Sphingomyelinases: their regulation and roles in cardiovascular pathophysiology

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Sphingomyelinases (SMases) hydrolyse sphingomyelin, releasing ceramide and creating a cascade of bioactive lipids. These lipids include sphingosine and sphingosine-1-phosphate, all of which have a specific signalling capacity. Sphingomyelinase activation occurs in different cardiovascular system cell types, namely cardiac myocytes, endothelial and vascular smooth muscle cells, mediating cell proliferation, cell death, and contraction of cardiac and vascular myocytes. Three main types of SMases contribute to cardiovascular physiology: the lysosomal and secreted acidic SMases (L- and S-ASMases, respectively) and the membrane neutral SMase (NSMase). These three enzymes have common activators, including ischaemia/reperfusion stress and proinflammatory cytokines, but they differ in their enzymatic properties and subcellular locations that determine the final effect of enzyme activation. This review focuses on the recent advances in the understanding of ASMase and NSMase pathways and their specific contribution to cardiovascular pathophysiology. Current knowledge indicates that the inhibitors of the different SMase types are potential tools for the treatment of cardiovascular diseases. Acid SMase inhibitors could be tools against post-ischaemia reperfusion injury and in the treatment of atherosclerosis. Neutral SMase inhibitors could be tools for the treatment of atherosclerosis, heart failure, and age-related decline in vasomotion. However, the design of bioavailable and more specific SMase-type inhibitors remains a challenge.

KEYWORDS
Sphingomyelinases; Ceramide; Heart; Glutathione; THF; N-acetylcysteine

1. Introduction

Once considered an inert constituent of mammalian cell membranes, sphingomyelin [(SM), ceramide–phosphocholine] now emerges as the starting point of a complex sphingolipid signalling pathway. Sphingomyelinases (SMases; EC 3.1.4.12), which hydrolyse SM into phosphocholine and ceramide,1 are key regulatory enzymes of this pathway. In fact, ceramide not only exerts multiple biological effects per se, but also elicits the production in cascade of other bioactive sphingolipids, including sphingosine and sphingosine-1-phosphate (S1P).2,3

According to their optimum pH (alkaline, acid, and neutral), SMase isoforms can be divided into three groups and are further distinguished by their primary structure, localization, and cation dependence.4 Alkaline SMase expression is confined to the intestinal mucosa in many species; in humans, it is also found in the bile and liver.5 Acid SMases (ASMases) and membrane neutral SMases (NSMases), however, are crucially involved in cardiovascular physiology and pathophysiology.6,7 The regulation and roles of sphingolipids and SMases in cell signalling and pathophysiology have been documented in excellent recent reviews by Levade et al.,8 Marchesini and Hannun,9 Holland and Summers,10 and Smith and Schuchman.11 In this review, after a brief overview on the central role of ceramide in the complex sphingolipid metabolic and signalling network, we focus on recent advances concerning mechanisms of regulation, and the roles of ASMases and NSMases in the cardiovascular field.

2. Ceramide

Sphingomyelinases ensure ceramide production. The term ceramide refers to a family of at least 50 distinct, highly hydrophobic molecules containing a variable length fatty acid (2–28 carbons) linked to sphingosine or a related long-chain base. Ceramide metabolism generates a cascade of bioactive lipids, all of which carry a specific signalling capacity. This sphingolipid signalling network is found in the different cardiovascular system cell types and is critically involved in cell proliferation, cell death, and cardiac myocyte (CM), and vascular smooth muscle cell (VSMC) contraction.8

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Most enzymes involved in sphingolipid metabolism show specific subcellular localization. The lysosomal ASMase (L-ASMase) localizes primarily in the endolysosomal compartment, but under certain conditions it can relocate to the outer leaflet of the plasma membrane.9,9 Neutral SMase has been identified in the endoplasmic reticulum and the Golgi apparatus,4,12 but would also localize in the inner leaflet of the plasma membranes.1,13,14 Ceramide levels may therefore be regulated by distinct mechanisms and in distinct compartments. Ceramide is converted by ceramidase into sphingosine, which, in turn, is phosphorylated by sphingosine kinase into S1P. These lipids exert opposite biological effects: ceramide and sphingosine are primarily antiproliferative and pro-apoptotic, whereas S1P promotes cell growth and counteracts apoptotic stimuli. As a result, the ratio between ceramide plus sphingosine and S1P level (also referred to as the ceramide/S1P rheostat) is the true determinant of a cell’s fate, rather than the individual ceramide, sphingosine, or S1P levels.15

In addition to its production via SM hydrolysis, ceramide can be created by a de novo pathway, the first and rate-limiting step of which is the condensation of palmitoyl coA with serine by serine palmitoyltransferase.3,16 Using pharmacological and genetic methods targeting the serine palmitoyltransferase, Park et al.17,18 have shown that the de novo ceramide pathway is involved not only in the pathogenesis of lipotoxic cardiomyopathy but also in the formation of atherosclerotic plaques. These authors further showed that myriocin, a serine palmitoyltransferase inhibitor, lowered plasma sphingolipids and atherogenic plasma lipids, leading to the regression of pre-existing atherosclerotic lesions and the formation of a stable plaque phenotype. This implies that the regulation of sphingolipid biosynthesis may have clinical applications in the treatment of advanced atherosclerosis.18

3. Sphingomyelinase assays

Sphingomyelinase activity is generally not difficult to measure, although it requires a certain amount of biological material. It can be assayed in vivo through labelling of cells with a radioactive SM precursor or in vitro using either radiolabelled SM or chromogenic, coloured, or fluorescent derivatives of natural SM.19 Recent colorimetric or fluorimetric kits also allow indirect measurements of phosphocholine released upon SMase activity. The activities of the three SMase types are determined using different buffers at alkaline, neutral, or acidic pH.20,21

4. Distinct sphingomyelinases: acid and neutral sphingomyelinases

In 1963, Gatt22 described an SMase activity, active at acidic pH. By the late 1960s, deficiency of ASMase was reported to be responsible for the rare recessively inherited lysosomal storage disorder, Niemann–Pick disease (NPD).23 The cDNA and gene-encoding ASMase (designated Smpd1) were cloned in 1989 and 1992, respectively.24,25 A secreted form of the ASMase, also encoded by the Smpd1 gene, was identified in foetal bovine serum.26 The total preservation of Mg2+-dependent NSMase activity with an optimum pH of 7.4 in tissues from NPD patients27 and in ASMase knockout mice28 proved that ASMases and NSMases were separate gene products.9 Three NSMase genes (Smpd2, 3, and 4) have now been cloned.12,29,30 Mice deficient for NSMase1 gene (Smpd2) do not show any functional phenotype31 and the in vivo role of NSMase1 as an SM hydrolysing enzyme remains unclear.12 The NSMase2 gene (Smpd3) is ubiquitously expressed and is essential in growth and skeletal development.32 Finally, the recently cloned NSMase3 gene (Smpd4) belongs to the family of C-tail-anchored membrane proteins and is an integral part of TNF-α receptor type 1 (TNFR1) and adaptor protein factor associated with NSMase activation (FAN) signalling.12 Interestingly, NSMase3 mRNA is highly expressed in cardiac tissues, raising the possibility of specific roles of NSMase3 in cardiac function and pathology.12

5. Acid sphingomyelinase activity: one gene, two enzymes, three sites of action

5.1 Acid sphingomyelinase activity in ischaemia/reperfusion injury

Many studies have examined ASMase activity without discriminating between the contribution of the two enzyme isoforms: the lysosomal ASMase (L-ASMase) and the secreted ASMase (S-ASMase). This is particularly true in studies dealing with ischaemia/reperfusion injury, but it does not lessen their significance. Acid SMase activity occurs in all cardiac tissue examined in the rat, the mouse, and in humans.28,34 It fulfils an essential housekeeping function in lysosomes, as shown by the multi-organ abnormalities in NPD, which results from lysosomal SM accumulation due to ASMase deficiency.23,35 Acid SMase activity also contributes to cellular signalling in response to external stress stimuli including ischaemia/reperfusion and stimulation of diverse receptors in the TNF receptor superfamily.

Prolonged myocardial ischaemia inevitably results in cell death, and the duration of ischaemia is a primary determinant of infarct size. Reoxygenation through reperfusion reduces ischaemic damage, but also triggers additional cell death.36 Preconditioning, which consists of applying transient episodes of ischaemia/reperfusion before the sustained ischaemic event, protects the heart from ischaemia/reperfusion injury by limiting apoptosis, both in vitro38 and in vivo.39 Postconditioning has recently emerged as a more relevant clinical strategy; it consists of applying transient episodes of ischaemia/reperfusion after the sustained ischaemic event, instead of before.40,41 Pre- and postconditioning cardioprotective strategies may rely on a similar signalling pathway in the reperfused heart.42

Several studies suggest a causal relationship between the increase in ceramide content and CM death in the post-ischaemic reperfused rat heart.43-45 Argaud et al.46 have shown that benefits of preconditioning are related to reduced-cardiac ceramide content. The ASMase inhibitor, tricyclodecan-9-yl-xanthate (D609), administered before the ischaemic period, reproduces preconditioning protection, proving the contribution of ASMase activity in the ischaemia-induced cell death.46 However, Lecour et al.47 report that preconditioning with TNF-α, that is likely to activate ASMase and/or NSMase,47 also exerts an ischaemic preconditioning-like protection. TNF-α protection is reproduced by the cell-permeable C2-ceramide. The discrepancy
between these two reports probably illustrates the multiple responses that ceramide may mediate depending on its subcellular location, which determines its proximal targets and downstream metabolism. It may be that ASMase activation triggered by the ischaemic preconditioning provides ceramide integral to a cell death pathway, whereas TNF-α and cell permeable C2-ceramide release ceramide for the ceramidase/sphingosine kinase metabolism cascade. In fact, the ceramidase inhibitor N-oleyl ethanolamine hinders the preconditioning-like protection provided by TNF-α or C2-ceramide, but does not hinder the protection induced by ischaemic preconditioning.40

Using the tricyclic antidepressant inhibitor desipramine (a potent ASMase inhibitor), Das and co-workers48,49 document the two-edged role of ceramide, mediating protection in ischaemic preconditioning but promoting apoptosis after the ischaemia/reperfusion event. Thus, ASMase-mediated accumulation of ceramide in the ischaemic heart is causally related with apoptosis and cardiac dysfunction. In contrast, ischaemic preconditioning leads to a limited accumulation of ceramide in the ischaemic/reperfused heart, along with an increase in S1P content.48 The connection is seen between ceramide generated in lipid rafts during ischaemia/reperfusion and the increased association of endothelial nitric oxide synthase (eNOS) with caveolin-1, which makes endothelial NO unavailable to the ischaemic heart.49 It is worth noting that the deletion of the sphingosine kinase 1 gene abolishes the cardioprotection produced by either ischaemic preconditioning or ischaemic post-conditioning.50,51

5.2 Lysosomal and secreted isoforms of acid sphingomyelinase

In the late 1990s, Tabas and co-workers52 found that, via differential protein trafficking, the single Smpd1 gene and the single ~75 kDa protein precursor can generate the two functionally distinct forms of ASMs: L-ASMase and S-ASMase. Lysosomal ASMase is ~70 kDa glycoprotein with oligosaccharide side chains containing mannose-6-phosphate residues, typical of lysosomal proteins. Its in vitro pH optimum is between 4.5 and 5, and SM accumulation in the lysosomes of NP patients further supports its classification as a lysosomal protein.53 Secreted ASMase contains complex N-linked oligosaccharides. Both L- and S-ASMase isoforms require Zn2+ for their activity; L-ASMase is tightly bound to Zn2+ and does not need exogenous Zn2+ to attain full activity, whereas S-ASMase requires exogenous Zn2+ for its optimum activation.11,54

Human coronary artery endothelial cells (ECs) secrete large amounts of S-ASMase in an active, Zn2+-complexed form that is stimulated by certain inflammatory cytokines, including interleukin-1 and interleukin-1β.55 Increase in S-ASMase is essentially related to a decrease in L-ASMase, supporting the hypothesis that the mechanism of cytokine-induced increase in S-ASMase relies on the shunting of the common precursor away from the lysosomal trafficking pathway and into the Golgi secretory pathway.54,55

5.3 Lysosomal acid sphingomyelinase and vascular tone

In human lymphocytes, Grassmé et al.56 were the first to show that diverse receptors, belonging to the TNF receptor superfamily and mediating apoptosis, triggered L-ASMase translocation from lysosomes to the extracellular surface of the cell membrane. The translocated L-ASMase localizes to sphingolipid-rich membrane lipid rafts and releases extra-cellularly orientated ceramide. This allows the formation of larger ceramide-enriched platforms, which serve to trap and cluster the receptors determining the initiation of apoptosis signalling.57 The mechanism described relies on the phosphorylation of L-ASMase by PKCδ/ε58 (or an ASMase coming from a cytosolic pool11). Lysosomal ASMase-dependent formation of ceramide-enriched lipid macrodomains in VSMCs and EC contributes to FasL-induced impairment of the vasodilator response59,60 and muscarinic-1 receptor-mediated coronary artery constriction,61 which are both major aggravating factors in atherosclerosis.

5.4 Secreted acid sphingomyelinase in atherosclerosis

Both proliferation and death of VSMCs contribute to the progression of the atherosclerotic lesions. Levade and colleagues54 were the first to reveal the possible involvement of the sphingomyelin/ceramide pathway in atherogenesis, through a mitogenic effect on VSMCs. Endothelial cells, which cover the atherosclerotic lesions, secrete S-ASMase. Enzyme secretion is enhanced by atherogenic pro-inflammatory cytokines.55 Secreted ASMase hydrolysates SM to ceramide for the cell death pathway, even at neutral pH.63 The resulting increase in lipoprotein ceramide promotes fusion and subendothelial aggregation of the lipoprotein particles, increasing their affinity for arterial wall proteoglycans and leading to foam cell formation.64 Studies in patients and experimental models confirm the presence of S-ASMase in atherosclerotic lesions,65 and show that the latter are significantly decreased upon pharmacological inhibition of SM synthesis.66 Also, oxidized phospholipids that are found in atherosclerotic lesions may promote VSMC death via ASMase activation67 Furthermore, in a recent study using two double knockout mice models [consisting of two hyperlipidaemic models of atherosclerosis crossed onto ASMase deficient mice (producing Ape1−/−, Asm−/− and Ldlr−/−, Asm−/−)], Tabas and colleagues58 showed that ASMase deficiency reduces both lesion development and arterial trapping of atherogenic lipoproteins.

5.5 Secreted acid sphingomyelinase in heart failure

In addition to neuro-hormonal activation, inflammation and oxidative stress are key components in chronic heart failure (HF) progression70-74 and severity.77-78 The ability of pro-inflammatory cytokines to trigger S-ASMase secretion from ECs,55,73 combined with the stimulatory effect of reactive oxygen species (ROS) on enzyme activity,76-78 are possible mechanisms explaining the increase in plasma S-ASMase activity in patients with HF.79 In their pilot study, Anker and colleagues79 discovered that this activity is increased by 90% in patients with HF, compared with controls, and was a significant predictor of impaired survival. Plasma S-ASMase activity was positively related to the disease severity (assessed by the New York Heart Association functional class and peak oxygen uptake) and main clinical markers (including creatinine, uric acid, plasma TNF-α, and sTNFR1). Impaired peripheral blood flow and vasodilator...
capacity are also associated with S-ASMase activation. This is relevant to the previously reported increase in plasma levels of TNF-α in HF patients with impaired peripheral blood flow, and the finding by Zhang et al. that desipramine neutralizes the inhibitory effect of TNF-α on endothelium-dependent vasorelaxation.

6. Multiple neutral sphingomyelinases

Clarke and Hannun recently reviewed overall NSMase properties and physiological roles. Neutral SMase hydrolyses an SM pool located in the inner leaflet of the plasma membrane. In the different cardiovascular system cell types, several external stimuli trigger NSMase activation, giving the enzyme a major regulatory role in ceramide-dependent apoptosis and cell growth. The mammalian NSMase genes have been cloned only recently and specific pharmacological tools are lacking. As a result, the distinct roles of NSMase isoforms in cardiovascular disorders are not yet well defined.

6.1 Neutral sphingomyelinase signalling pathways

In isolated CM, NSMase mediates apoptosis elicited by TNF-α, or IL-1β. TNF-α activates the NSMase3 isoform through its recruitment to TNFR1 by the FAN adapter.

6.2 Neutral sphingomyelinase in ischaemia/reperfusion

Early NSMase activation in isolated CM in response to hypoxia/reoxygenation is consistent with the reported deficiency in cardiac glutathione (its cellular inhibitor) following ischaemia/reperfusion in isolated hearts or in vivo. In isolated CM, NSMase/sphingosine pathway determines the apoptotic response to hypoxia/reoxygenation or TNF-α, that involves the impairment of the mitochondrial function and/or the activation of caspases.

6.3 Neutral sphingomyelinase in heart failure

Oxidative stress and inflammation are major interrelated contributors to the development of HF. Glutathione contributes to many metabolic cell functions, in particular cell defence against oxidative stress, and is essential to cell survival. In its reduced form (GSH), glutathione serves as a cofactor to glutathione peroxidase to reduce intracellular ROS, being oxidized to the disulfide-linked dimer (GSSG). In situations involving prolonged oxidative stimuli, GSSG cannot be recycled and is pumped out of the cell such that the cellular glutathione content decreases if glutathione is not resynthesized through other pathways. In the failing heart, prolonged oxidative stress creates cardiac glutathione deficiency; this deficiency, together with TNF-α upregulation, causes NSMase activation.

6.4 Neutral sphingomyelinase in atherosclerosis

Apoptosis of VSMCs is a critical event in the rupture of the atherosclerotic plaque, leading to thrombosis, myocardial infarction, and possible death. In vitro studies highlight...
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the ability of apoC-1 enriched HDLs to induce VSMC death via NSMase activation.93 In patients, the apoC-1 content of lipoprotein remnants appears as an early marker of coronary artery disease risk.114 Using a Watanabe hyperlipidaemic rabbit model of plaque rupture and employing novel non-invasive advanced high-resolution MRI techniques, Steen et al.115 further established the co-localization of apoC-1, ceramide, caspase-1 and -3 in regions of plaque rupture, thus pointing to the in vivo relevance of the in vitro findings.

Through NSMase activation, oxLDLs induce cultured VSMC proliferation,94,97 which in situ contributes to the formation and progression of atherosclerotic lesions. OxLDLs are present in both animal and human atherosclerotic lesions and trigger the progression of atherosclerosis and plaque rupture.116

7. Conclusion

7.1 Therapeutic perspectives

It is now clear that stress-induced activation of ASMases and NSMases may contribute in different ways to the development of cardiac and vascular dysfunction (Table 1).

Acid SMase deficiency in NPD leads to lipid abnormalities that may be associated with early atherosclerotic heart disease.117 Nevertheless, S-ASMase activation in atherosclerotic lesions contributes to the progression of the lesion.64,68 These results imply therefore that therapy for atherosclerosis would have specifically target the inhibition of the S-ASMase isoform of ASMase. This is further supported by the demonstration that in a genetically engineered mouse model, where S-ASMase was suppressed but L-ASMase was preserved, there was no development of central nervous system dysfunction or systemic disease that occurs in complete ASMase deficiency.118 However, the only currently available ASMase inhibitors are non-specific. They comprise the tricyclic antidepressants imipramine and desipramine,48,49 D60946, NB6,119 l-carnitine,120 and the multi-drug resistance reversal agent SR33557, which also blocks C₂⁺ channels.121 Neutral SMase activation is associated with HF progression and endothelial dysfunction. The most studied specific inhibitors of NSMase include scyphostatin122 and GW4869,123 which inhibit vascular EC NSMase activity when added either to the cell medium or to the isolated vessel perfusate.14,101 However, in vivo, the effectiveness of scyphostatin has only been documented in a rat model of paw oedema.122

Another new non-specific ASMase and NSMase inhibitor (SMA-7, a difluoromethylene analogue of sphingomyelin) reduces colitis in mice when given orally.124 Such a lack of specificity may be advantageous in pathological situations with concomitant activation of ASMase and NSMase. In contrast, glutathione specifically inhibits NSMase, and cellular glutathione content is a major determinant of cellular NSMase activity.88,125 Ageing and most of the chronic inflammatory diseases are featured by systemic and/or tissue glutathione deficiency. Several studies in animal models and patients suggest that oral or intra-peritoneal administration of NAC or lipoic acid (which are both antioxidant molecules, but are above all precursors of glutathione) restored tissue glutathione. In HF, as in age-related decline in vasomotion, the benefits of NAC or lipoic acid treatment are related to NSMase inhibition.92,102

In conclusion, SMases are potential targets for drug development in the treatment of atherosclerosis, HF, and age-related cardiovascular diseases. In particular, ASMase inhibitors could be tools against post-ischaemia reperfusion injury, and in the treatment of atherosclerosis, bearing in mind that S-ASMase might be a preferable target than L-ASMase.64,68,118 Neutral SMase inhibitors could be tools for the treatment of atherosclerosis, HF, and age-related decline in vasomotion. Pharmacological studies have already identified possible therapeutic substances targeting NSMase, such as NAC and lipoic acid to be used to complement current treatments for HF or decline in vasomotion. However, these should be further developed by taking the advantage of new experimental models and molecular biology techniques (such as genetically modified mice and siRNA) that should allow a better understanding of the SMase isoforms specifically involved in the different disease pathways and the design of bioavailable and more specific SMase-type inhibitors.

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References

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