes (Trajkovic et al., 2008), discussed in Section 5.4.

2.2 What Ceramide Does to a Bilayer

Three membrane-level effects recur throughout the disease literature and are worth stating explicitly, because they are the level at which most of ceramide's downstream actions are actually produced.

It orders and rigidifies. Ceramide-rich domains are thicker, stiffer, and more tightly packed than the surrounding bilayer. Proteins whose function depends on membrane thickness or on lateral

mobility are affected by ceramide's appearance in their neighbourhood without any direct binding event taking place (Goñi & Alonso, 2009).

It displaces cholesterol. Ceramide and cholesterol compete for association with sphingomyelin. When a sphingomyelinase converts sphingomyelin to ceramide within an ordered domain, cholesterol is expelled from that domain, and the local sterol composition changes at the same moment as the sphingolipid composition. Any argument about ceramide's effect on a raft-resident protein is therefore simultaneously an argument about cholesterol, and the two cannot be cleanly separated in most experiments.

It coalesces small domains into large platforms. The best-characterised consequence of sphingomyelinase activation at a membrane is the fusion of small, ordered microdomains into a much larger *ceramide-enriched platform*, which traps and concentrates whatever receptors and signalling proteins were resident in the domains that merged (Gulbins & Kolesnick, 2003; Bollinger et al., 2005). The functional effect is amplification: a signal too weak to fire from scattered receptors becomes decisive once those receptors are clustered. Platform formation is the mechanism by which death receptors are clustered and committed, and it is the mechanism most often invoked to explain how a change in a membrane lipid can produce a large change in a protein-mediated outcome.

2.3 The Raft Caveat, Stated Once

A great deal of the mechanistic reasoning in Sections 5 and 9 runs through membrane microdomains, and the reader is entitled to know at the outset how solid that construct is. Much of the early evidence for rafts came from detergent-resistant membrane fractions, and it was reasonably objected that a fraction defined by cold non-ionic detergent need not correspond to any structure present in a living membrane. The modern position, supported by super-resolution and single-molecule methods, is that nanoscale, dynamic, cholesterol- and sphingolipid-dependent assemblies do exist, but that they are smaller, more transient, and more heterogeneous than the original picture implied (Sezgin et al., 2017).

Two qualifications follow. First, "raft" should be read throughout this paper as shorthand for a real but fluid nanoscale ordering, not for a purifiable platform. Second, the induced ceramide-enriched platform stands on firmer ground than the resting raft, because it is large, signal-triggered, and directly imageable. Where an argument depends specifically on the resting raft — as the secretase-geometry argument of Section 9.1 does — that dependence is carried forward into the evidence assessment of Section 13 rather than quietly assumed.

2.4 "Ceramide" Is a Family, Not a Molecule

The most consequential fact about ceramide, and the one most often lost in translation between laboratories, is that the fatty acid attached to the sphingoid base varies in length from roughly fourteen to twenty-six carbons, and that these species are made by different enzymes, occupy different membranes, and do different things.

The convention adopted here follows the standard notation: d18:1/16:0 denotes a ceramide with a dihydroxy eighteen-carbon sphingoid base bearing one double bond, N-acylated with palmitate; it is abbreviated C16 ceramide. The brain's characteristic neuronal species is C18; the myelin-associated species are the very-long-chain C22 to C24 ceramides; C16 predominates in many peripheral tissues and in glia. Six mammalian ceramide synthases (CerS1–CerS6) generate these species with characteristic and largely non-overlapping acyl-chain preferences, and their tissue distribution is what gives an organ its sphingolipid signature (Merrill, 2011; Hannun & Obeid, 2018).

The practical corollary is severe and applies to every study cited in Part II. A measurement of "total ceramide" sums over species that are made by different enzymes in different cells for different purposes, and that may move in opposite directions within the same tissue. It is a number whose components can cancel. Section 12 develops this into a general principle for reading the literature; here it is enough to record that the chemistry itself forbids treating ceramide as a single analyte.

3. The Apparatus: Three Roads, Six Synthases, Four Exits

Ceramide sits at a metabolic crossroads, and the traffic through that crossroads — not the size of the pool sitting in it — is what the cell actually regulates. This section sets out the routes in.

3.1 The De Novo Road

The de novo pathway builds ceramide from primary metabolites on the cytosolic face of the endoplasmic reticulum. Serine palmitoyltransferase (SPT), a multi-subunit enzyme encoded principally by *SPTLC1*, *SPTLC2* and *SPTLC3* with regulatory ORMDL subunits, condenses L-serine with palmitoyl-coenzyme A to give 3-ketodihydrosphingosine. This is reduced to dihydrosphingosine, N-acylated by one of the six ceramide synthases to dihydroceramide, and finally desaturated by dihydroceramide desaturase (DEGS1) to yield ceramide (Merrill, 2011).

Three features of this road matter downstream. It is the *rate-limiting* entry point for the whole sphingolipid economy, and SPT is accordingly under tight homeostatic control by the ORMDL proteins, which sense sphingolipid abundance and restrain the enzyme. It is *slow* relative to the alternatives, and is engaged by sustained nutrient or metabolic stress rather than by acute signalling. And its final step, the DEGS1 desaturation, is not a formality: dihydroceramide lacks the 4,5-*trans* double bond, and the difference is functional rather than cosmetic — dihydroceramide does not form the mitochondrial channels that ceramide forms (Siskind et al., 2002), and inherited DEGS1 failure causes human leukodystrophy (Section 6).

3.2 The Sphingomyelinase Road

The second road does not build ceramide but liberates it. Sphingomyelin, one of the most abundant lipids of the plasma membrane's outer leaflet, is hydrolysed to ceramide and phosphocholine by a sphingomyelinase. Because the substrate is already present and already positioned in the membrane, this route can raise local ceramide within seconds to minutes of a stimulus. It is a signalling route, not a housekeeping one.

Two enzymes dominate the nervous system. Acid sphingomyelinase (ASM, encoded by *SMPD1*) acts in the lysosome and, in a secreted zinc-dependent form, at the outer leaflet of the plasma membrane; it is the enzyme mutated in Niemann–Pick disease types A and B, and it is central to the death-receptor platform mechanism of Section 2.2. Neutral sphingomyelinase 2 (nSMase2, encoded by *SMPD3*) is a magnesium-dependent enzyme resident at the plasma membrane and the Golgi, highly expressed in brain, and required for the ceramide-dependent

vesicle budding described in Section 5.4. A third enzyme, alkaline sphingomyelinase, is essentially confined to the intestinal tract and is not further considered.

3.3 The Salvage Road

The third road recycles. Complex sphingolipids delivered to the late endosome and lysosome are catabolised stepwise to ceramide and then, by acid ceramidase (*ASAH1*), to sphingosine, which can be re-acylated by the ceramide synthases to regenerate ceramide. A substantial fraction of cellular ceramide is produced this way. Because salvage passes through the same six synthases as the de novo road, it too is subject to the chain-length code, and because it depends on lysosomal function, it is the road most directly compromised by the lysosomal failure that characterises Alzheimer neurons (Section 9.3).

3.4 The Chain-Length Code

Which ceramide a cell makes is determined by which ceramide synthase is doing the acylation. CerS1 generates principally C18 ceramide and is enriched in neurons; CerS2 generates the very-long-chain C22–C24 species and is the dominant synthase of oligodendrocytes and of myelin; CerS5 and CerS6 generate C16; CerS3 and CerS4 have their principal roles in skin and other peripheral tissues (Merrill, 2011; Hannun & Obeid, 2018).

The consequence for the nervous system is that different cell types depend on different synthases for different structural products, and that a global manipulation of "ceramide synthesis" is in fact a differential manipulation of several distinct cellular programmes. The mouse genetics in Section 6 shows how sharply these programmes dissociate: deleting CerS2 damages myelin, while deleting CerS1 kills Purkinje cells, and the two phenotypes are not interchangeable.

3.5 The Four Exits

Ceramide leaves the hub by four routes, and which exit is open determines whether a rise in synthesis becomes a rise in the ceramide pool at all.

- **To sphingomyelin.** Sphingomyelin synthases (SGMS1/SGMS2) transfer phosphocholine from phosphatidylcholine onto ceramide, mostly in the Golgi. This exit converts a signalling lipid into a bulk structural one, and it is reversible through the sphingomyelinases — the pair constitutes the fastest available buffer on local ceramide concentration.
- **To glycosphingolipids.** Glucosylceramide synthase (UGCG) adds glucose, opening the route to lactosylceramide and the gangliosides; galactosylceramide synthase (UGT8/CGT) adds galactose, opening the route to galactosylceramide and — via cerebroside sulfotransferase (CST/GAL3ST1) — to sulfatide. In the brain this second branch is not a minor one: it is the route by which myelin is built (Chrast et al., 2011).

- **To sphingosine and sphingosine-1-phosphate.** Ceramidases hydrolyse the amide bond to release sphingosine, which sphingosine kinases 1 and 2 phosphorylate to sphingosine-1-phosphate (S1P). S1P acts through a family of five G-protein-coupled receptors and is broadly pro-survival, pro-migratory and pro-angiogenic, in contrast to ceramide and sphingosine, which are broadly pro-apoptotic and growth-arresting. The relative disposition of the cell between these poles is the long-standing "sphingolipid rheostat" concept (Hannun & Obeid, 2008), and it is directly relevant to Alzheimer's disease because S1P falls with advancing pathology (Section 7.1).
- **To ceramide-1-phosphate.** Ceramide kinase phosphorylates ceramide to ceramide-1-phosphate, a distinct signalling lipid with pro-inflammatory and pro-survival actions. This exit is the least studied of the four in the nervous system and is not load-bearing in what follows.

3.6 Topology: Where Matters More Than How Much

Ceramide is highly insoluble and does not diffuse freely through the cytosol. Its distribution between organelles is therefore controlled by dedicated machinery, of which the best characterised is CERT, the cytosolic protein that extracts ceramide from the endoplasmic reticulum and delivers it to the Golgi for conversion to sphingomyelin (Hanada et al., 2003). Transfer to the glycosphingolipid branch proceeds by a different, largely vesicular route. The existence of dedicated, saturable, separately regulated transport for different downstream fates means that the cell treats "ceramide in the ER" and "ceramide at the Golgi" as different quantities — as, functionally, they are.

That specificity extends to protein recognition. A transmembrane domain has been shown to discriminate a *single* sphingolipid species — a particular sphingomyelin — with the selectivity ordinarily associated with a soluble ligand-binding site (Contreras et al., 2012). Membrane lipids are not an undifferentiated solvent in which proteins float; individual species are recognised individually.

The principle that follows is the organising one of this paper's second half. A molecule of ceramide generated slowly in the bulk endoplasmic reticulum, destined for glycosylation and export into a myelin sheath, is a structural precursor. A molecule generated in seconds by nSMase2 at the plasma membrane inside a coalescing platform, or by a ceramide synthase resident at a mitochondrial contact site (Bionda et al., 2004), is a signal. They are the same compound and they are not the same event. A lipidomic measurement on a tissue homogenate cannot distinguish them.

4. What Ceramide Talks To

If ceramide were only a structural lipid, changes in its abundance would matter only through membrane biophysics. It is also a signal, and the specific proteins it acts upon are worth naming, because the list contains at least one entry that complicates the standard Alzheimer narrative.

Protein phosphatase 2A. Ceramide directly activates heterotrimeric protein phosphatase 2A (Dobrowsky et al., 1993), the founding member of the "ceramide-activated protein phosphatase" class. This is a well-replicated biochemical result and it is the most direct enzymatic effector of ceramide known. It is also, from an Alzheimer standpoint, awkward. Protein phosphatase 2A is the principal phosphatase acting on tau; its activity is reduced in the Alzheimer brain, and that reduction is one of the standard explanations for tau hyperphosphorylation. A lipid that activates PP2A should, all else equal, *decrease* tau phosphorylation. The naive inference "more ceramide, therefore more phospho-tau" thus has a sign problem at the level of ceramide's best-characterised effector, and any account that asserts a direct ceramide-to-tau-phosphorylation arrow owes the reader an explanation of why the PP2A arm does not dominate. Section 9.4 argues that the credible ceramide–tau link is not phosphorylation but *propagation*, which is a distinct claim resting on distinct evidence.

Cathepsin D. Ceramide generated by acid sphingomyelinase binds and activates the lysosomal aspartate protease cathepsin D, driving its autocatalytic maturation (Heinrich et al., 1999). This places a ceramide effector inside the lysosome, the compartment whose failure is among the earliest cell-biological abnormalities in Alzheimer neurons.

The autophagy machinery. Ceramide participates in autophagosome formation and, more specifically, in the selective targeting of autophagosomes to mitochondria, producing lethal mitophagy (Sentelle et al., 2012). This is a genuine physiological function — the controlled elimination of damaged mitochondria — that becomes pathological only when it runs beyond the cell's capacity to replace what it removes.

The mitochondrial outer membrane itself. At sufficient local concentration, ceramide self-assembles into large, stable, barrel-like channels that raise the permeability of the mitochondrial outer membrane to proteins of the size of cytochrome *c*. The effect is specific to ceramide and is not produced by dihydroceramide, and the channels are regulated by the Bcl-2 family: anti-apoptotic members disassemble them, and activated Bax acts synergistically with ceramide at concentrations at which neither alone is sufficient (Siskind et al., 2002; Ganesan et al., 2010; Colombini, 2017). Here ceramide is not a ligand for a protein but a structural element in its own right — a lipid that becomes a pore.

The heterogeneity of this list is itself informative. Ceramide acts through a phosphatase, through a protease, through the autophagy machinery, and through direct self-assembly into a channel. It is not a hormone with a receptor. It is closer to a state variable of the membrane, read out by several unrelated systems, which is why its effects are so strongly determined by where it appears rather than by how much of it there is.

5. The Offices of Ceramide in the Nervous System

5.1 The Myelin Organ

The single largest physiological commitment of sphingolipid in the body is myelin. The myelin sheath is lipid-dominated, and its characteristic constituents are galactosylceramide and sulfatide — ceramide with galactose, and ceramide with sulfated galactose (Chrast et al., 2011). An oligodendrocyte producing myelin is running the ceramide hub at high throughput and directing nearly all of the output into the glycosphingolipid exit.

The genetic evidence that this matters is unambiguous. Mice lacking UDP-galactose:ceramide galactosyltransferase, and therefore unable to make galactosylceramide or sulfatide, still assemble myelin, but the myelin is functionally abnormal and regionally unstable, with disrupted conduction and progressive degeneration (Coetzee et al., 1996); the nodes of Ranvier do not form properly (Dupree et al., 1998). Mice lacking only cerebroside sulfotransferase — which make galactosylceramide but no sulfatide — have defective paranodal junctions (Honke et al., 2002), and sulfatide proves to be required not for the initial assembly of myelin but for its *maintenance*, with progressive deterioration of the sheath and of axonal structure in the adult (Marcus et al., 2006). The distinction between assembly and maintenance is important for Part II: it means that adult sulfatide loss is expected to produce a slowly progressive white-matter phenotype rather than a developmental one.

The chain-length dimension appears here too. Mice lacking ceramide synthase 2, and therefore unable to make very-long-chain ceramides, develop myelin sheath defects, cerebellar degeneration, and hepatocarcinomas in adulthood (Imgrund et al., 2009). The myelin sheath does not merely need ceramide; it needs ceramide of the right acyl-chain length, made by the right synthase.

5.2 The Neuron's Own Species

Neurons rely characteristically on C18 ceramide, generated by CerS1. Ablation of neuronal CerS1 in mice reduces ganglioside levels and, notably, reduces expression of myelin-associated glycoprotein in oligodendrocytes — a neuron-to-glia consequence of a neuronal lipid lesion (Ginkel et al., 2012). A spontaneous mouse mutation that impairs ceramide biosynthesis produces cerebellar Purkinje cell neurodegeneration with lipofuscin accumulation (Zhao et al., 2011). Reduced synthesis of the neuron's own ceramide species is thus neurodegenerative in the mouse, and Section 6 shows that it is neurodegenerative in humans as well.

5.3 The Synapse

Sphingolipids participate directly in neurotransmitter release. Sphingosine — ceramide's immediate degradation product — facilitates SNARE complex assembly and activates synaptic vesicle exocytosis, an effect demonstrated across preparations from neuromuscular junction to central synapse (Darios et al., 2009). In *Drosophila*, mutation of ceramidase disrupts synaptic vesicle exocytosis and trafficking, establishing that the enzymes controlling flux between ceramide and sphingosine are required for normal transmission (Rohrbough et al., 2004).

The behavioural consequence of perturbing this system in the mammalian brain is measurable and, for the therapeutic argument of Section 15, sobering: pharmacological inhibition of nSMase2 in mice perturbs brain sphingolipid balance and impairs spatial memory (Tabatadze et al., 2010). The enzyme most frequently proposed as an Alzheimer drug target is an enzyme whose inhibition, in a normal mouse, degrades performance on a hippocampus-dependent task.

Ceramide also participates in the acute regulation of synaptic strength under inflammatory conditions: interleukin-1β suppresses chemically induced long-term potentiation and the surface expression of the AMPA receptor subunit GluA1 through a ceramide-mediated activation of Src (Tong et al., 2018). This is a physiological signalling pathway — the mechanism by which an immune signal is translated into a change in synaptic efficacy — that becomes a liability when inflammation is chronic.

5.4 Vesicle Biogenesis and Intercellular Traffic

Ceramide's inverted-cone geometry is used by the cell to make vesicles. The inward budding of intraluminal vesicles into multivesicular endosomes — the process that generates exosomes — depends on ceramide generated *in situ* by neutral sphingomyelinase; blocking the enzyme reduces exosome release, and ceramide itself triggers the budding (Trajkovic et al., 2008). This is normal cell biology, and in the brain it is the substrate of a large intercellular communication system by which neurons, astrocytes, microglia and oligodendrocytes exchange proteins and RNA.

It is worth being explicit that this machinery is not pathological in origin. Extracellular vesicle release is a constitutive function of every brain cell type. What Part II will describe is the *misuse* of an existing conduit by a propagating protein — not the appearance of a new one.

5.5 Quality Control, Senescence, and Development

Ceramide's role in programmed cell death is a physiological office, not only a pathological one. Developmental sculpting of the nervous system requires large-scale apoptosis, and ceramide signalling participates in the differentiation and selection of neural precursors (Bieberich, 2011). Ceramide induces the senescence programme in primary human cells (Venable et al., 1995), and it directs autophagosomes to mitochondria for selective elimination (Sentelle et al., 2012). Each of these is a function the tissue requires; each becomes an injury when it is engaged in a post-mitotic cell that cannot replace what is destroyed.

The acid sphingomyelinase arm has a further physiological role with direct clinical relevance: the ASM/ceramide system mediates the action of several antidepressant drugs, which are functional inhibitors of the enzyme, and its inhibition increases neuronal proliferation and survival in the adult hippocampus (Gulbins et al., 2013). A widely prescribed class of drugs is, incidentally, a class of acid sphingomyelinase inhibitors — a fact returned to in Section 15.

6. The Argument From Deficiency

The strongest available evidence that ceramide is load-bearing rather than merely toxic comes from the human genetics of sphingolipid deficiency. If ceramide were a poison whose removal returns a system to baseline, then inherited lesions that reduce its synthesis, alter its species, or block its degradation ought to be neutral or protective. They are not. Nearly every such lesion that reaches clinical attention presents as neurological disease.

Table 1 — Inherited human disorders of the ceramide pathway.

Gene	Enzyme	Direction of lesion	Human phenotype
SPTLC1	Serine palmitoyltransferase, subunit 1	Altered substrate specificity; neurotoxic deoxysphingolipids	Hereditary sensory and autonomic neuropathy type 1 (Dawkins et al., 2001; Penno et al., 2010)
SPTLC1	Serine palmitoyltransferase, subunit 1	Loss of ORMDL-mediated restraint; unrestrained synthesis	Childhood-onset amyotrophic lateral sclerosis (Mohassel et al., 2021)
CERS1	Ceramide synthase 1 (C18 ceramide)	Impaired synthesis	Progressive myoclonic epilepsy with cognitive decline (Vanni et al., 2014)
DEGS1	Dihydroceramide desaturase	Impaired desaturation; dihydroceramide accumulation	Hypomyelinating leukodystrophy (Karsai et al., 2019; Pant et al., 2019)
ASAH1	Acid ceramidase	Impaired degradation; ceramide accumulation	Farber disease; spinal muscular atrophy with progressive myoclonic epilepsy (Zhou et al., 2012)
SMPD1	Acid sphingomyelinase	Impaired sphingomyelin hydrolysis	Acid sphingomyelinase deficiency (Niemann–Pick A/B), with neurodegeneration in the infantile neurovisceral form (Geberhiwot et al., 2023)

Read as a set, the table makes three points that the standard Alzheimer narrative does not accommodate.

Both directions are pathogenic. *ASAH1* deficiency causes ceramide to accumulate and is neurodegenerative; *CERS1* deficiency causes a specific ceramide species to fall and is also

neurodegenerative. The pathway is bounded above and below. There is no monotonic axis on which lower is safer.

Species matters more than total. The *CERS1* phenotype — progressive myoclonic epilepsy with intellectual disability — arises from failure to make one species, C18, in a tissue that has five other synthases available (Vanni et al., 2014). The remaining ceramide does not substitute. Likewise the *DEGS1* phenotype is produced not by a shortage of sphingolipid but by accumulation of the *wrong* one, dihydroceramide, which is chemically one double bond away from ceramide and functionally quite different (Karsai et al., 2019; Pant et al., 2019).

Dysregulation, not level, is the lesion. The two *SPTLC1* phenotypes are the clearest demonstration. In hereditary sensory and autonomic neuropathy, mutations shift the enzyme's substrate preference so that it condenses alanine or glycine instead of serine, generating 1-deoxysphingolipids that cannot be converted to complex sphingolipids and are neurotoxic (Penno et al., 2010). In childhood-onset amyotrophic lateral sclerosis, a different class of *SPTLC1* variant escapes ORMDL-mediated feedback restraint, so that sphingolipid synthesis runs unchecked (Mohassel et al., 2021). One gene, two diseases, both caused by the loss of *control* over the pathway rather than by its absolute setting.

The mouse genetics reinforces the same conclusion from the other end. Deleting CerS2 damages myelin and the cerebellum (Imgrund et al., 2009); deleting neuronal CerS1 disturbs gangliosides and myelin protein expression (Ginkel et al., 2012); impairing ceramide biosynthesis kills Purkinje cells (Zhao et al., 2011); deleting nSMase2 in mice disrupts the Golgi secretory pathway and produces dwarfism and skeletal disease (Stoffel et al., 2005; Stoffel et al., 2016; Khavandgar et al., 2011); deleting the glycosphingolipid branch destabilises myelin and the node of Ranvier (Coetzee et al., 1996; Dupree et al., 1998; Honke et al., 2002; Marcus et al., 2006).

This is the floor referred to in the abstract. It is not a rhetorical caution; it is a set of specific, replicated, dose-dependent phenotypes produced by lowering ceramide synthesis, by altering ceramide species, and by inhibiting the very enzymes most frequently nominated as Alzheimer drug targets. Section 15 returns to what this implies for therapeutic design. Part II now turns to what actually changes in the Alzheimer brain.

Part II — The Dysfunction

7. What Changes in the Alzheimer Brain

7.1 Tissue

The observation that the Alzheimer brain accumulates ceramide is among the better-replicated findings in the lipid biology of the disease, and it long predates the current interest in lipids as drivers rather than markers.

Cutler and colleagues, examining normal brain ageing and Alzheimer tissue together, reported accumulation of long-chain ceramides and cholesterol in association with membrane-associated oxidative stress, and showed that exposing hippocampal neurons to amyloid-β reproduced both the oxidative stress and the lipid accumulation — an effect prevented by α-tocopherol or by inhibition of sphingomyelin synthesis (Cutler et al., 2004). A survey of six ceramide species across brains with Alzheimer's disease, other neuropathological disorders, or both found C16, C18, C20 and C24 all elevated, with the highest levels in brains carrying more than one neuropathology (Filippov et al., 2012). Ceramide has been detected immunohistochemically in senile plaques themselves, together with the sphingomyelinases that generate it (Panchal et al., 2014), and astroglial ceramide immunoreactivity is increased in Alzheimer tissue (Satoi et al., 2005). Comprehensive lipidomic surveys of the disease have repeatedly recovered a disturbance of sphingolipid metabolism as one of its more prominent metabolic features, and the observation is old enough and stable enough to have generated its own review literature (He et al., 2010; Haughey et al., 2010; Czubowicz et al., 2019).

Two details of the Filippov result deserve emphasis because they cut against a simple reading. First, the *ratios* between the tested ceramide species were not altered — all species rose together — which is not what a lesion confined to one synthase would produce. Second, the variance among affected brains was larger than among controls, which the authors interpreted as loss of a normally tight regulatory control (Filippov et al., 2012). The Alzheimer brain, on this reading, is not a brain that has moved to a new set point so much as a brain that has lost the ability to hold one.

The opposite arm of the pathway moves in the opposite direction. Sphingosine-1-phosphate declines with advancing neurofibrillary stage, and does so most in the regions most heavily affected: the S1P-to-sphingosine ratio was reduced by sixty-six per cent in hippocampus and sixty-four per cent in inferior temporal cortex at Braak stage III/IV compared with controls, with parallel declines in the activity of both sphingosine kinases (Couttas et al., 2014). A separate analysis of the human hippocampus across the adult lifespan found age-dependent changes in sphingolipid balance that are sex-specific and, the authors argue, may sensitise the tissue to later neurodegeneration (Couttas et al., 2018). The rheostat of Section 3.5 is displaced toward ceramide not only by a rise on one side

but by a fall on the other.

7.2 The Sulfatide Collapse

The largest single lipid change reported in early Alzheimer's disease is not an increase in ceramide. It is a loss of sulfatide, and it deserves separate treatment because it is quantitatively dominant, mechanistically informative, and routinely omitted from summaries of "the ceramide story."

Analysing brain lipid extracts by electrospray ionisation mass spectrometry across twenty-two subjects spanning no dementia to very severe dementia, Han and colleagues found sulfatide depleted by up to ninety-three per cent in grey matter and up to fifty-eight per cent in white matter in subjects at the stage of *very mild* dementia — while all other major lipid classes except plasmalogen were unchanged relative to age-matched controls. In the same subjects, ceramide content in white matter was elevated more than threefold, and it peaked at the very mild stage. Crucially, galactocerebroside sulfotransferase activity was not deficient, indicating that the loss was not a failure of synthesis (Han et al., 2002).

Read carefully, this is a remarkable result. The depletion is enormous, it is selective for one lipid class, it is present at the earliest clinically recognisable stage, it is not explained by reduced synthesis — and the ceramide elevation that accompanies it is in white matter and is of the magnitude expected if sulfatide were being degraded back through the hub. The most parsimonious interpretation is that the early lipid lesion of Alzheimer's disease involves accelerated catabolism or mistrafficking of a myelin sphingolipid, with ceramide rising as the degradation product.

The trafficking arm has an identified mediator. Apolipoprotein E modulates brain sulfatide content (Han et al., 2003), and ApoE mediates sulfatide depletion in animal models of the disease (Cheng et al., 2010); ApoE4 disrupts sterol and sphingolipid metabolism in Alzheimer brain but not in normal brain (Bandaru et al., 2009). The strongest genetic risk factor for the disease is thus mechanistically coupled to the largest lipid change in it.

The decisive experiment is a sufficiency test. Inducing myelin sulfatide deficiency in adult mice — by tamoxifen-inducible, myelinating-glia-specific deletion of cerebroside sulfotransferase — was sufficient to activate disease-associated microglia and astrocytes, to raise expression of Alzheimer risk genes including *Apoe*, *Trem2* and *Cd33* and of established causal regulators of the late-onset Alzheimer immune network, and to produce chronic neuroinflammation and mild cognitive impairment, more pronounced in females; the effect proceeded independently of ApoE, and astrogliosis was not secondary to microgliosis (Qiu et al., 2021). Sulfatide loss alone, in an otherwise normal adult brain, reproduces a substantial part of the Alzheimer glial phenotype. A companion study found that sulfatide deficiency causes brain ventricular enlargement in the absence of the classical neuropathological hallmarks (Palavicini et al., 2022).

This is the strongest causal evidence in the entire ceramide-pathway literature on Alzheimer's disease, and it points to a *deficiency*, not an excess.

7.3 Cerebrospinal Fluid

The cerebrospinal-fluid picture is directionally consistent with the tissue picture but temporally more informative. Sphingomyelin is elevated in prodromal Alzheimer's disease (Kosicek et al., 2012). A careful longitudinal analysis found that glycerophospholipids and sphingolipids *accumulate* in cognitively healthy participants who already carry Alzheimer biomarkers, with frank lipolysis appearing only later, at the dementia stage (Fonteh et al., 2020). Ceramide has also been detected in cerebrospinal fluid in association with the disease (Satoi et al., 2005).

The temporal ordering matters for the causal question of Section 11: accumulation appears to precede clinical disease rather than merely accompany its end, and the switch from accumulation to lipolysis at the dementia stage is exactly what one would expect if membrane breakdown became the dominant source of measured lipid late in the course.

7.4 Plasma

Blood is the least relevant compartment and the most studied, for obvious practical reasons, and the case for developing plasma sphingolipids as accessible biomarkers of this disease has been made repeatedly (Mielke & Lyketsos, 2010). The findings are moderately consistent and modestly sized.

Serum sphingomyelins and ceramides predict subsequent memory impairment (Mielke et al., 2010a); plasma ceramides are altered in mild cognitive impairment and predict both cognitive decline and hippocampal volume loss (Mielke et al., 2010b). In a longitudinal population cohort followed for up to nine years, higher baseline serum ceramides — but not sphingomyelins — were associated with incident Alzheimer's disease, with the middle and highest tertiles of ceramide d18:1/16:0 carrying roughly ten-fold and seven-and-a-half-fold increased risk respectively, though on a small sample with correspondingly wide confidence intervals; d18:1/24:0 and lactosylceramide showed similar associations, while total and high-density-lipoprotein cholesterol and triglycerides did not (Mielke et al., 2012). Shotgun lipidomics identified an altered plasma sphingolipidome in early Alzheimer's disease (Han et al., 2011), and targeted metabolomics recovered sphingolipid signatures of pathology and progression in both brain and blood (Varma et al., 2018).

The association is not uniform. In the Baltimore Longitudinal Study of Aging, the relationship between plasma ceramides and sphingomyelins and Alzheimer risk differed by sex and by *APOE* genotype (Mielke et al., 2017) — a finding that recurs in mouse brain, where ceramide and S1P levels depend jointly on sex, age and *APOE* genotype (den Hoedt et al., 2021). Any single plasma ceramide threshold is therefore likely to perform differently in different strata of the population.

Table 2 — Direction of sphingolipid change in Alzheimer's disease by compartment.

Compartment	Analyte	Direction	Stage first reported	Principal sources
Grey and white matter	Sulfatide	Down, up to 93% (grey)	Very mild dementia	Han et al., 2002; Cheng et al., 2010
White matter	Ceramide (total)	Up, >3-fold, peaking early	Very mild dementia	Han et al., 2002
Cortex, hippocampus	Ceramide (C16–C24)	Up, ratios preserved	Established disease	Cutler et al., 2004; Filippov et al., 2012
Hippocampus, temporal cortex	S1P / sphingosine	Down ~65%	Braak III/IV	Couttas et al., 2014
Brain transcriptome	De novo synthesis genes	Up	Mild dementia	Katsel et al., 2007
Brain transcriptome	Glycosphingolipid synthesis genes	Down	Mild dementia	Katsel et al., 2007
Cerebrospinal fluid	Sphingomyelin	Up	Prodromal	Kosicek et al., 2012
Cerebrospinal fluid	Sphingolipids (general)	Up, then lipolysis	Preclinical, then dementia	Fonteh et al., 2020
Plasma / serum	Ceramide d18:1/16:0, /24:0	Up	Preclinical (predictive)	Mielke et al., 2010a, 2012

The table is the argument of Section 12 in compressed form. The direction of change is not a property of "sphingolipids in Alzheimer's disease." It is a property of a particular analyte in a particular compartment at a particular stage.

8. Which Enzymes Move

Levels are outcomes; enzymes are mechanisms. The transcriptional and activity data identify a consistent pattern of re-routing.

De novo synthesis is upregulated. Serine palmitoyltransferase expression is increased in Alzheimer brain, and this increase is under post-transcriptional control by a set of microRNAs — miR-137, miR-181c, miR-9 and miR-29a/b — whose manipulation changes SPT levels and, in turn, amyloid-β (Geekiyanage & Chan, 2011). Across seventeen brain regions, the genes controlling de novo ceramide synthesis were upregulated as early as mild dementia (Katsel et al., 2007).

Glycosphingolipid synthesis is downregulated. The same transcriptional survey found the enzymes of glycosphingolipid synthesis reduced from mild dementia onward (Katsel et al., 2007) — the transcriptional counterpart of the sulfatide collapse measured directly by Han and colleagues (2002).

Sphingomyelinases are activated. Amyloid-β activates neutral sphingomyelinase. This has been shown in several independent systems: fibrillar amyloid-β kills human primary neurons through NADPH-oxidase-mediated activation of neutral sphingomyelinase (Jana & Pahan, 2004); soluble oligomers induce neuronal apoptosis through a cytosolic phospholipase A2-dependent sphingomyelinase–ceramide pathway (Malaplate-Armand et al., 2006); amyloid-β induces oligodendrocyte death by the same route (Lee et al., 2004). Working from the other direction, Aβ42 was shown to directly activate neutral sphingomyelinase and lower sphingomyelin, while Aβ40 reduced cholesterol synthesis by inhibiting HMG-CoA reductase — establishing a physiological role for amyloid precursor protein processing in lipid homeostasis, and showing that presenilin mutations shift both lipids (Grimm et al., 2005). Expression analysis in neurodegenerative brains found acid sphingomyelinase, nSMase2 and galactosylceramidase upregulated relative to age-matched controls (Filippov et al., 2012).

Acid sphingomyelinase is elevated in patients. ASM is increased in fibroblasts, brain and plasma from Alzheimer patients and in mouse models, and the consequence identified was lysosomal: ASM elevation depleted lysosomes and impaired autophagic degradation (Lee JK et al., 2014).

The S1P arm is suppressed — with a contradiction that should not be smoothed over. Sphingosine kinase 1 is reduced and S1P lyase enhanced in Alzheimer brain, indicating deregulated S1P signalling (Ceccom et al., 2014), and both sphingosine kinase activities decline with Braak stage in hippocampus (Couttas et al., 2014). Against this, an independent group reported that

the *relative activity of SphK2* is upregulated in the brains of Alzheimer patients, and showed that S1P binds full-length BACE1 and increases its proteolytic activity, so that inhibiting sphingosine kinase reduced amyloid-β production (Takasugi et al., 2011). These results are difficult to reconcile: one line makes S1P a lost neuroprotective factor whose restoration should help, the other makes S1P a cofactor for the amyloidogenic enzyme whose suppression should help. The isoform distinction (SphK1 versus SphK2), the regional and stage differences, and the difference between bulk lipid measurement and cell-associated pools are the plausible reconciliations, but none has been demonstrated. The disagreement is recorded here as unresolved and is graded accordingly in Section 13.

Sphingomyelin synthase couples to BACE1 turnover. Inhibition of sphingomyelin synthase 1 ameliorated Alzheimer-like pathology in APP/PS1 mice by promoting lysosomal degradation of BACE1 (Lu et al., 2019) — evidence that the sphingolipid economy controls the amyloidogenic enzyme's *stability*, from a direction independent of the withdrawn report discussed in Section 9.1.

The glycosphingolipid branch accumulates a specific product. Ganglioside GM3 is elevated in Alzheimer brain and in mouse models, and plasma GM3 correlates with disease severity; inhibiting glucosylceramide synthase reduced GM3, lowered soluble Aβ42 and plaque burden — including in aged mice with established pathology — and stabilised remote contextual memory (Dodge et al., 2022).

The composite picture is coherent: more flux in at the top, less flux out toward the structural glycosphingolipids, less flux out toward the survival lipid, and a specific glycosphingolipid intermediate backing up. It is a traffic problem at a crossroads, not a simple overproduction.

9. Mechanisms of Harm

9.1 Membrane Geometry and the Secretases

Amyloidogenic processing of the amyloid precursor protein is a membrane-domain-dependent event. It depends on lipid rafts (Ehehalt et al., 2003); forcing BACE1 into rafts by adding a lipid anchor increases β-site cleavage (Cordy et al., 2003); and the general dependence of amyloid-β production on membrane raft organisation has been reviewed extensively (Vetrivel & Thinakaran, 2010). Because ceramide restructures precisely these domains — ordering them, displacing cholesterol, coalescing them into platforms (Section 2.2) — any change in ceramide is simultaneously a change in the physical environment in which the secretases work.

Here an obligation of accuracy must be discharged. The most cited mechanistic claim in this area is that ceramide stabilises BACE1 post-translationally, extending its half-life and increasing amyloid-β production. That claim traces to a 2003 paper in the *Journal of Biological Chemistry* which the journal formally withdrew in 2022 (Puglielli et al., 2022, withdrawal notice). It continues to be cited, often at second or third hand, as established mechanism. No part of the argument in this paper rests on it, and readers encountering the ceramide–BACE1 stabilisation claim elsewhere should verify its source.

What survives without it is substantial but different in character. Amyloid-β is an upstream regulator of the sphingolipid pathway rather than only its victim: Aβ42 activates neutral sphingomyelinase and lowers sphingomyelin, and presenilin mutations shift the balance of cholesterol and sphingomyelin accordingly (Grimm et al., 2005). Sphingolipids reciprocally regulate BACE1 through at least two demonstrated routes — the degradative route, in which inhibiting sphingomyelin synthase 1 promotes lysosomal degradation of BACE1 and improves pathology (Lu et al., 2019), and the allosteric route, in which cell-associated S1P binds full-length BACE1 and increases its activity (Takasugi et al., 2011). A feed-forward relationship between amyloid-β and the sphingolipid pathway is therefore well supported; the specific step from ceramide to BACE1 protein stability is not.

9.2 The Mitochondrion

Ceramide is competent to permeabilise the mitochondrial outer membrane directly. It self-assembles into large channels that pass proteins of the size of cytochrome *c*; the effect requires the 4,5-double bond, is reversible, is not a detergent artefact, and is regulated by the Bcl-2 family, with activated Bax acting synergistically at concentrations at which neither agent alone suffices (Siskind et al., 2002; Ganesan et al., 2010; Colombini, 2017).

Two qualifications belong with this mechanism. First, the channel evidence is from isolated mitochondria and defined planar bilayers; that ceramide channels form and release cytochrome *c* in an intact human neuron *in situ* is a reasonable extrapolation rather than a demonstrated fact. Second, the local concentrations required are substantial, which is why the topology principle of Section 3.6 is load-bearing: ceramide synthase activity is recoverable at mitochondria-associated endoplasmic reticulum membranes and at the mitochondrial membranes themselves (Bionda et al., 2004), so a lethal pool can be generated at the target without any change in bulk tissue ceramide.

An adjacent and better-evidenced route to the same organelle runs through membrane composition rather than through pores. The 99-residue carboxy-terminal fragment of the amyloid precursor protein, C99, accumulates at mitochondria-associated endoplasmic reticulum membranes in cell models of the disease, where it drives elevated sphingolipid turnover and alters the lipid composition of both that membrane and the adjacent mitochondrial membrane, interfering with the assembly and activity of the respiratory supercomplexes (Pera et al., 2017). C99 also behaves as a cholesterol-sensing peptide that mobilises cholesterol into these domains and expands them (Montesinos et al., 2020). On this account the bioenergetic deficit of Alzheimer's disease is a lipid-composition failure at a specific organelle contact rather than a direct action of amyloid-β on the matrix — and ceramide turnover is one of its proximate mediators.

9.3 The Lysosome and Autophagy

Autophagic and lysosomal failure is among the earliest and most consistent cell-biological abnormalities in Alzheimer neurons, and the sphingolipid pathway sits inside it in two ways.

Acid sphingomyelinase is elevated in patient fibroblasts, brain and plasma, and the consequence demonstrated was a depletion of lysosomes and a resulting defect in autophagic degradation. Partial genetic inhibition of ASM in APP/PS1 mice restored lysosomal biogenesis, corrected the autophagic defect, reduced amyloid-β deposition and improved memory; pharmacological restoration of ASM to the normal range achieved the same, and autophagic dysfunction in neurons derived from familial Alzheimer patient induced pluripotent stem cells was corrected by partial ASM inhibition (Lee JK et al., 2014). The word *partial* is the operative one and is returned to in Section 15.

Ceramide also acts inside the lysosome, activating cathepsin D (Heinrich et al., 1999), and directs the selective autophagy of mitochondria (Sentelle et al., 2012). The salvage road (Section 3.3) runs through the lysosome, so a lysosomal defect is simultaneously a defect in ceramide recycling — an example of the loops that make direction of causation so difficult to establish in this system.

9.4 Propagation: Extracellular Vesicles and Tau

The claim that ceramide participates in the spread of Alzheimer pathology rests on the vesicle biogenesis function of Section 5.4 and is, in outline, well supported.

Depletion of microglia, or inhibition of exosome synthesis with the nSMase2 inhibitor GW4869, halts tau propagation in a mouse model (Asai et al., 2015). Genetically nSMase2-deficient 5XFAD mice have reduced brain exosomes and ceramide, reduced glial activation, lower total Aβ42 and plaque burden, less tau phosphorylation, and improved performance in fear conditioning; astrocyte-derived exosomes accelerate Aβ42 aggregation and block glial clearance of Aβ42 in vitro, and Aβ42 aggregates co-localise with extracellular ceramide (Dinkins et al., 2016). Astrocytes secrete exosomes enriched in ceramide and the pro-apoptotic protein PAR-4, a proposed mechanism of apoptosis induction in the disease (Wang et al., 2012), and association of amyloid-β with ceramide-enriched astrocyte-derived vesicles mediates its neurotoxicity (Elsherbini et al., 2020).

The pharmacological arm, however, contains an instructive failure that is usually omitted from summaries. A dendrimer-conjugated formulation of the potent nSMase2 inhibitor DPTIP, given orally, blocked the spread of phospho-tau to the contralateral hippocampus in an adeno-associated-virus tau propagation model (Tallon et al., 2022). The same compound, tested by the same group in the PS19 transgenic mouse, produced no benefit. The explanation the authors identified is precise and important: the dendrimer conjugate is internalised predominantly by microglia and inhibits nSMase2 selectively in that cell type, which suffices where microglial vesicles carry the propagation but not where they do not (Huang et al., 2023).

This is a cell-type result, not a failure of the mechanism, but it establishes something the field has generally assumed away: the vesicular route of tau propagation is not the same in every model, and an nSMase2 inhibitor's efficacy depends on which cell it reaches. Section 12 treats this as one of the four coordinates.

9.5 The Glia

Astrocytes. Beyond vesicle secretion, astrocytes are the site of a demonstrated therapeutic mechanism. Amyloid-β-induced generation of ceramide by acid sphingomyelinase triggers release of C1q, TNF-α and IL-1α by microglia, which induces the reactive astrocyte phenotype and the secretion of ceramide-enriched vesicles that impair the capacity of neurons to meet energy demand; inhibiting ASM with imipramine reduced the astrocytic marker, ceramide and amyloid-β content of brain-derived vesicles, abolished their mitotoxicity, and reduced pathology in 5XFAD mice (Crivelli et al., 2023).

An honest counterpoint belongs here. The most rigorous identification to date of the lipid species by which neurotoxic reactive astrocytes actually kill neurons found them to be *long-chain saturated free fatty acids* carried in ApoE and ApoJ lipoparticles, not ceramides (Guttenplan et al., 2021). Astrocytic lipid toxicity in neurodegeneration is therefore established; that ceramide is its principal effector is supported by the specific experiments above but is not the only or the best-evidenced candidate.

Microglia. Microglia are the cell type through which the strongest genetic risk signals in Alzheimer's disease act, and their interface with this pathway is lipid recognition. TREM2 senses a broad array of anionic and zwitterionic lipids associated with fibrillar amyloid-β and exposed on damaged neurons, and the risk-conferring R47H variant impairs that detection (Wang et al., 2015). Sulfatide is an anionic myelin lipid; the conjunction of a massive early loss of sulfatide (Han et al., 2002; Qiu et al., 2021) with a lipid-sensing microglial receptor whose loss of function is a major risk factor is suggestive, but the direct experiment linking the two has not, to this author's knowledge, been reported, and the connection is offered here as a hypothesis rather than a result.

What has been shown is that sulfatide deficiency alone activates disease-associated microglia and astrocytes and raises *Trem2* and *Cd33* expression (Qiu et al., 2021), and that the ceramide-driven cytokine release described by Crivelli and colleagues originates in microglia (Crivelli et al., 2023). Ceramide is also an established activator of the NLRP3 inflammasome in metabolic disease (Vandanmagsar et al., 2011), a pathway independently implicated in Alzheimer neuroinflammation.

Oligodendrocytes and white matter. The oligodendrocyte is the cell with the largest sphingolipid commitment and is therefore the cell most exposed to a disturbance of the pathway. Amyloid-β induces oligodendrocyte death through neutral sphingomyelinase and ceramide (Lee et al., 2004). Adult sulfatide loss degrades myelin maintenance (Marcus et al., 2006) and, when induced experimentally, produces the glial and cognitive phenotype described in Section 7.2 (Qiu et al., 2021). Independently, *APOE4* impairs myelination through cholesterol dysregulation in oligodendrocytes (Blanchard et al., 2022), and *APOE4* dysregulates cholesterol and matrisome pathways in astrocytes and microglia (Tcw et al., 2022). The white matter is not a bystander

compartment in this disease, and it is the compartment in which the ceramide elevation was largest and earliest (Han et al., 2002).

9.6 Metabolic Coupling

Ceramide is a mediator of insulin resistance. Inhibition of ceramide synthesis ameliorates glucocorticoid-, saturated-fat- and obesity-induced insulin resistance in rodents (Holland et al., 2007), and targeting the dihydroceramide desaturase step — removing the 4,5-double bond requirement — improves insulin resistance and hepatic steatosis (Chaurasia et al., 2019). Ceramide-mediated insulin resistance has been linked experimentally to impairment of cognitive and motor function (de la Monte et al., 2010).

This is a real and mechanistically specified link between a major modifiable risk factor for dementia and the pathway under discussion. It is also the arm of the argument in which ceramide's role is most firmly established as *causal*, because the interventional evidence in metabolic disease is extensive. The inference from metabolic tissue to brain remains an inference.

10. Genetics: *APOE*, and a Signal That Is Missing

10.1 The APOE Coupling

The ceramide pathway and the dominant genetic risk factor for Alzheimer's disease are not parallel; they are coupled at several points.

ApoE modulates brain sulfatide content (Han et al., 2003) and mediates sulfatide depletion in animal models (Cheng et al., 2010). ApoE4 disrupts sterol and sphingolipid metabolism in Alzheimer brain but not in normal brain (Bandaru et al., 2009) — that is, the genotype effect on lipids is conditional on the disease state, which is itself an important and under-discussed observation. *APOE4* allelic dosage alters the lipidome of the entorhinal cortex, the region where the disease characteristically begins, in aged mice (Miranda et al., 2022). The hippocampal S1P-to-sphingosine ratio is two-and-a-half-fold higher in ApoE2 carriers than in ApoE4 carriers, and *APOE* genotype associates with that ratio in multivariate regression (Couttas et al., 2014). Brain ceramide and S1P levels depend jointly on sex, age and *APOE* genotype in mouse models (den Hoedt et al., 2021), and the plasma ceramide association with incident disease differs by sex and *APOE* in humans (Mielke et al., 2017). *APOE4* impairs oligodendrocyte myelination through cholesterol dysregulation (Blanchard et al., 2022).

The coupling is therefore documented at the level of lipid measurement in several systems. It is much less well explained. No mechanism has been established by which the ApoE4 protein produces the sulfatide loss, and the conditional nature of the effect — present in Alzheimer brain, absent in normal brain — suggests that the genotype acts as a modifier of a process initiated elsewhere rather than as its initiator.

10.2 The Missing Signal

An honest account must record a negative. Genome-wide association studies of Alzheimer's disease have repeatedly implicated lipid biology — *APOE*, *CLU*, *ABCA7*, *SORL1*, *PICALM* — but the enzymes of ceramide metabolism are not among the established risk loci. There is no *SPTLC*, *CERS*, *SMPD3*, *ASAH1* or *SGMS* signal comparable to those.

Several readings are available and none is decisive. Common variation in essential metabolic enzymes may be under strong purifying selection, so that the relevant alleles are rare and individually underpowered in common-variant studies. The pathway may be perturbed

downstream of other lesions rather than by its own genetic variation. Or the pathway may indeed be a consequence rather than a cause. The absence of a genetic signal does not refute the mechanism, but it removes a class of evidence that would otherwise be available, and it is one reason the causal claims in Section 13 are graded below the descriptive ones.

The Mendelian randomisation evidence, which uses inherited variants to probe causality and is comparatively robust to reverse causation, is mixed. A bidirectional analysis of sphingomyelin and Alzheimer's disease reported a relationship but with the usual caveats of instrument strength (Zhu et al., 2023), while a broad metabolome-wide causal screen across neurodegenerative and psychiatric disorders did not elevate ceramide species to confident causal factors (Gilchrist et al., 2025). Both studies interrogate *circulating* sphingolipids, which need not track brain sphingolipids; their weak or null results neither confirm nor refute a brain-tissue mechanism, and this limitation is itself a testable proposition (Section 14).

11. Timing

Whether the sphingolipid change is early or late determines whether it can be causal, and the evidence is better on this question than on most.

Four independent lines place the change early. Sulfatide depletion and white-matter ceramide elevation are present, and the ceramide elevation actually *peaks*, at the stage of very mild dementia (Han et al., 2002). Transcriptional shift toward ceramide accumulation is detectable at the earliest recognisable stages of the disease (Katsel et al., 2007). Loss of S1P and of sphingosine kinase activity is present early in pathogenesis and prior to diagnosis, tracking Braak stage from its low ranges (Couttas et al., 2014). Cerebrospinal-fluid sphingolipids accumulate in cognitively healthy people who already carry Alzheimer biomarkers, before the dementia stage (Fonteh et al., 2020). To these may be added the prospective plasma data, in which baseline ceramides predict incident disease years later in people without dementia at sampling (Mielke et al., 2010a; Mielke et al., 2012).

Against this stands the reverse-causation problem, which in this system is not hypothetical. Neurodegeneration is, among other things, the physical dismantling of membranes, and membranes are where sphingolipids live. Some fraction of the ceramide measured in a degenerating brain is a product of the degeneration. The Fonteh result is instructive in both directions: accumulation before the dementia stage is encouraging for an upstream role, but the appearance of frank lipolysis at the dementia stage demonstrates that the relationship between sphingolipid measurement and neuronal death is bidirectional across the course of the illness (Fonteh et al., 2020). The peak-then-decline pattern of white-matter ceramide (Han et al., 2002) is consistent with the same reading: an early active process that later exhausts its substrate.

Two features nevertheless resist the pure reverse-causation account. The first is selectivity: at very mild dementia, sulfatide fell by up to ninety-three per cent while other major lipid classes were unchanged (Han et al., 2002). Non-specific membrane breakdown does not remove one lipid class and leave the others. The second is sufficiency: inducing the same lipid deficiency in an adult mouse produces a substantial part of the disease's glial and cognitive phenotype (Qiu et al., 2021). A pure epiphenomenon does not, when installed on its own, generate the syndrome.

Part III — Reading the Evidence

12. The Four Coordinates of Harm

The ceramide literature on Alzheimer's disease has a reputation for inconsistency. Levels are up in one study and unchanged in another; an enzyme inhibitor works in one model and fails in the next; a plasma marker predicts in one cohort and not in another stratum of the same cohort. The proposal advanced here is that most of this inconsistency is not disagreement about the biology but under-specification of the measurement, and that four coordinates must be fixed before any ceramide result can be interpreted.

12.1 Species

Ceramide is a family whose members are made by different enzymes and serve different structural purposes (Sections 2.4 and 3.4). A rise in C16 ceramide made by CerS5/6 in a reactive glial cell and a fall in C24 ceramide made by CerS2 in an oligodendrocyte are, in a homogenate, partially cancelling contributions to one number.

The evidence that species matters is strongest where it is genetic: *CERS1* failure produces progressive myoclonic epilepsy despite five other synthases remaining intact (Vanni et al., 2014), and *CERS2* deletion damages myelin specifically (Imgrund et al., 2009). The evidence that species matters *in Alzheimer's disease specifically* is weaker, and one result cuts against it: the ratios between C16, C18, C20 and C24 were preserved in affected brains even as all rose (Filippov et al., 2012). This is an honest complication. It may mean that the human disease drives a general rather than a species-selective rise; it may mean that a species-selective change in one cell type is invisible in bulk tissue dominated by another. The measurement that would resolve it — species-resolved ceramide quantification with cell-type resolution — has not, to this author's knowledge, been reported at scale in human Alzheimer tissue.

12.2 Compartment

Ceramide's effect is set by where it is generated. Ceramide made at a mitochondria-associated membrane can permeabilise the adjacent organelle (Bionda et al., 2004; Siskind et al., 2002); ceramide made in the bulk endoplasmic reticulum and delivered by CERT to the Golgi becomes sphingomyelin (Hanada et al., 2003); ceramide made at the plasma membrane by nSMase2 buds a vesicle (Trajkovic et al., 2008); ceramide made in the lysosome by acid sphingomyelinase activates cathepsin D (Heinrich et al., 1999). These are four different events with four different consequences and one shared chemical name.

The compartment coordinate also operates at tissue scale. The largest ceramide elevation reported in early disease was in *white* matter, not grey (Han et al., 2002); the S1P collapse was measured in hippocampus and temporal cortex (Couttas et al., 2014); most human data of any kind come from plasma, the compartment furthest from the lesion. Table 2 shows that the direction of change is compartment-dependent even within a single study population.

12.3 Cell Type

The brain's sphingolipid economy is not uniform across its cell types. The oligodendrocyte runs the pathway at high throughput toward galactosylceramide and sulfatide; the neuron depends on CerS1 and C18; astrocytes and microglia use the pathway for secretion and inflammatory signalling. A single tissue ceramide number averages over cells whose sphingolipid programmes have almost nothing in common.

The clearest demonstration that this coordinate is decisive is pharmacological. A dendrimer-conjugated nSMase2 inhibitor blocked tau propagation in one model and failed in another, and the explanation was cellular: the conjugate was internalised predominantly by microglia and inhibited nSMase2 only there, which sufficed where microglial vesicles carried the propagation and not otherwise (Tallon et al., 2022; Huang et al., 2023). The same molecular target, the same inhibitor, opposite outcomes — determined by which cell the drug reached.

12.4 Time

The pathway does not move in one direction across the course of the illness. White-matter ceramide rises more than threefold and then *peaks* at very mild dementia (Han et al., 2002). Cerebrospinal-fluid sphingolipids accumulate in the preclinical phase and give way to lipolysis at the dementia stage (Fonteh et al., 2020). A cross-sectional measurement in end-stage tissue and a prospective measurement in a preclinical cohort are not sampling the same phenomenon, and a therapeutic that would help in one window may be inert or harmful in the other.

12.5 What the Coordinates Buy

Fixing the four coordinates converts several apparent contradictions into consistent statements.

- The contradiction between "ceramide is elevated" and "the dominant lipid change is a *loss*" resolves once species and compartment are separated: sulfatide falls catastrophically in grey and white matter while its degradation product rises in white matter, at the same stage, in the same brains (Han et al., 2002). One flux, two signs.
- The contradiction between S1P as a lost neuroprotectant (Couttas et al., 2014; Ceccom et al., 2014) and S1P as a BACE1 cofactor whose suppression is beneficial (Takasugi et al., 2011) is, at minimum, a compartment and isoform difference — bulk hippocampal lipid versus

cell-associated pools, SphK1 versus SphK2 — though it has not been resolved experimentally and should not be presented as though it had.

- The contradiction between nSMase2 inhibition as a promising therapy (Asai et al., 2015; Dinkins et al., 2016; Tallon et al., 2022) and nSMase2 inhibition as a cause of impaired spatial memory in normal mice (Tabatadze et al., 2010) resolves along the cell-type and dose axes, and is the empirical core of the floor argument in Section 15.

The coordinates are not a rhetorical device. They are a specification for how the next generation of measurements in this field should be reported, and Section 14 states them as testable propositions.

13. Strength of Evidence

The argument of this paper is a chain of claims of very unequal strength, and it would be misleading to present them at a uniform level of confidence. The table below grades each on a four-level scale, defined as follows.

Established — convergent evidence across independent models including interventional or human genetic data, with a mechanism specified to the level of enzyme and effect. **Probable** — strong and reproduced association with a partly demonstrated mechanism, but a material gap in causal or human in-vivo evidence. **Plausible** — a coherent mechanism supported mainly by cell-culture or single-model data, or by association vulnerable to confounding or reverse causation. **Contested** — competent groups have reported incompatible results, and the disagreement is unresolved.

Table 3 — Strength of evidence for the principal claims.

Claim	Grade	Basis and principal limitation
Ceramide is an obligatory intermediate of all complex sphingolipid metabolism	Established	Biochemistry; not in dispute (Merrill, 2011; Hannun & Obeid, 2018)
Ceramide-pathway deficiency causes human neurodegeneration	Established	Six independent gene–disease relationships with concordant mouse models (Table 1)
Galactosylceramide and sulfatide are required for myelin maintenance	Established	Multiple targeted mouse deletions with convergent phenotypes (Coetzee et al., 1996; Honke et al., 2002; Marcus et al., 2006)
Ceramide forms channels permeabilising the mitochondrial outer membrane	Established in vitro; Plausible in the intact neuron	Isolated mitochondria and planar bilayers (Siskind et al., 2002; Ganesan et al., 2010); not demonstrated in situ in human brain
Ceramide is elevated in Alzheimer brain tissue	Established	Replicated across laboratories and species panels (Cutler et al., 2004; Filippov et al., 2012; Han et al., 2002)
Sulfatide is depleted early and massively in Alzheimer brain	Established	Large selective effect at very mild dementia, replicated in models (Han et al., 2002; Cheng et al., 2010)

Claim	Grade	Basis and principal limitation
Sulfatide loss is sufficient to produce Alzheimer-like glial activation and cognitive impairment	Probable	Single strong adult-onset conditional-knockout study; not yet independently replicated (Qiu et al., 2021)
S1P and sphingosine kinase activity fall early with Braak stage	Probable	Post-mortem cohort with stage stratification (Couttas et al., 2014; Ceccom et al., 2014)
Direction of the S1P arm's contribution to amyloidogenesis	Contested	Opposite findings on SphK2 activity and on the consequence of its inhibition (Couttas et al., 2014 vs Takasugi et al., 2011)
Amyloid-β activates sphingomyelinases and raises ceramide	Probable	Several independent cell systems and a direct biochemical demonstration (Jana & Pahan, 2004; Malaplate-Armand et al., 2006; Grimm et al., 2005); human in-vivo evidence absent
Ceramide stabilises BACE1 post-translationally	Not supported	Foundational report withdrawn by the journal (Puglielli et al., 2022)
Sphingolipid metabolism controls BACE1 turnover and activity	Probable	Two independent mechanisms in mouse and cell models (Lu et al., 2019; Takasugi et al., 2011)
nSMase2-dependent vesicles carry tau between cells	Probable	Genetic and pharmacological blockade in several models (Asai et al., 2015; Dinkins et al., 2016; Tallon et al., 2022), with one negative model whose cause is identified (Huang et al., 2023)
Acid sphingomyelinase elevation impairs lysosomal biogenesis and autophagy in AD	Probable	Patient tissue plus genetic and pharmacological rescue in mice and patient iPSC neurons; single principal group (Lee JK et al., 2014)
Ceramide-enriched astrocyte vesicles are mitotoxic to neurons	Plausible	Mechanistically detailed but from a single laboratory lineage (Wang et al., 2012; Elsherbini et al., 2020; Crivelli et al., 2023); a rigorous competing study identifies saturated free fatty acids rather than ceramide as the astrocytic killer (Guttenplan et al., 2021)
Plasma ceramides predict incident Alzheimer's disease	Probable	Several prospective cohorts, small samples, wide intervals, effect modified by sex and APOE (Mielke et al., 2010a, 2012, 2017)
Circulating sphingolipids are causal for Alzheimer's disease	Plausible at best	Mendelian randomisation mixed to null; blood instruments may not index brain (Zhu et al., 2023; Gilchrist et al., 2025)

Claim	Grade	Basis and principal limitation
The four-coordinate framework explains the literature's inconsistency	Interpretive	An organising proposal, not a result; judged by whether the predictions of Section 14 hold

Three summary observations follow from the table.

First, the **descriptive** claims are strong and the **causal** claims are not. That ceramide rises, that sulfatide falls, that S1P falls, that the enzymes shift — all of this is well established. That any of it drives the disease rather than reporting it remains, with the single exception of the sulfatide sufficiency experiment, unproven in the direction that matters.

Second, the **strongest causal evidence in the field points at a deficiency**. The one experiment that installed a lipid abnormality in a normal adult brain and obtained a substantial part of the Alzheimer phenotype installed a *loss* of sulfatide, not an excess of ceramide (Qiu et al., 2021). This is the observation that most constrains therapeutic design.

Third, several of the most attractive mechanistic claims rest on **single laboratory lineages**. The astrocytic ceramide-vesicle mechanism and the acid-sphingomyelinase–lysosome mechanism are each mechanistically detailed, internally consistent, and largely unreplicated outside the groups that developed them. This is not a criticism of those groups; it is a statement about what the field has and has not yet done.

14. What Would Refute This Account

An account that cannot fail is not worth holding. The following are the specific results that would falsify or substantially damage the argument advanced here.

On the four coordinates. If species-resolved, cell-type-resolved sphingolipid measurement in human Alzheimer tissue showed that all species move together in all cell types at all stages, the four-coordinate framework would be superfluous and the field's inconsistency would have to be attributed to something else — most likely to simple measurement error. The preserved species ratios reported by Filippov and colleagues (2012) are a first, partial result in this direction and should be taken seriously rather than explained away.

On the floor. If chronic pharmacological suppression of ceramide synthesis in an aged mammalian brain produced no myelin, synaptic or cognitive cost at doses sufficient to lower brain ceramide substantially, the deficiency argument of Section 6 would not generalise from the germline to the pharmacological setting, and the therapeutic caution of Section 15 would be unnecessary. The existing contrary datum is the impairment of spatial memory by nSMase2 inhibition in normal mice (Tabatadze et al., 2010); a well-powered negative replication would matter.

On sulfatide primacy. If independent laboratories failed to reproduce the finding that adult-onset myelin sulfatide deficiency generates disease-associated glial states and cognitive impairment (Qiu et al., 2021), the strongest causal claim in this paper would fall, and the sulfatide collapse would revert to the status of a large, early, unexplained correlate.

On the vesicular tau route. If nSMase2 inhibition adequate to suppress extracellular vesicle release in *neurons* — not only in microglia — failed to reduce tau propagation in multiple independent models, the propagation mechanism would be substantially weakened. The existing negative result is explicitly attributed to cell-type-restricted drug delivery (Huang et al., 2023), and that explanation is itself a testable claim.

On compartment and causality. If Mendelian randomisation instruments constructed specifically from *brain-expressed* ceramide-pathway variants — rather than from circulating sphingolipid levels — still failed to recover a causal signal for Alzheimer's disease, the argument that the null blood-based results reflect a compartment mismatch (Section 10.2) would lose its principal defence, and a genuinely non-causal interpretation of the sphingolipid changes would become the more parsimonious reading.

On the mitochondrial channel. If direct measurement in intact neurons showed that ceramide never reaches the local concentrations required for channel formation under any physiological or pathological condition, that mechanism would have to be retired from accounts of neuronal death in this disease, however elegant its in-vitro demonstration.

15. Therapeutic Implications: Direction, Selectivity, and the Floor

15.1 The Direction Is Not Simply Down

The reflexive therapeutic proposition in this field is to lower ceramide. Part I and Section 13 together show why that proposition, unqualified, is unsafe.

The pathway has a floor established by human genetics: impaired ceramide synthesis (*CERS1*), impaired desaturation (*DEGS1*), impaired degradation (*ASAH1*) and impaired sphingomyelin hydrolysis (*SMPD1*) each cause neurological disease (Table 1). It has a floor established by mouse genetics: loss of CerS2 damages myelin, loss of neuronal CerS1 disturbs gangliosides and myelin protein expression, loss of the glycosphingolipid branch destabilises the node of Ranvier, loss of nSMase2 disrupts Golgi secretion and growth. And it has a floor established pharmacologically in the normal adult animal: nSMase2 inhibition impairs spatial memory in mice (Tabatadze et al., 2010).

The clinical proof that the floor is real comes from the opposite direction. In acid sphingomyelinase deficiency — a disease of *too little* sphingomyelin hydrolysis — the therapeutic strategy is enzyme *replacement*, and it produces sustained clinical improvement over years of treatment (Wasserstein et al., 2026; Geberhiwot et al., 2023). A field that proposes to inhibit the same class of enzyme in a different disease should be explicit that it is moving a patient toward, not away from, a state with an established phenotype.

The most instructive single word in the therapeutic literature here is *partial*. The successful acid-sphingomyelinase intervention in Alzheimer models was **partial** genetic inhibition, or pharmacological restoration of an elevated enzyme **to the normal range** — not suppression below it (Lee JK et al., 2014). That is a normalisation strategy, not a suppression strategy, and it is the correct model for the whole pathway.

15.2 The Candidate Nodes

Within that constraint, the mechanism identifies several rational intervention points, each with its own evidence and its own caveat; the pharmacological options across the pathway have been catalogued in detail elsewhere (Crivelli et al., 2020).

Neutral sphingomyelinase 2. The most mechanistically motivated target, sitting at the intersection of ceramide generation and extracellular-vesicle biogenesis. Genetic nSMase2 deficiency improves pathology and cognition in 5XFAD mice (Dinkins et al., 2016); inhibition of exosome synthesis halts tau propagation (Asai et al., 2015); medicinal chemistry has produced potent and increasingly brain-penetrant inhibitors, from cambinol (Figuera-Losada et al., 2015) through DPTIP (Rojas et al., 2018; Rojas et al., 2019; Šála et al., 2020) to a dendrimer-conjugated formulation with improved pharmacokinetics (Tallon et al., 2022). *Caveats*: efficacy is cell-type-dependent and model-dependent (Huang et al., 2023), and inhibition of this enzyme impairs memory in normal mice (Tabatadze et al., 2010).

Acid sphingomyelinase. Elevated in patient fibroblasts, brain and plasma; partial inhibition restores lysosomal biogenesis and improves pathology and memory in APP/PS1 mice and corrects autophagic dysfunction in patient-derived neurons (Lee JK et al., 2014). Inhibiting ASM with imipramine reduced mitotoxic astrocyte-derived vesicles and pathology in 5XFAD mice (Crivelli et al., 2023). A large class of existing drugs — several antidepressants — are functional inhibitors of this enzyme, which makes both repurposing and pharmacoepidemiological investigation feasible (Gulbins et al., 2013). *Caveat*: the therapeutic window is a normalisation window, and complete inhibition reproduces a known lysosomal storage disease.

Serine palmitoyltransferase. Inhibition with L-cycloserine lowered cortical Aβ42 and tau hyperphosphorylation in TgCRND8 mice with no evident toxicity in that experiment (Geekiyanage et al., 2013), and the enzyme is under microRNA control that is itself altered in the disease (Geekiyanage & Chan, 2011). *Caveat*: this is the rate-limiting step of the entire sphingolipid economy, and *SPTLC1* dysregulation in either direction causes human neurological disease (Dawkins et al., 2001; Mohassel et al., 2021). Of all the nodes, this one has the least margin.

Sphingomyelin synthase. Inhibition of SMS1 promoted lysosomal degradation of BACE1 and ameliorated pathology in APP/PS1 mice (Lu et al., 2019) — a route to lowering amyloid production that does not depend on the withdrawn ceramide–BACE1 result.

Glucosylceramide synthase. Inhibition reduced ganglioside GM3, lowered soluble Aβ42 and plaque burden even in aged mice with established pathology, and stabilised remote contextual memory (Dodge et al., 2022); modification of lipid microdomains by the same general strategy sustains neuronal viability in Alzheimer models (Herzer et al., 2016). This node has the practical advantage that clinically advanced inhibitors already exist for lysosomal storage indications.

The S1P arm. S1P falls early in the disease (Couttas et al., 2014; Ceccom et al., 2014), which argues for restoration. Fingolimod, an S1P receptor modulator, modulates neuroinflammatory markers in an Alzheimer mouse model (Aytan et al., 2016), ameliorates amyloid deposition and neurodegeneration in APP/PS1 mice (Wang MT et al., 2025), and has been examined for its effect on sphingolipid imbalance and cognitive decline in aged EFAD mice (Luo et al., 2024). *Caveat*: the

contested BACE1 result (Takasugi et al., 2011) implies that raising cell-associated S1P could increase amyloid production, so this node carries an explicit risk of acting in the wrong direction on one pathology while helping another.

15.3 A Design Rule and a Measurement Agenda

Three design rules follow from the four coordinates.

Interventions should be **specified by species and by enzyme**, not by "ceramide." A drug that lowers the C16 pool generated by glial CerS6 and a drug that lowers the C24 pool generated by oligodendrocyte CerS2 are different drugs with different expected toxicities, and only the latter should be expected to injure myelin.

Interventions should be **cell-targeted where possible**. The dendrimer result establishes both the feasibility and the necessity of this: the same inhibitor delivered to a different cell is a different therapy (Tallon et al., 2022; Huang et al., 2023).

Interventions should aim at **normalisation, not suppression**, and should carry a pre-specified floor — a level of brain sphingolipid function below which dosing stops. The natural readouts are myelin integrity and white-matter structure, precisely because those are the functions the deficiency states damage.

The measurement agenda follows from the same analysis. What is needed is not more bulk ceramide quantification in accessible fluids but species-resolved, cell-type-resolved sphingolipid measurement in brain tissue across the disease course, with sulfatide and the very-long-chain species reported alongside the C16–C18 species that currently dominate. Given the compartment problem (Section 10.2), the most valuable single addition to the human evidence would be causal-genetic instruments built on brain-expressed sphingolipid-pathway variation rather than on circulating lipid levels.

16. Limitations

This paper is a synthesis and inherits the limitations of its sources, but four specific weaknesses should be named directly.

The **bulk-measurement problem cuts both ways.** The four-coordinate framework is used here to explain why the literature disagrees; it could equally be used to explain away any inconvenient result, and that is a form of unfalsifiability. Section 14 exists to prevent it, and the framework should be judged by whether the species- and cell-resolved measurements it calls for actually recover the structure it predicts.

Human causal evidence is thin. The strongest causal result in this field is a mouse experiment (Qiu et al., 2021). The human data are almost entirely cross-sectional post-mortem tissue, cerebrospinal fluid, and plasma, and the Mendelian randomisation results are mixed to null (Zhu et al., 2023; Gilchrist et al., 2025). An account resting this heavily on model systems must be held loosely.

Reverse causation cannot be excluded for the ceramide elevation, and this paper does not claim to have excluded it. The arguments in Section 11 — selectivity of the sulfatide loss, sufficiency of its experimental installation — weaken the pure epiphenomenon reading but do not defeat it, and the late-stage lipolysis documented by Fonteh and colleagues (2020) demonstrates that degradation-derived signal is real at some point in the course.

Several load-bearing mechanisms rest on single laboratory lineages, as noted in Section 13. Independent replication of the astrocytic vesicle mechanism and of the acid-sphingomyelinase lysosomal mechanism would materially change confidence in both directions.

Finally, this paper deliberately does not attempt to adjudicate whether ceramide sits upstream or downstream of amyloid and tau. The evidence assembled here is compatible with a lipid disturbance that initiates, with one that amplifies, and with one that merely accompanies. What it is not compatible with is the view that the sphingolipid changes are a peripheral detail, or that they can be corrected by simply making the numbers smaller.

17. Conclusion

Ceramide is not an intruder in the Alzheimer brain. It is the compound at the centre of the brain's largest structural investment, the obligatory intermediate through which myelin is built and dismantled, the geometry that buds a vesicle, the signal that eliminates a damaged mitochondrion, and — at sufficient local concentration in the wrong place — the lipid that opens the mitochondrion and kills the cell. It has no off position. The inherited diseases of its insufficiency are neurodegenerative, and so are the inherited diseases of its excess.

Read with that symmetry in place, the Alzheimer literature looks different. The disease is not well described as a state of too much ceramide. It is better described as a state in which the traffic through the sphingolipid crossroads has been re-routed: more entering by de novo synthesis, less leaving toward the glycosphingolipids from which the white matter is built, less leaving toward the survival signal — with the largest and earliest measured change being not an accumulation at all but the near-total loss of a myelin lipid in tissue from patients with the mildest recognisable dementia. Ceramide rises in that setting partly because the structures made from it are coming apart, and the rise is real, and it is also a symptom of the deeper lesion.

That reading carries a therapeutic consequence sharper than the one usually drawn. If the disorder were a simple excess, lowering the lipid would be straightforwardly right. If it is a re-routing bounded by a floor, then the goal is to restore the distribution of flux and not to reduce the total — to normalise an elevated enzyme rather than to abolish it, to specify the species and the cell rather than the pathway, and to treat white-matter integrity as the constraint that any dose must respect. The single most successful causal experiment in this literature produced Alzheimer-like glial activation and cognitive impairment by *removing* a sphingolipid from the adult brain. A therapy that lowers ceramide without regard to species, compartment, cell, or stage risks reproducing that experiment in a patient.

The lipid is load-bearing. That is the fact the disease literature has tended to omit, and it is the fact that should govern what is done about it.

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