Heparin Cofactor II Modulates the Response to Vascular Injury

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Abstract—Heparin cofactor II (HCII) has several biochemical properties that distinguish it from other serpins: (1) it specifically inhibits thrombin; (2) the mechanism of inhibition involves binding of an acidic domain in HCII to thrombin exosite I; and (3) the rate of inhibition increases dramatically in the presence of dermatan sulfate molecules having specific structures. Human studies suggest that high plasma HCII levels are protective against in-stent restenosis and atherosclerosis. Studies with HCII knockout mice directly support the hypothesis that HCII interacts with dermatan sulfate in the arterial wall after endothelial injury and thereby exerts an antithrombotic effect. In addition, HCII deficiency appears to promote neointima formation and atherogenesis in mice. These results suggest that HCII plays a unique and important role in vascular homeostasis. (Arterioscler Thromb Vasc Biol. 2007;27:454-460.)

Key Words: heparin cofactor II ■ thrombin ■ thrombosis ■ atherogenesis ■ restenosis

Thirty years have elapsed since Briginshaw and Shanberger demonstrated that human plasma contains 2 heparin-dependent inhibitors of thrombin.1,2 They reported that the 2 inhibitors could be separated by gel filtration and ion-exchange chromatography. One of the inhibitors resembled the known protein antithrombin (formerly called antithrombin III) because it inactivated both thrombin and factor Xa and had easily detectable progressive (ie, heparin-independent) antithrombin activity. The second inhibitor did not react with factor Xa and had comparatively weak progressive antithrombin activity, yet it appeared to comprise a significant fraction of the total heparin cofactor activity in plasma. A few years later, Tollefsen and Blank demonstrated that 125I-thrombin forms 2 SDS-stable complexes in plasma containing heparin,3 and other investigators noted that the heparin cofactor activity of plasma exceeds the amount predicted from the antithrombin antigen concentration.4,5 The existence of a second heparin cofactor (now called heparin cofactor II or HCII) was firmly established when the inhibitor was purified to homogeneity from human plasma and was shown to be distinct from antithrombin.6

Although much has been learned about the structure, mechanism of action, and genetics of HCII, relatively little is known about its physiological function. This review summarizes our current knowledge of the biochemistry of HCII and then focus on recent insights gained from clinical studies and experiments with knockout mice.

Biochemistry of HCII

The HCII gene (designated SERPIND1 in humans) has been identified in a variety of vertebrate species, including humans, chimpanzee, rhesus monkey, house mouse, Norway rat, rabbit, cow, chicken, African clawed frog, European flounder, and zebrafish (http://www.ncbi.nlm.nih.gov/entrez). HCII mRNA is highly expressed in the liver, which appears to be the major source of plasma HCII.7 Low levels of HCII mRNA are also detectable in other tissues, but the significance of extrahepatic expression of HCII is unclear.8

HCII circulates in human plasma at a concentration of \( \approx 1 \) \( \mu \text{mol/L} \) and has a half-life of 2 to 3 days.9,10 The thrombin–HCII complex is cleared within minutes by the low-density lipoprotein receptor-related protein on hepatocytes.11 Human HCII is a single-chain glycoprotein containing 480 amino acid residues.12,13 It is homologous to antithrombin and other members of the serpin family, with which it shares \( \approx 30\% \) amino acid sequence identity. HCII inhibits
thrombin but has no activity against other proteases involved in coagulation or fibrinolysis. By contrast, antithrombin targets several coagulation proteases, including thrombin, factor Xa, and factor IXa. HCII by itself inhibits thrombin at a very slow rate ($t_{1/2} \approx 5$ minutes at 1 μmol/L HCII), but the rate increases dramatically in the presence of heparin, heparan sulfate, or dermatan sulfate (DS) ($t_{1/2} \approx 50$ ms). Certain other natural, synthetic, or semi-synthetic polyanions, some of which are of pharmacological interest, also stimulate HCII activity. In comparison with antithrombin, much higher concentrations of heparin or heparan sulfate are necessary to activate HCII, and HCII is activated by heparin chains that lack the 3-O-sulfated glucosamine residues required for high-affinity binding to antithrombin (Figure 1). When present in plasma at typical therapeutic concentrations, heparin preferentially stimulates antithrombin.

Activation of HCII by DS

HCII is unique among serpins in its ability to be activated by DS. DS is synthesized as a repeating polymer of D-glucuronic acid (GlcA) and N-acetyl-D-galactosamine (GalNAc), which is then modified by epimerization of GlcA to L-iduronic acid (IdoA), sulfation of the 2-OH group of IdoA, and sulfation of the 4-OH and/or 6-OH groups of GalNAc. Incomplete epimerization and O-sulfation lead to microheterogeneity within the DS polymers. HCII binds to a minor subpopulation of oligosaccharides obtained by partial depolymerization of DS. The smallest fragment of porcine skin DS that binds to HCII with high affinity is a hexasaccharide containing 3 IdoA2SO3GalNAc4SO3 disaccharide subunits (Figure 1), which comprise only 5% of the total disaccharides present in the polymer. Hexasaccharides that contain only 1 or 2 of these disulfated disaccharides also bind to HCII, albeit with lower affinity, whereas hexasaccharides composed entirely of monosulfated uronic acid (UA)→GalNAc4SO3 subunits do not bind. Pavão et al showed that the ability of DS to bind and activate HCII is not simply a function of its overall charge density but appears to require the presence of GalNAc4SO3 residues. Thus, invertebrate DS polymers composed mainly of IdoA2SO3→GalNAc4SO3 activate HCII at low concentrations, whereas polymers composed mainly of IdoA2SO3→GalNAc6SO3 are 1000-times less active. HCII-binding sites in DS from other tissues, such as porcine intestinal mucosa, contain one or more UA→GalNAc4,6SO3 disaccharide subunits. Therefore, modification of UA→GalNAc4SO3 subunits in the DS polymer by either 2-O-sulfation of IdoA or 6-O-sulfation of GalNAc can generate HCII-binding sites. Hypothetically, the distribution of glycosaminoglycans with these particular structures may localize HCII activity to specific tissue compartments.

**Role of the N-terminal Acidic Domain in Thrombin Inhibition**

The mechanism of inhibition of thrombin by HCII is that of a typical serpin. Proteolytic cleavage of the reactive site peptide bond (Leu444-Ser445) causes HCII to assume a conformation that deforms the protease and traps it as a covalent acyl ester complex. The presence of leucine in the reactive site contributes to the very slow rate of thrombin inhibition by HCII in the absence of a glycosaminoglycan. The ability of heparin or DS to stimulate thrombin inhibition largely depends on the presence of an acidic region near the N-terminus of HCII. The acidic domain resembles the C-terminal portion of hirudin, which binds with high affinity to anion-binding exosite I of thrombin. A synthetic peptide corresponding to the acidic domain of HCII competes with hirudin for binding to thrombin but does not affect the ability of thrombin to hydrolyze tripeptide p-nitroanilide substrates. Thus, binding of thrombin to the acidic domain of HCII may facilitate covalent complex formation by bringing the active site of thrombin into approximation with the reactive site of HCII.

Experiments with recombinant HCII have established the importance of the N-terminal acidic domain. Deletion of the acidic domain greatly diminishes the ability of DS or heparin to stimulate inhibition of thrombin but has little effect on the rate of inhibition in the absence of a glycosaminoglycan. In addition, N-terminal deletion mutants bind heparin more tightly than native HCII, suggesting that the acidic domain may occupy the glycosaminoglycan-binding site in native HCII. The rate of thrombin inhibition, particularly in the presence of a glycosaminoglycan, is greatly reduced by introduction of novel disulfide bonds that tether the N-terminal acidic domain to the body of HCII. These findings are consistent with a model in which binding of heparin or DS to HCII induces a conformational...
change that renders the N-terminal acidic domain more accessible for binding to thrombin exosite I (Figure 2). Mutations of amino acid residues in exosite I impair the ability of HCII to inhibit thrombin in the presence of a glycosaminoglycan, providing additional support for this model.\(^3^1\)–\(^3^3\) Interaction of the N-terminal acidic domain of HCII with exosite I of thrombin was recently demonstrated by X-ray crystallography.\(^3^4\) The thrombin-HCII reaction appears to be stimulated further by a bridging mechanism, in which both proteins bind to a single glycosaminoglycan chain.\(^3^5\)

**Physiological Function of HCII: Human Studies**

Detection of thrombin–HCII complexes in normal human plasma strongly suggests that HCII inhibits thrombin in vivo.\(^3^6\) Cultured fibroblasts and vascular smooth muscle cells accelerate inhibition of thrombin by HCII, but endothelial cells do not.\(^3^7\)–\(^3^8\) In the case of fibroblasts, which synthesize both heparan sulfate and DS, a small DS proteoglycan is responsible for the stimulatory effect. Two DS-containing proteoglycans, biglycan and decorin, are capable of stimulating HCII activity in vitro.\(^3^9\) These results suggest that HCII may inhibit thrombin at sites within the vessel wall where DS is abundant. Tovar et al reported that DS is the major anticoagulant glycosaminoglycan present in the human thoracic aorta and saphenous vein.\(^4^0\) Although they found similar amounts of DS and heparan sulfate in both vessels, vascular DS was 4-fold more potent than heparan sulfate in its ability to prolong the activated partial thromboplastin time (aPTT). A small amount of heparan sulfate (<5% of the total), which was assumed to be endothelial in origin, bound to immobilized antithrombin. Most of the DS was presumed to reside in subendothelial layers of the vessel wall, where it could come in contact with plasma HCII after disruption of the endothelium.

**Thrombosis**

Despite much effort on the part of many investigators, a convincing association between HCII deficiency and venous or arterial thrombosis has not been established.\(^4^1\) Several individuals with inherited partial deficiency of HCII (≈50% of normal) have been reported to have histories of venous thromboembolic disease. However, heterozygous HCII deficiency appears to be equally prevalent (≈1%) in individuals with or without venous thromboembolism, suggesting that HCII deficiency is not a significant risk factor for this disease. Two sisters with HCII activities only 10% to 15% of normal have been reported; one of these individuals was also heterozygous for antithrombin deficiency and had recurrent venous thromboembolism, but the other was asymptomatic.\(^4^2\) Although individuals who completely lack HCII have not been identified, the expected prevalence of this condition is only ≈1:40 000 (0.01×0.01×0.25).

**Pregnancy**

Elevated plasma concentrations of HCII have been reported in women who are pregnant or use oral contraceptives,\(^4^3\) and thrombin–HCII complexes are increased 4-fold over baseline at term.\(^3^0\) Conversely, decreased HCII levels (≈40% to 50% of normal) have been reported in patients with severe preeclampsia.\(^4^4\) During pregnancy, both the maternal and fetal plasma contain trace amounts of a DS proteoglycan that stimulates inhibition of thrombin by HCII.\(^4^5\) The placenta is rich in DS and may be the source of this proteoglycan. Whereas placental heparan sulfate has little or no anticoagulant activity when assayed with either HCII or antithrombin, DS appears to be the major anticoagulant glycosaminoglycan in this organ.\(^4^6\) Immunohistochemical studies have shown that DS is associated with fetal blood vessels and stromal regions of placental villi but is notably absent from the syncytiotrophoblast cells in contact with the maternal circulation; HCII co-localizes with DS in the walls of fetal blood vessels and is also associated with syncytiotrophoblasts.\(^4^6\) These data suggest that DS is in a position to activate HCII in the fetal blood vessels or in the stroma of placental villi after injury to the syncytiotrophoblast layer.

**Restenosis**

Two recent clinical studies suggested that high levels of HCII may protect patients from in-stent restenosis. Takamori et al reported 134 patients with coronary artery disease who were treated with angioplasty and stent placement.\(^4^7\) Angiograms were obtained during the procedure and 6 months later, and plasma HCII activity was measured at the 6-month follow-up visit. In-stent restenosis, defined as ≈50% decrease in lumen diameter, occurred at rates of 6.7% in patients with HCII ≥110%, 18.5% in patients with HCII between 80% and 110%, and 30.0% in patients with HCII <80%. The difference between the high-HCII and low-HCII groups was significant (P=0.0039). In the second study, Schillinger et al measured HCII activity in 63 patients 24 hours before femoropopliteal stent implantation.\(^4^8\) In agreement with the first study, restenosis after 12 months of follow-up occurred at a significantly lower rate (P=0.024) in patients with HCII >100% (28%) than in patients with HCII ≤100% (65%).
Atherosclerosis

Other investigators have explored the relationship between HCII levels and atherosclerotic disease. Aihara et al used carotid ultrasonography to detect atherosclerotic lesions in 306 elderly Japanese patients, most of whom had one or more of the common risk factors for cardiovascular disease. A weak negative correlation was observed between plasma HCII activity and maximum plaque thickness ($r = -0.202; P < 0.0005$), suggesting that $\approx 4\%$ ($r^2 = 0.041$) of the variance in maximum plaque thickness was caused by variability in plasma HCII activity. In a multiple regression analysis, HCII remained a negative predictive factor for carotid atherosclerosis after adjustment for the effects of other variables. In fact, plasma HCII activity was somewhat more strongly correlated with maximum plaque thickness than was high-density lipoprotein cholesterol. By contrast, Giri et al found no correlation between HCII levels and symptomatic coronary heart disease. In this study, plasma HCII antigen levels were measured in 378 middle-aged subjects in the Atherosclerosis Risk in Communities Study cohort who developed clinical manifestations of coronary heart disease during an average follow-up of 11.7 years; 382 noncases selected by stratified sampling comprised the control group. HCII was not associated with the time to development of coronary heart disease after adjusting for the effects of other prognostic factors ($P = 0.56$). These results suggest that a low plasma concentration of HCII is not an important risk factor for development of symptomatic coronary heart disease. The apparent discrepancy between the results of the 2 studies may be caused by differences in study design (prospective versus cross-sectional), the age or ethnic background of the subjects, or the clinical endpoint (symptomatic coronary heart disease versus early carotid atherosclerosis).

Thrombin Generation After Arterial Injury

How might HCII regulate the physiological response to arterial injury? Disruption of the endothelium and/or the fibrous cap of an atheromatous plaque allows factor VIIa in the plasma to come in contact with tissue factor in the arterial intima (Figure 3). The factor VIIa/tissue factor complex then converts factor X to factor Xa, which in combination with factor Va converts prothrombin to thrombin. Thrombin not only converts fibrinogen to fibrin monomers, which polymerize to form a clot, but it also cleaves G-protein-coupled protease activated receptors (specifically, PAR1 and PAR4) on the platelet membrane to stimulate platelet aggregation and degranulation. The earliest histological response to stent placement includes local deposition of fibrin and platelets, providing good evidence for the presence of thrombin in this setting. Thrombin can also activate PAR1 on nearby endothelial cells. In response, the endothelial cells express adhesion molecules on their surface and release a variety of chemokines and other mediators that recruit platelets and leukocytes. Thus, thrombin could play a role in the infiltration of neutrophils, lymphocytes, and macrophages that occurs within the first few days after stent placement. Over the next 2 to 4 weeks, the fibrin and platelets disappear, and restenosis occurs as a result of proliferation of smooth muscle cells and deposition of extracellular matrix in the neointima. Thrombin may induce smooth muscle cell proliferation both directly, by activation of PAR1 on these cells and, indirectly, by causing platelets to secrete platelet-derived growth factor. Therefore, thrombin could have multiple effects in both the early and late stages of in-stent restenosis.

Several lines of experimental evidence suggest that thrombin participates in formation of the neointima. For example, neointima formation in response to mechanical injury of the carotid artery is less intense in PAR1-null mice than in wild-type mice. This difference appears to reflect defective thrombin signaling in smooth muscle cells or perhaps endothelial cells, because the platelets of PAR1-null mice remain responsive to thrombin (in contrast to human platelets, mouse platelets express PAR3 and PAR4, but not PAR1). In addition, a synthetic peptide analog that selectively antagonizes PAR1 reduces neointima formation in rats. Various thrombin-specific inhibitors (eg, hirudin and derivatives thereof) also diminish neointima formation in experimental animals, but other anticoagulants such as heparin are ineffective. Some of the thrombin generated after vascular injury may remain bound to fibrin or to components of the vessel wall in an active form that is protected from inhibition by circulating antithrombin/heparin complexes but is susceptible to inhibition by HCII/dermatan sulfate. Infusion of dermatan sulfate, but not heparin, attenuates smooth muscle cell proliferation after carotid injury in rabbits. The anti-proliferative effect of dermatan sulfate is most readily explained by stimulation of HCII to inhibit thrombin. It is reasonable to speculate that, after stent

**Figure 3.** Activation of HCII and antithrombin by vascular glycosaminoglycans. Antithrombin inhibits coagulation factors IXa, Xa, and thrombin when bound to heparan sulfate (HS) proteoglycans associated with vascular endothelial cells. After disruption of the endothelium, HCII is activated by DS proteoglycans in the vessel wall and inhibits thrombin. TF indicates tissue factor.
placement, circulating HCII interacts with dermatan sulfate present in the vessel wall, inhibits thrombin, and thereby attenuates one or more of the reactions that lead to restenosis. Patients with higher levels of HCII may be protected to a greater extent than are those with lower levels.

Many of the thrombin-dependent cellular events that lead to restenosis, including platelet activation, stimulation of endothelial cells to express mediators of inflammation, and proliferation of smooth muscle cells, also occur during development of the atherosclerotic plaque.51,52 Thrombin activity has been detected in the neointima of atherosclerotic lesions with hirudin and chromogenic substrates as probes.60 Tissue factor is abundant in atherosclerotic plaques and provides a strong stimulus for thrombin generation during episodes of limited endothelial desquamation or disruption of the microvessels present within the plaque. Such episodes are thought to initiate rapid expansion of the atheroma.51 Heterozygous deficiency of tissue factor pathway inhibitor, which blocks the procoagulant activity of factor VIIa bound to tissue factor, promotes atherosclerosis in apolipoprotein E-null mice.61 Experimental observations such as this one support the idea that coagulation and atherogenesis are intimately linked. HCII antigen has been detected in the intima of normal human arteries where it might inhibit thrombin.62 Arterial smooth muscle cells synthesize proteoglycans that stimulate the thrombin-HCII reaction and may serve as part of an autoregulatory mechanism to prevent proliferation of these cells in the intima.38 Although dermatan sulfate is more abundant in atherosclerotic plaques than in normal arteries, its structure is altered such that its ability to stimulate HCII is reduced.63 Therefore, an HCII-dependent mechanism to limit smooth muscle cell proliferation might be lost during atheroma formation, and higher levels of circulating HCII could provide partial compensation for this loss in some patients.

### Studies With HCII Knockout Mice
Direct evidence that HCII modulates the physiological response to arterial injury has been obtained from experiments with knockout mice. He et al deleted ~2 kb of the mouse HCII gene, which encodes the N-terminal half of the protein, by homologous recombination in embryonic stem cells.64 Crosses of F1 HCII⁺⁻ animals produced HCII⁻⁻ offspring at close to the expected Mendelian frequency (21.6%). Biochemical assays confirmed the absence of HCII antigen and activity (DS-dependent thrombin inhibition) in the plasma of HCII⁻⁻ animals. Crosses of HCII⁻⁻ animals in a mixed genetic background (C57/129) produced litters similar in size to those obtained from heterozygous matings. At 1 year of age, HCII-deficient mice were indistinguishable from their wild-type littermates in weight and survival, and they did not appear to have spontaneous thrombosis or other morphological abnormalities. Blood tests indicated normal hepatic, renal, and hematopoietic function. Tail vein bleeding times were also normal.

### HCII Inhibits Arterial Thrombosis After Endothelial Injury
In contrast to the apparently normal phenotype of unchallenged HCII knockout mice, the time to thrombotic occlusion of the carotid artery after photochemically induced endothelial cell injury was significantly shorter in HCII⁻⁻ mice.64 The short occlusion time was corrected by intravenous infusion of purified human HCII but not by infusion of another serpin (ovalbumin). Backcrosses (≥N10) have been performed to generate congenic C57BL/6 and 129/SvJ strains heterozygous for the targeted HCII allele, and thrombosis studies have been repeated in each congenic strain. Although the carotid artery occlusion time of wild-type mice was approximately twice as long in C57BL/6 mice as in 129/SvJ mice, both strains showed ~40% reduction in occlusion time in the absence of HCII (Table). This work provides direct evidence that HCII has antithrombotic activity in vivo and focuses attention on the arterial system as a potential site of action of HCII.

### The Role of Endogenous DS
Does the antithrombotic effect of HCII depend on its interaction with endogenous DS in the vessel wall? To answer this question, preliminary experiments have been performed in which HCII⁻⁻ mice were reconstituted by intravenous injection with wild-type recombinant HCII or with previously characterized variants having selective defects in binding to DS (HCIIR189H) or to heparin (HCIIK173Q).65,66 Reconstitution of HCII⁻⁻ mice with either wild-type HCII or HCIIK173Q prolonged the carotid artery occlusion time from ~35 minutes to ~60 minutes, a value indistinguishable from that observed with HCII⁻⁻ controls (L. He, C. Vicente, T. Giri, and D.M. Tollefsen, manuscript in preparation). By contrast, the occlusion time of mice reconstituted with HCIIR189H remained short. These results indicate that the DS binding site of HCII is required for antithrombotic activity in vivo and suggest that HCII interacts with endogenous DS present in the arterial wall. Immunohistochemical experiments demonstrated the presence of DS mainly in the adventitia of the mouse carotid artery, whereas heparan sulfate was located

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<td>30±8</td>
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*From He et al.64 †From Vicente et al67 and unpublished data. ‡Unpublished data.
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predominantly in the intima and media. Little or no HCII antigen was present in the wall of the uninjured carotid artery. Soon after photochemical injury, however, HCII antigen could be detected in the adventitia, where it co-localized with DS. These findings suggest that disruption of the endothelium allows movement of HCII from the plasma into the vessel wall, where it may exert its antithrombotic activity.

Antithrombotic Activity of Exogenous DS
Intravenous administration of porcine skin DS induced a dose-dependent prolongation of the carotid artery occlusion time in wild-type mice but had no effect in HCII+/− animals.67 By contrast, heparin was equally effective in both HCII+/+ and HCII−/− mice. The pharmacokinetic behavior of DS in HCII+/+ mice is complex and suggests that the antithrombotic effect may occur after transfer of DS from the plasma to sites in the vessel wall. Experiments with invertebrate DS preparations that are composed predominantly of IdoA2SO3→GalNAc4SO3 or IdoA2SO3→GalNAc6SO3 revealed that O-sulfation is required for the HCII-dependent antithrombotic effect.67 Furthermore, invertebrate DS preparations, which have higher charge densities than mammalian DS, slightly prolonged the thrombotic occlusion time of HCII−/− mice. These results indicate that HCII mediates the antithrombotic effect of porcine skin DS after injury to the carotid arterial endothelium in mice, whereas more highly charged DS polymers possess weak antithrombotic activity independent of HCII.

HCII Deficiency Promotes Neointima Formation and Atherogenesis in Mice
Additional preliminary experiments support a role for HCII in neointimal smooth muscle cell proliferation and atherosclerosis. Neointima formation was induced in mice by mechanical dilation of the common carotid artery using a wire probe tipped with an epoxy bead.68 3 weeks after injury, serial cross-sections of the artery were prepared and the neointimal area determined. The mean lesion area was ~50% greater in HCII−/− mice in comparison with HCII+/+ mice (C. Vicente and D.M. Tollefsen, unpublished observations). Furthermore, administration of DS over a 2-day period after surgery greatly decreased neointima formation in HCII+/+ mice but not in HCII−/− mice. Atherogenesis was induced by feeding an atherogenic diet for 12 weeks to HCII−/− or HCII−/+ mice bred into an apolipoprotein E-null background. The aortas were then harvested, and the percentage of the vessel surface occupied by atherosclerotic plaques was determined. HCII−/− mice had larger plaque areas than HCII+/+ mice, particularly in the aortic arch (L. He and D.M. Tollefsen, unpublished observations). No plaques were observed in HCII−/− or HCII+/+ mice with wild-type apolipoprotein E. Plasma lipid and glucose levels were elevated in apolipoprotein E-null mice to the same degree regardless of the HCII genotype. These experiments directly implicate HCII in the regulation of neointima formation and atherogenesis and support the human studies which concluded that HCII exerts a protective effect on in-stent restenosis and atherosclerosis.

In summary, there is a growing body of evidence that thrombin is involved not only in thrombosis but also in neointimal smooth muscle cell proliferation and atherosclerosis. As a potent inhibitor of thrombin, HCII may regulate these processes when activated by DS in the arterial wall.

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None.

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