Sphingomyelinases: their regulation and roles in cardiovascular pathophysiology

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Abstract

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. SMase 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 which 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. ASMase inhibitors could be tools against post-ischaemia reperfusion injury, and in the treatment of atherosclerosis. NSMase 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.

MESH Keywords Cardiovascular Diseases ; physiopathology ; Cardiovascular System ; physiopathology ; Ceramides ; physiology ; Coronary Artery Disease ; physiopathology ; Heart Failure ; physiopathology ; Humans ; Myocardial Reperfusion Injury ; physiopathology ; Signal Transduction ; physiology ; Sphingomyelin Phosphodiesterase ; physiology

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 ceramide1 , are key regulatory enzymes of this pathway. In fact, ceramide not only exert 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) SMases isoforms can be divided into three groups, and are further distinguished by their primary structure, localization and cation dependence4 . 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 pathophysiology6 ,7 . The regulation and roles of sphingolipids and SMases in cell signalling and pathophysiology have been documented in excellent recent reviews by Levade and colleagues8 , Marchesini and Hannun9 , Holland and Summers10 and Smith and Schuchman11 . 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.

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) contraction8 .

Most enzymes involved in sphingolipid metabolism show specific subcellular localisation. The lysosomal ASMase, L-ASMase, localises primarily in the endolysosomal compartment, but under certain conditions it can relocate to the outer leaflet of the plasma membrane4 ,9 . NSMase has been identified in the endoplasmic reticulum and the Golgi apparatus4 ,12 , but would also localise in the inner leaflet of the plasma membranes2 ,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 the 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 levels15 .

In addition to its production via sphingomyelin 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 palmitoyltransferase3 ,16 . Using pharmacologic and genetic methods targeting the serine palmitoyltransferase, Park and colleagues have shown that the de novo ceramide pathway is involved not only in the pathogenesis of lipotoxic cardiomyopathy17 but also in the formation of atherogenic plaques18 . 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 atherosclerosis18 .

SMASE ASSAYS

SMase 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 SM19 . 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 pH20 ,21 .

DISTINCT SMASES: ASMASES AND NSMASES

In 1963, Gatt and colleagues described an SMase activity, active at acidic pH22 . 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, respectively24 ,25 . A secreted form of the ASMase, also encoded by the Smpd1 gene, was identified in foetal bovine serum26 . The total preservation of Mg^{2+}-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 products9 . Three NSMase genes (Smpd2, 3 and 4) have now been cloned29 ,30 ,12 . Mice deficient for NSMase1 gene (Smpd2) do not show any functional phenotype31 and the in vivo role of NSMase1 as a sphingomyelin hydrolysing enzyme remains unclear32 . The NSMase2 gene (Smpd3) is ubiquitously expressed, and is essential in growth and skeletal development33 . Finally, the recently cloned NSMase3 (encoded by the Smpd4 gene) belongs to the family of C-tail-anchored membrane proteins, and is an integral part of TNF-alpha receptor type 1 (TNFR1) and adaptor protein FAN (factor associated with NSMase activation) signalling12 . Interestingly, NSMase3 mRNA is highly expressed in cardiac tissues, raising the possibility of specific roles of NSMase3 in cardiac function and pathology12 .

ASMASE ACTIVITY: ONE GENE, TWO ENZYMES, THREE SITES OF ACTION

ASMase 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. ASMase activity occurs in all cardiac tissue examined in the rat, the mouse and in humans28 ,34 . It fulfils an essential housekeeping function in lysosomes, as shown by the multi organ abnormalities in NPD, which results from lysosomal sphingomyelin accumulation due to ASMase deficiency23 ,35 . ASMase 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 death36 . Preconditioning, which consists of applying transient episodes of ischaemia/reperfusion before the sustained ischaemic event, protects the heart from ischaemia/reperfusion injury37 by limiting apoptosis, both in vitro 38 and in vivo 39 . Post-conditioning 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 before40 ,41 . Pre- and post-conditioning cardioprotective strategies may rely on a similar signalling pathway in the reperfused heart42 .

Several studies suggest a causal relationship between the increase in ceramide content and CM death in the post-ischaemic reperfused rat heart43 –45 . Argaud and colleagues46 have shown that benefits of preconditioning are related to reduced cardiac ceramide content. The ASMase inhibitor, tricyclodecan 9 y-xanthate (D609), administered before the ischaemic period, reproduces preconditioning protection, proving the contribution of ASMase activity in the ischaemia-induced cell death46 . However, Lecour and colleagues47 report that preconditioning with TNF-alpha, that is likely to activate ASMase and/or NSMase9 , also exerts an ischaemic preconditioning-like

protection. TNF-alpha 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 metabolism3 . It may be that ASMase activation triggered by the ischaemic preconditioning provides ceramide integral to a cell death pathway, whereas TNF-alpha and cell permeable C2-ceramide release ceramide for the ceramidase/sphingosine kinase metabolism cascade. In fact, the ceramidase inhibitor N-oleoylethanolamine (NOE) hinders the preconditioning-like protection provided by TNF-alpha or C2-ceramide, but does not hinder the protection induced by ischaemic preconditioning47 .

Using the tricyclic antidepressant inhibitor desipramine (a potent ASMase inhibitor), Das and colleagues48 ,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 content48 . 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 heart49 . It is worth noting that deletion of the sphingosine kinase 1 gene abolishes the cardioprotection produced by either ischaemic preconditioning or ischaemic postconditioning50 ,51 .

The lysosomal (L) and secreted (S) isoforms of ASMase

In the late 90's, Tabas and coworkers52 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 ASMases, L-ASMase and S-ASMase. Lysosomal ASMase is a ≈ 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 sphingomyelin accumulation in the lysosomes of NPD patients further support its classification as a lysosomal protein53 . Secreted-ASMase contains complex N-linked oligosaccharides. Both L- and S-ASMase isoforms require Zn^{2+} for their activity; L-ASMase is tightly bound to Zn^{2+} and does not need exogenous Zn^{2+} to attain full activity, whereas S-ASMase requires exogenous Zn^{2+} for its optimum activation (reviewed in11 ,54).

Human coronary artery endothelial cells (ECs) secrete large amounts of S-ASMase in an active, Zn^{2+} -complexed form that is stimulated by certain inflammatory cytokines, including interferon-gamma (IFN-gamma) and interleukin-1beta (IL1-beta)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 pathway54 ,55 .

L-ASMase and vascular tone

In human lymphocytes, Grassmé and colleagues56 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 localises to sphingolipid-rich membrane lipid rafts and releases extracellularly orientated ceramide. This allows the formation of larger ceramide-enriched platforms, which serve to trap and cluster the receptors determining the initiation of apoptosis signalling57 . The mechanism described relies on the phosphorylation of L-ASMase by PKCdelta58 (or an ASMase coming from a cytosolic pool11). L-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 constriction61 , which are both major aggravating factors in atherosclerosis.

S-ASMase in atherosclerosis

Both proliferation and death of VSMCs contribute to the progression of the atherosclerotic lesions. Levade and colleagues62 were the first to reveal the possible involvement of the sphingomyelin/ceramide pathway in atherogenesis, through a mitogenic effect on VSMCs. ECs, which cover the atherosclerotic lesions, secrete S-ASMase. Enzyme secretion is enhanced by atherogenic pro-inflammatory cytokines 55 . Secreted-ASMase hydrolyses sphingomyelin to ceramide on the surface of atherogenic lipoprotein particles, even at neutral pH63 . 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 formation64 . Studies in patients and experimental models confirm the presence of S-ASMase in atherosclerotic lesions65 , and show that the latter are significantly decreased upon pharmacological inhibition of sphingomyelin synthesis66 . 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 $Apoe^{-/-}$; $Asm^{-/-}$ and $Ldlr^{-/-}$; $Asm^{-/-}$)), Tabas and colleagues68 showed that ASMase deficiency reduces both lesion development and arterial trapping of atherogenic lipoproteins.

S-ASMase in heart failure

In addition to neuro-hormonal activation, inflammation and oxidative stress are key components in chronic heart failure (HF) progression69 –71 and severity72 –74 . The ability of pro-inflammatory cytokines to trigger S-ASMase secretion from ECs55 ,75 , combined with the stimulatory effect of reactive oxygen species (ROS) on enzyme activity76 –78 are possible mechanisms explaining the increase in plasma S-ASMase activity in patients with HF79 . In their pilot study, Anker and colleagues discovered that this activity is increased by 90% in patients with HF, compared with controls, and was a significant predictor of impaired survival79 . 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-alpha and sTNFR1). Impaired peripheral blood flow and vasodilator capacity is also associated with S-ASMase activation79 . This is relevant to the previously reported increase in plasma levels of TNF-alpha in heart failure patients with impaired peripheral blood flow80 , and the finding by Zhang et al81 that desipramine neutralises the inhibitory effect of TNF-alpha on endothelium-dependent vasorelaxation.

MULTIPLE NSMASES

Clarke and Hannun recently reviewed overall NSMase properties and physiological roles32 ,82 . NSMase hydrolyses a SM pool located in the inner leaflet of the plasma membrane13 ,14 . 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.

NSMase signalling pathways

In isolated CM, NSMase mediates apoptosis elicited by TNF-alpha83 ,84 or IL-1beta85 . TNF-alpha activates the NSMase3 isoform through its recruitment to TNFR1 by the FAN adapter protein86 ,87 . Inhibition by the tripeptide glutathione (L-γ -glutamyl-cysteinyl-glycine) is a common feature of NSMase isoforms 1 and 330 ,88 . In fact, we have shown that cellular glutathione determines NSMase responsiveness to TNF-alpha89 ,90 , and that the enzyme's activation in failing rat and human hearts is related to a deficiency in glutathione91 ,92 .

In cultured VSMC, apolipoprotein C-1 (apoC-1)-enriched high-density lipoproteins (HDLs) stimulate NSMase, triggering an apoptotic response via the release of cytochrome c from mitochondria and caspase-3 activation93 . Oxidised low-density lipoproteins (oxLDLs) and TNF-alpha also stimulate NSMase in VSMCs94 ,95 . However, these stimuli do not trigger apoptosis, but instead contribute to VSMC proliferation resulting from the metabolism of ceramide into S1P, and downstream activation of ERK1/2 MAPKinases94 ,95 . In cultured VSMC and using the small interfering RNA strategy (siRNA), Auge et al. demonstrated both, the specific involvement of the NSMase2 isoform in the mitogenic effect of ROS96 and oxLDL97 , and the process of NSMase2 activation that relies on a proteolytic cascade involving furin/MT1-MPP/MMP-2 proteases96 ,97 . This MMP/NSMase2 pathway also drives the mitogenic effect of TNF-alpha on VSMC95 .

In cultured bovine aortic EC, the cellular response to mechanical stimulation is inhibited by the NSMase inhibitor scyphostatin, and is reproduced by addtion of exogenous bacterial NSMase or ceramide14 . As Schnitzer and colleagues discovered, using microvascular lung EC, the mechanoactivation signalling pathway relies on ceramide generation in caveolae, and on eNOS phosphorylation and activation14 , 98 ,99 . This is in agreement with a study in isolated arteries showing that exogenous bacterial NSMase triggers vasorelaxation via eNOS phosphorylation and activation, independently of raised intracellular Ca^{2+} level100 . In contrast, NSMase activation in ageing rat arteries is related to ceramide-activated protein phosphatase 2A activity and subsequent decrease in eNOS phosphorylation and activation, leading to a loss of vasomotor function101 . Recently, Smith et al.102 (commented in103) further showed that lipoic acid supplementation of isolated aortic rings reversed age-related loss of endothelial glutathione, leading to reduced NSMase activation and ceramide level in the endothelium and improved endothelial NO-dependent vasomotor function.

NSMase in ischaemia/reperfusion

Early NSMase activation in isolated CM in response to hypoxia/reoxygenation104 is consistent with the reported deficiency in cardiac glutathione (its cellular inhibitor) following ischaemia/reperfusion in isolated hearts or in vivo 105 –108 . In isolated CM, NSMase/sphingosine pathway determines the apoptotic response to hypoxia/reoxygenation104 ,109 or TNF-alpha83 ,87 that involves the impairment of the mitochondrial function110 and/or the activation of caspases92 ,111 . In addition, the NSMase/sphingosine pathway promotes the negative effect on CM contraction triggered by TNF-alpha84 ,112 or IL1-beta85 . Taken together, these in vitro findings indicate the deleterious consequences of NSMase/sphingosine pathway activation on CM survival and functioning, and predict a critical role for NSMase in the development of cardiac failure.

NSMase 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-alpha upregulation, causes NSMase activation91 ,92 . However, in animal models, glutathione repletion (produced by oral administration of a precursor of glutathione synthesis, N-acetylcysteine (NAC)) blunts the activation of the NSMase/caspase-3 apoptotic pathway, regresses fibrosis and inflammation and improves cardiac function91 ,92 . Treatment with NAC for 3 days replenishes cardiac glutathione only partially, but is enough to dampen down NSMase activity and related caspase-3 activation to control values. This suggests the early involvement of NSMase inhibition in NAC-induced cardiac recovery 92 . The regression of cardiac fibrosis seen with NAC treatment that may rely not only on the decrease in ceramide-induced CM apoptosis, but also on the impairment of S1P-induced cardiac myofibroblast activation113 .

NSMase 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 the ability of apoC-1 enriched HDLs to induce VSMC death via NSMase activation93 . In patients, the apoC-1 content of lipoprotein remnants appears as an early marker of coronary artery disease risk114 . Using a Watanabe hyperlipidaemic rabbit model of plaque rupture and employing novel non-invasive advanced high-resolution MRI techniques, Steen and colleagues115 , further established the colocalisation of apoC-1, ceramide, caspase-1 and 3 in regions of plaque rupture, thus pointing to an in vivo relevance of the in vitro findings.

Via NSMase activation, oxLDLs induce cultured VSMC proliferation 94 ,97 , which in situ contributes to the formation and progression of atherosclerotic lesions. Ox-LDLs are present in both animal and human atherosclerotic lesions and trigger the progression of atherosclerosis and plaque rupture116 .

CONCLUSION: 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).

ASMase deficiency in NPD leads to lipid abnormalities that may be associated with early atherosclerotic heart disease117 . Nevertheless, S-ASMase activation in atherosclerotic lesions contributes to the progression of the lesion64 ,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 occur in complete ASMase deficiency 118 . However, the only currently available ASMase inhibitors are nonspecific. They comprise the tricyclic antidepressants imipramine and desipramine48 ,49 , D60946 , NB6119 , L-carnitine120 and the multi-drug resistance reversal agent SR33557, which also blocks Ca^{2+} channels121 .

NSMase activation is associated with heart failure progression and endothelial dysfunction. The most studied specific inhibitors of NSMase include scyphostatin122 and GW4869123 which inhibit vascular EC NSMase activity when added either to the cell medium or to the isolated vessel perfusate14 ,101 . However, in vivo, the effectiveness of scyphostatin has only been documented in a rat model of paw oedema122 .

Another new nonspecific ASMase and NSMase inhibitor (SMA-7, a difluoromethylene analogue of sphingomyelin) reduces colitis in mice when given orally124 . 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 activity88 ,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 inhibition92 ,102 .

In conclusion, SMases are potential targets for drug development in the treatment of atherosclerosis, heart failure 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-ASMase64 ,68 ,118 . NSMase inhibitors could be tools for the treatment of atherosclerosis, heart failure 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 heart failure or decline in vasomotion. However, these should be further developed by taking 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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Sphingomyelinases in cardiovascular physiology and pathophysiology

Group	Acid sphingomyelinases		Neutral sphingomyelinases		
Gene	**Smpd1** [24,25]		**Smpd2** [29]	**Smpd3** [30]	**Smpd4** [12]
Protein	**L-ASMase** [52]	**S-ASMase** [52]	**NSMase1** [29]	**NSMase2** [30]	**NSMase3** [12]
Biochemical properties	Zn^{2+}, pH 5 optimum [4,9,11,22]		Mg^{2+}, pH 7.4 optimum [4,9,29]	Mg^{2+}, pH 7.4 optimum [4,9,29]	Mg^{2+}, pH 7.4 optimum [4,9,29]
Subcellular compartment	Lysosomes/endosomes [9,53], Outer plasma membrane [56]	Secreted [9,11,26,52,54]	ER [29]	Golgi [30,33] Plasma membrane [2]	ER, golgi [12] Plasma membrane [13,14]
Cellular expression	Ubiquitous [23,28,34]	with high expression in EC [54,55]	Ubiquitous [27]	Ubiquitous [33]	Ubiquitous with high expression in heart [12]
Biological activator	I/R insult (CM) [46–48] Ischemic preconditioning (CM) [47,49] Fas/FasL (EC) [59–60] MR1 agonist (VSMC) [61] Oxidized phosholipids (VSMC) [67] ROS [76–78]	IFN gamma (EC) [55] IL1-beta (EC) [55]		TNF, ROS, oxLDL (VSMC) [95–97]	TNF (CM, VSMC) [83–84,95] IL1-beta (CM) [85] ApoC1HDL, oxLDL (VSMC) [93–94] Hypoxia/reoxygenation (CM) [104]
Biological effect	Lysosomal sphingolipid storage (all cell types) [23] Post-IR cell death, contractile dysfunction (CM) [46–49] Vascular tone constriction (EC, VSMC) [59–61] Oxidized phospholipids -induced apoptosis (VSMC) [67]			Growth [33] TNF-, ROS-, oxLDL-induced proliferation (VSMC) [95–97]	TNF-, IL-1, hypoxia/reoxygenation-induced apoptosis (CM) [83–85,104,109] TNF-, IL1-beta-induced negative inotropic effect (CM) [84,112,85] ApoC1HDL-induced apoptosis (VSMC) [93] OxLDL-, TNF-induced proliferation (VSMC) [94–95] Vasorelaxation (EC) [14,100–101]
Pathophysiology	Niemann-Pick disease (smpd1 null mutation) [23,35] Atherosclerosis [59–61,68]	Atherosclerosis [62–66,68] Heart failure [79,81]			Heart failure [91–92] Atherosclerosis [93,95–97]
Biological inhibitor		Oxidized glutathione [9]	Oxidized/reduced glutathione [29,88]		Oxidized/reduced glutathione [29,88–92]
Pharmacological inhibitor	D609 [46], Desipramine [48–49,81], NB6 [119], L-carnitine [120]				NAC [89,92], Lipoic acid [102] Scyphostatin [14,122], GW4869 [101,123]
Pharmacological activator	Doxorubicine [120]				

Therapeutical target	Atherosclerosis[59–68] Pre/post conditioning[46,48]		Atherosclerosis[93–97] Heart failure[91–92]
Diagnostic tool	Heart failure[79,81]		

VSMC, vascular smooth muscle cells; EC, endothelial cells; CM, cardiomyocytes; ER, endoplasmic reticulum; I/R, ischemia/reperfusion; ROS, reactive oxygen species.