Dietary sphingolipids: Metabolism and potential health implications

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1. Sphingolipid structure and synthesis

Sphingolipids are a group of amphipathic lipids composed of a hydrophobic moiety, ceramide (N-acylsphingosine), and a hydrophilic head group. According to their head group they are divided into two subgroups: (i) the sphingophospholipids, which include SM, ceramide-1-phosphate, sphingosine-1-phosphate (S1P) and sphingosylphosphorylcholine, and (ii) numerous glycosphingolipids, like cerebrosides, gangliosides, sulfatides and others. Cerebroside is the term often used for simple glycosphingolipids, like glucosylceramide, galactosylceramide, lactosylceramide (LacCer) and so on. The head group of SM is phosphorylcholine, which is also the lecithin headgroup. See figure 1 for chemical structures.

Ceramide forms the backbone of all sphingolipids. Long-chain fatty acids (C16 – C30), usually saturated, are added in amide linkage to sphingoid bases. Sphingoid bases contain 16-20, in mammals mostly 18 carbon atoms. Ceramide synthesis occurs at the cytosolic face of the endoplasmic reticulum, starting from the condensation of a serine with a fatty acyl-CoA, mostly palmitoyl-CoA, to give 3-ketosphinganine, whose reduction results in sphinganine. By the action of a ceramide synthase, the N-acylation of sphinganine produces dihydroceramide, which is then desaturated to give ceramide. The most prevalent long-chain base of mammalian sphingolipids is D-erythro-sphingosine (1,3-dihydroxy, 2-amino-octadec-4-ene or trans-4-sphingenine). Serine palmitoyltransferase is a key enzyme of sphingolipid (and thus also SM) synthesis, while SMase is a key enzyme of SM degradation.

2. Occurrence in food

Dairy products, eggs and soybeans are the richest dietary sources of sphingolipids, with up to 1-2 g/kg. The sphingolipid backbones, fatty acids and head groups vary considerably with type of food. Sphingolipids of plants are mainly cerebrosides, while there is a more complex spectrum of sphingomyelins, cerebrosides, gangliosides and sulfatides in animal tissues. SM is the dominant sphingolipid in milk and milk products. Milk contains (per L) 39-119 mg of SM, 6-11 mg of glucosylceramide, 6.5-15 mg of lactosylceramide and around 11 mg of gangliosides (figures compiled in 51). In human milk levels may be even higher. Here, too, SM represents about one third of total milk phospholipids (52).

3. Digestion and utilization

Alkaline SMase activity is present in human hepatic and gallbladder bile (31). No SMase activity was found in the stomach, but activity increased in the duodenum, was highest in the small intestine and slightly declined in colon and rectum. This pattern of activity was observed in humans, rats, mice and hamsters (11). Human milk contains a bile salt-stimulated milk lipase, which cleaves ceramide after previous cleavage of SM into ceramide and phosphorylcholine (32). Furthermore, a ceramidase with a neutral to slightly alkaline pH optimum and an acid lysosomal ceramidase is found in the gut. Like alkaline SMase, ceramidase activity is enriched in the brush border (10). Nyberg et al. (33) studied the disappearance of radioactively labelled SM across the small intestine of mice. The more SM was given, the more radioactivity was recovered, most of it in the chyme rather than in the small intestine tissues, which shows that SM digestive capacity is limited. The course of SM digestion extended over the whole digestive tract. Little ceramide is absorbed intact, but is hydrolyzed to sphingosine and fatty acid before absorption. Some of the absorbed sphingoid bases are reacylated to ceramide after absorption. Neither SM nor its metabolites are transported very efficiently from the intestine to other organs (31, 45).

4. Sphingolipids in cells and organs

As little dietary sphingolipids or metabolites reach the circulation, it is obvious that endogenous sphingolipids are largely of endogenous origin. All organs seem to be capable of de novo sphingolipid biosynthesis. Hepatocytes produce SM and ceramide and incorporate them into VLDL, in addition to incorporation into membranes. Precursor availability appears to be one of the determinants of the rate of sphingolipid biosynthesis, as addition of palmitic but not stearic or oleic acid increased secretion in rat hepatocytes, and incubation of cells with a sphinganine N-acyltransferase inhibitor caused a drastic reduction by 90% (26).

Sphingolipids are both structural and functional lipids. Their physical properties affect membrane properties. They serve as ligands for extracellular matrix proteins and receptors on neighbouring cells, as well as for some microorganisms, microbial toxins and viruses (51). SM is the major sphingolipid in the body. It is found in all cells and in all cellular membranes, but approximately 90% of SM is located in the plasma membrane, mostly in the outer leaflet (7). There is a close positive correlation between SM and cholesterol content in membranes, i.e. they are co-localized in microdomains, such as caveolae, which are also enriched in receptors (51). Not surprisingly, the folate receptor requires both cholesterol and SM in the membrane for full activity (48). It is believed that SM is required to keep cholesterol solubilized in the membranes. The relative proportion of all sphingolipid types in cell membranes tends to increase with cell differentiation and, more generally, with age (23, 40). Furthermore, the SM content varies considerably between different organs.

5. Sphingolipids in plasma lipoproteins

SM represents the second most abundant phospholipid in human plasma. It is found in all classes of lipoproteins, and comprises 23% of phospholipid in VLDL, 25% in LDL and 13% in HDL (23). Whereas SM is the major sphingolipid of rat LDL and HDL, VLDL contain mainly ceramide (26, 51). As VLDL are rich in ceramide, they may deliver ceramide to various organs in the body. Some ceramides, like the acetylceramide, also named C_2-

ceramide, are cell permeable and do not require receptors for uptake. No data are available concerning SM and ceramide levels in chylomicrons. Sphingosine-1-phosphate (S1P) is also found in plasma and serum, both in lipoproteins and in the non-lipoprotein fraction (29).

SM lipoprotein levels affect lipoprotein metabolism. SM in lipid emulsions, as a model of lipoproteins, decreased affinity and catalytic activity of lipoprotein lipase (LPL) (39), mainly by changing the surface structure (42). Due to a decreased affinity for the apoE receptor, SM decreased also lipoprotein clearance (1). In apolipoprotein E knockout mice both a defective catabolism and increased production was observed, and plasma SM pools showed a 400% increase (19). SM in HDL and LDL inhibited LCAT-mediated cholesterol esterification (49) and SM in LDL impaired binding to cellular receptors, while removal of SM improved affinity and subsequent LDL processing. SMase treatment of cells increased uptake even further (16).

6. Sphingomyelin and cholesterol metabolism

SM and cholesterol metabolism are directly interrelated. There is a close positive correlation between cholesterol and SM rather than with other phospholipids in all cell membranes. SM is probably required for solubilization of cholesterol. As a consequence, factors that upregulate plasma and tissue cholesterol levels also regulate SM levels and vice versa. This may affect cholesterol absorption in the intestine. In vitro studies showed that when the brush-border membranes contain less SM, due to SMase pretreatment, uptake of cholesterol from bile salt micelles is decreased (8). Obviously there is less capacity to solubilize cholesterol.

Likewise, treatment of fibroblasts with SMase, that depletes membranes of SM, rapidly altered the distribution of cholesterol between plasma membranes and intracellular cholesterol pools (47), while removal of phosphatidylcholine had no such effect (18). SM depeletion decreased cholesterol biosynthesis (8) and increased the intracellular cholesterol esterification by ACAT (18). Vice versa, SM enrichment of cells enhanced cholesterol synthesis (23). In the presence of apoA-I there may be an increased efflux of cellular cholesterol into HDL, but this transfer to HDL was diminished when cells were enriched in SM (18).

7. Effect of diet on endogenous sphingomyelin metabolism

Dietary regimens that increase or decrease tissue cholesterol levels also increase or decrease SM levels, both in lipoproteins and cell membranes. Thus dietary pectin not only lowered VLDL cholesterol, but also SM levels, and raised hepatic SMase activity in rats (5), while dietary cholesterol increased both VLDL cholesterol and SM levels, and decreased hepatic SMase activity (14). There was a transient increase of SM levels in VLDL following feeding of casein instead of soy protein in rats, due to enhanced synthesis and decreased degradation in the liver (13). Dietary (n-3) polyunsaturated fatty acids suppressed ceramide and diacylglycerol formation (20), while incubation of cells with stearate and particularly palmitate increased de novo ceramide synthesis and induced apoptosis (37). Other saturated fatty acids like myristate and palmitoleic acid had no such apoptotic effect. This response was acerbated when mitochondrial uptake of fatty acids for β-oxidation was impaired. This phenomenon was explained by the fact that stearate is the preferred ceramide fatty acid and palmitate is the precursor for ceramide sphingosine.

The dietary fatty acid pattern modified the fatty acid pattern of rat liver and heart SM (4) and probably of other tissues. But whether this is relevant to metabolic regulation is not known.

There are inconclusive data concerning the effect of sphingolipid feeding on plasma cholesterol levels. While one study reported reduced plasma and increased liver cholesterol levels in rats (22), no such effect was seen in another rat experiment (17). In both studies dietary sphingolipids mainly comprised glycosphingolipids.

Little information is available concerning the effect of diet on glycosphingolipids in plasma and tissues. But there is one report that an exogenous source of sialic acids derived from human milk may contribute to higher concentrations of sialic acid in body fluids (50). This is interesting, as supplementary sialic acid is associated with increased learning behaviour in animals and because sialic acid glycosphingolipids (gangliosides) may prevent attachment of bacteria to intestinal and other cells.

8. Sphingolipids and derivatives in cell signalling

The role of glycerophospholipids and their metabolic products (such as diacylglycerol, inositol triphosphate (IP_3), eicosanoids, and platelet-activating factor (PAF)) in signal transduction and cell regulation is well established. Likewise, the SM derivatives ceramide, sphingosine and S1P serve a function as second messengers for a wide variety of stimuli, like growth factors, inflammatory cytokines such as IL-1β and TNF-α, differentiation factors, vitamin D_3, oxidized LDL, complement components and so forth. A detailed list of activators is given elsewhere (40). According to the so-called sphingomyelin cycle (34) the binding of an extracellular ligand to its receptor activates a plasma membrane-bound SMase, thus releasing ceramide, which may then be transformed further. The metabolic pathways and the enzymes involved are depicted in figure 2. It depends on the activating agent whether ceramide or the more downstream components sphingosine and S1P are generated. Thus, platelet derived growth factor (PDGF) activates both SMase, ceramidase and sphingosine kinase, leading to S1P formation, while TNF-α induces only ceramide formation. These differences in enzyme induction have profound consequences for cellular regulation. In general, ceramide induces apoptosis, while S1P is a mitogen and inhibits apoptosis. The exact action of the respective signalling molecule depends also on the particular cell type involved. Furthermore, a given agonist can produce a different profile of these signalling molecules over time, or at varying concentrations. For example, IL-1β treatment of hepatocytes activates or inhibits ceramidase in a bimodal manner, to elevate sphingosine at the expense of ceramide or vice versa (30). Maybe such a biphasic regulation is also brought about by oxidized LDL (oxLDL), which is a mitogen in low concentrations, as observed in smooth muscle cells (2), and which induces apoptosis and is cytotoxic in higher concentrations. Thus, sphingolipid signalling is emerging as a mechanism that is strictly integrated with other cellular signalling pathways. Besides SM, glycosphingolipids are involved in cell signalling (7). There is obviously a fine-tuning between different regulatory pathways (6).

9. Sphingolipids and health

9.1 Sphingolipids and colon cancer

Sphingolipids, particularly SM, are potentially important anticarcinogenic lipids of milk fat and as such have been covered in more detail in previous reviews (36, 51). Both cell culture and animal studies suggest that SM may protect against cancer. Cancer of the colon has attracted particular attention. Cells of the human adenocarcinoma cell line HT29 became apoptotic upon exposure to sphingosine and ceramide (44, 51). Colon tumour incidence in mice was also reduced by feeding SM, at levels close to the estimated SM intake in the US. Dairy glycosphingolipids (43) and SM (9) reduced cell proliferation and aberrant crypt foci formation in 1,2-dimethylhydrazine-treated mice. Furthermore, epidemiologic studies suggest that dairy product consumption is associated with a reduced risk of colon cancer (15). Due to the role of SM and its derivatives in cell signalling, such an effect would not be surprising. There are also observations which suggest that SM is protective against cancer in other cell types and at other sites of the body.

But there may be another mechanism by which SM may protect against tumour development in the intestine. Secondary bile salts have been suspected to promote adenomas and cancer in the colon due to their cytotoxicity. Now it was shown that SM, as well as dipalmitoylphosphatidylcholine, are far more efficiently incorporated into taurocholate micelles than phosphatidylcholine and do protect erythrocytes and Caco cells against bile-salt cytotoxicity (28). This might not only be relevant in the intestinal tract, but also at the hepatocyte canicular membrane level.

9.2 Potential implication for atherogenesis

Sphingolipids and sphingolipid metabolizing enzymes may play important roles in atherogenesis, not only through lipoprotein modifications, but also by mediating a number of cellular events which are believed to be crucial in the development of vascular lesions. Hepatic production of lipoproteins enriched in SM and ceramide has been reported to occur in hamsters upon administration of endotoxin or inflammatory cytokines. Particularly LDL became enriched in SM, as well as in ceramide. This increase in lipoprotein sphingolipid levels may increase their atherogenicity. In addition, SMase treatment of lipoproteins supports aggregation. As vascular endothelial cells are a rich source of SMase (24), this SMase may induce LDL aggregation, subsequent retention in the subendothelial space and fatty streak formation. Indeed, SMase treatment enhanced LDL binding to aortic proteoglycans (35).

Fatty streaks are greatly enriched in ceramide, as well as in the glycolipid lactosylceramide (LacCer). LacCer is normally present in all cells of the vasculature, i.e. in endothelial cells, smooth muscle cells, macrophages, neutrophils, platelets and monocytes. It has been shown that oxLDL stimulates LacCer formation, and LacCer in turn stimulates smooth muscle cell proliferation. LacCer furthermore induces production of superoxide, which in turn induces the expression of adhesion molecules. Ceramide is both involved in induction of adhesion molecule expression and apoptosis in endothelial cells. Adhesion molecules are involved in the recruitment of blood cells to the endothelium. Induction of adhesion molecule expression and apoptosis is also brought about by inflammatory cytokines, such as TNF-α and IL-1β. This expression, as well as increased plaque instability due to excessive apoptosis, are hallmark features of atherosclerosis. A more thorough outline of mechanisms is given in recent reviews (2, 7). Also, dysregulation of cholesterol metabolism due to SM signalling should be taken in account.

9.3 Sphingolipids in glucose and insulin metabolism

Information concerning this aspect is still rather scant, though a connection seems plausible from the role of SM in the regulation of apoptosis and proliferation. In islet cells of ZDF obese rats, β-cell apoptosis was induced by increased concentrations of (long-chain) fatty acids via de novo ceramide formation (46). It was also assumed that the SMase signalling pathway is involved in the TNF-α-induced disturbance of insulin transmembrane signalling pathways (21).

9.4 Sphingolipids in the protection against bacteria toxins and infection

A health aspect applying more to glycosphingolipids than to SM is protection against bacteria toxins and infection. Many bacteria utilize glycosphingolipids to adhere to cells, e.g. Escherichia coli, Helicobacter pylori, Pseudomonas aeruginosa and Cancida albicans. Also, virus binding can be mediated via glycosphingolipids (see 51 for more details). As synthetic sphingolipids effectively inhibit the binding of bacteria and viruses (12), it is probable that sphingolipids in food compete for cellular binding sites and facilitate the elimination of pathogenic organisms from the intestine. It is also presumed that glycosphingolipids in human milk protect against pathogens, as preterm infants given adapted milk formula supplemented with gangliosides had significantly fewer E. coli in feces (and higher fecal bifidobacterial counts) than infants fed the control formula (41).

10. Perspectives

There is rich evidence that SM plays an important role for various metabolic physiological functions with potentially important implications for health. Dietary sphingolipids may directly exert beneficial effects in the intestinal tract, protecting against cancer and against bacteria infection.

The fast growing knowledge on SM and other sphingolipids and derivatives in cell signalling may also provide new aspects to the explanation of long known phenomena. It is not very probable that dietary sphingolipids are directly involved, but several dietary measures affect the endogenous sphingolipid metabolism. The close association between cholesterol and SM regulatory mechanisms suggests that cholesterol may to some extent affect CHD risk via modification of SM metabolism.

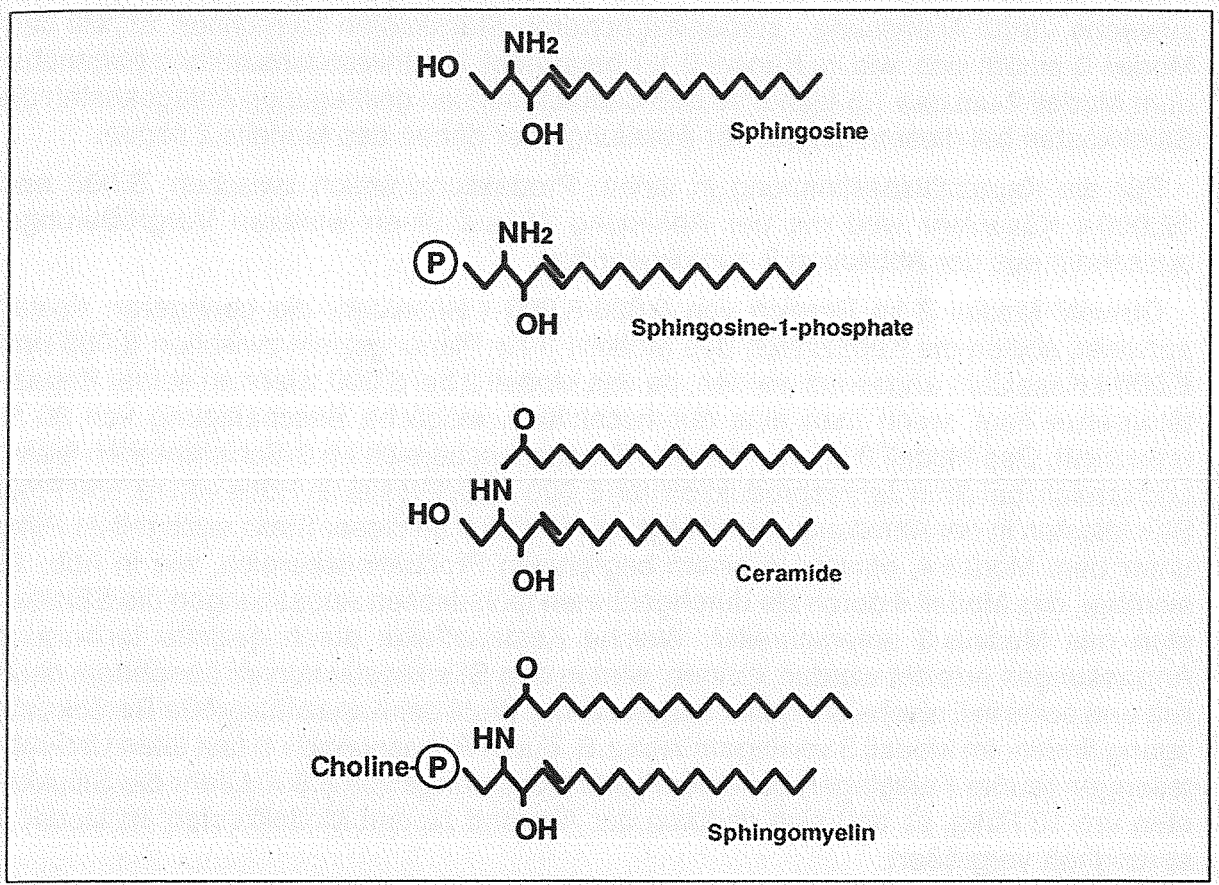

Figure 1: Structure of sphingomyelin and derivatives

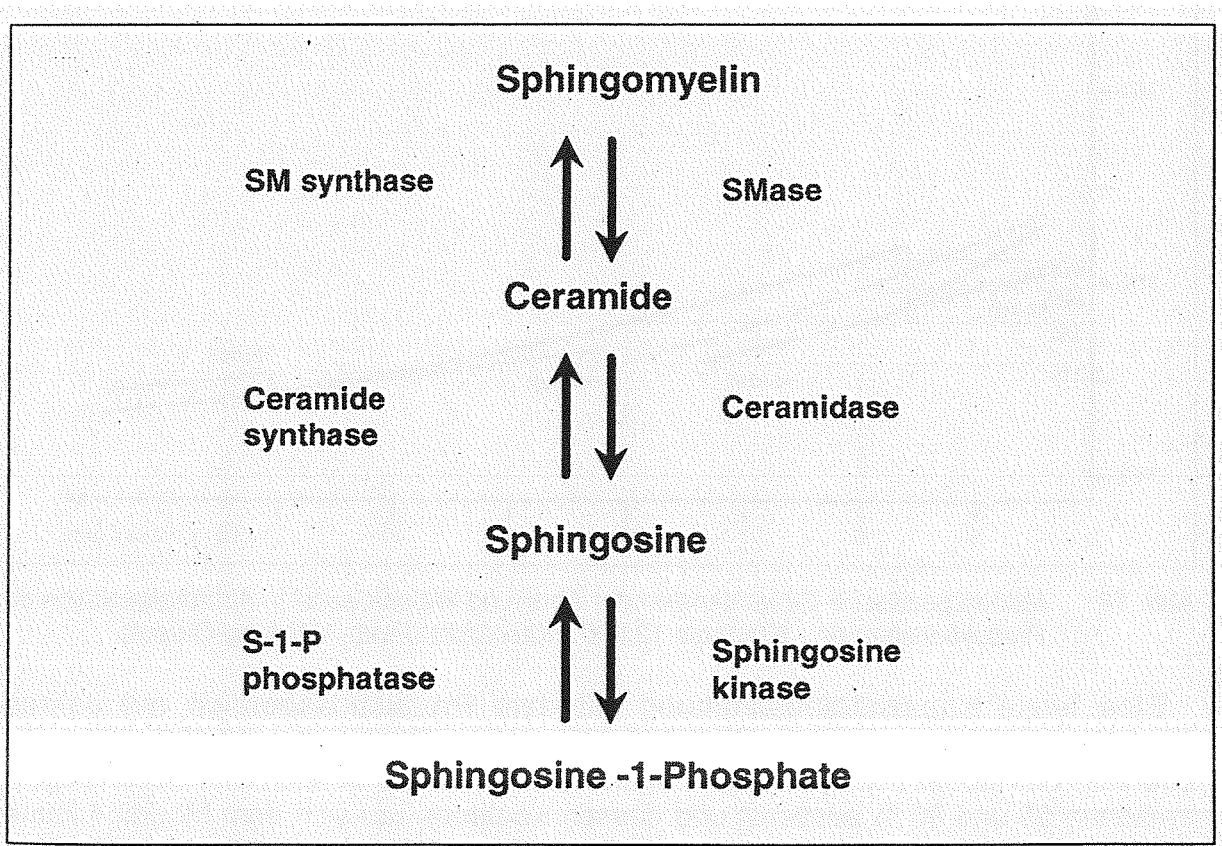

Figure 2: Interrelationship between sphingomyelin (SM) and derivatives relevant in cell signalling

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Abbreviations

Cer	Ceramide
CHD	Coronary heart disease
HDL	High density lipoprotein(s)
IL-1β	Interleukin-1β
LacCer	Lactosylceramide
LDL	Low density lipoprotein(s)
LPL	Lipoprotein lipase
oxLDL	oxidized LDL
S1P	Sphingosine-1-phosphate
SM	Sphingomyelin
SMase	Sphingomyelinase
TNF-α	Tumor necrosis factor α
ZDF rats	Zucker rats, diabetic, fat

12. Summary

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23 Physiology of Nutrition (phospholipids, resorption)

Milk is a rich source of sphingolipids, particularly sphingomyelin (SM). SM represents about one third of total milk phospholipids (52). Traditionally, there has been interest in SM as an anticarcinogenic agent acting in the intestinal tract. But since it was discovered that SM (and more generally sphingolipid) derivatives are cellular signalling substances with possibly important implications for human health, there is a renewed and growing interest and research in this field. This is highlighted by a number of excellent reviews in

recent years (2, 7, 23, 25, 36, 38, 40, 51).

Dietary SM probably exert a beneficial effect in the gastrointestinal tract, protecting against cancer and bacterial infection. Furthermore, it is reported that the SM content of intestinal cells may regulate cholesterol absorption. But far less is known about the impact of dietary SM and sphingolipids in general on endogenous sphingolipid metabolism. SM is degraded in the intestinal tract, but SM digestive capacity is limited and neither SM nor its metabolites are transported very efficiently from the intestine to other organs. Therefore, it is questionable whether dietary sphingolipids interfere directly with endogenous regulatory mechanisms. But nevertheless, several dietary measures may affect SM levels in lipoproteins and cells, including intestinal cells, and thus SM metabolism. Furthermore, the closely coordinated regulation of cholesterol and SM metabolism deserves attention. It may well be that modifications of cholesterol metabolism, brought about by dietary measures, causes indirectly changes in cell signalling, with potentially important implications for health.

Zusammenfassung

Pfeuffer, M., Schrezenmeir, J.: **Diätetische Sphingolipide: Metabolismus und potentielle Auswirkungen auf die Gesundheit.** Kieler Milchwirtschaftliche Forschungsberichte **53** (1) 31-42 (2001)

23 Ernährungsphysiologie (Phospolipide, Resorption)

Milch ist eine reiche Quelle für Sphingolipide, insbesondere Sphingomyelin (SM). Sphingomyelin macht etwa ein Drittel der gesamten Phospholipide in der Milch aus. Seit bekannt ist, daß Abkömmlinge des SM (und allgemeiner Sphingolipide) zu den zellulären Botenstoffen gehören, mit möglicherweise weitreichenden Konsequenzen für die Gesundheit, geniessen sie ein neues vermehrtes Interesse.

SM aus der Nahrung dient wahrscheinlich im Darm dem Schutz vor Krebs und bakterieller Infektion. Weiterhin wurde berichtet, dass der SM-Gehalt intestinaler Zellen die Cholesterinresorption beeinflusst. Weit weniger ist über den Einfluss des Nahrungs-SM und der Sphingolipide allgemein auf den endogenen Sphingolipidstoffwechsel bekannt. SM wird im Magen-Darmtrakt verdaut, aber die Verdauungskapazität ist begrenzt und weder SM noch dessen Abkömmlinge werden effizient resorbiert. Deshalb ist es fraglich, ob SM aus der Nahrung direkt den endogenen Stoffwechsel beeinflusst. Einige Ernährungsmaßnahmen könnten jedoch die SM-Spiegel in Lipoproteinen und Zellen beeinflussen, einschließlich der intestinalen Zellen. Die enge Verzahnung von Cholesterin- und SM-Stoffwechsel ist von hohem Interesse. Ernährungsbedingte Änderungen im Cholesterinstoffwechsel könnten somit indirekt Änderungen in der Stoffwechselregulation der Zellen auslösen, die für die Gesundheit von Bedeutung sind.

Résumé

Pfeuffer, M., Schrezenmeir, J.: **Sphingolipides diététiques: métabolisme et les effets potentiels sur la santé.** Kieler Milchwirtschaftliche Forschungsberichte (1) **53** 31-42 (2001)

23 Physiologie de la nutrition (phospholipides, résorption)

Le lait est riche en sphingolipides, particulièrement en sphingomyéline (SM). SM représente à peu près un tiers du total des phospholipides lactiques (52). Traditionnellement, on s'est intéressé à SM comme agent anticarcinogène, agissant dans le tract intestinal. Mais depuis la découverte que SM, et plus généralement les dérivatifs de sphingolipides, sont des substances de signalement cellulaire pouvant exercer une grande influence sur la santé humaine, l'intérêt scientifique pour ce domaine s'est renforcé. Des récentes analyses excellentes en témoignent (2, 7, 23, 25, 36, 38, 40, 51).

SM diététique a une influence positive sur le tract gastrointestinal et protège contre le cancer et les infections bactériennes. En plus, il est rapporté que la teneur en SM des cellules intestinales pourrait avoir une action régulatrice sur l'absorption de cholestérol. Cependant, il existe peu d'informations sur l'influence générale de SM diététique et des sphingolipides sur le métabolisme endogène sphingolipidique. Bien que SM soit décomposée dans le tract intestinal, sa capacité digestive est limitée. Ni SM, ni ses métabolites sont transportés de manière efficace de l'intestin vers d'autres organes. C'est la raison pour laquelle il est mis en question si les sphingolipides diététiques interviennent directement dans les mécanismes endogènes régulateurs. Néanmoins, il est possible que plusieurs mesures diététiques influencent les niveaux de SM dans les lipoprotéines et cellules, y inclus les cellules intestinales et, par conséquent, le métabolisme SM. En plus, l'intérêt porté à la régulation bien coordonnée entre le cholestérol et le métabolisme SM est justifié. Serait-il possible que des modifications du métabolisme du cholestérol, provoquées par des mesures diététiques, soient indirectement à l'origine de changements dans le signalement cellulaire, avec des conséquences importantes pour la santé ?