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Endothelial Glycocalyx: Sweet Shield of Blood Vessels[☆]

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At the time that the term glycocalyx (“sweet husk”) was introduced as a description of the extracellular polysaccharide coating on cells (Bennett HS: 1963. Morphological aspects of extracellular polysaccharides. J Hist Cytochem 11:14-23.), early electron microscopic observations had shown that anionic polysaccharides were also presented by the inner surface of blood vessels but the length of these structures was considered to be small and their functional significance was unknown. Research in the past decades in the glycocalyx field has evolved, and recent estimations indicate that the endothelial glycocalyx constitutes a voluminous intravascular compartment that plays an important role in vascular wall homeostasis. Pathologic loss of glycocalyx may be associated with an impaired vascular wall protection throughout the circulatory system, whereas agonist-induced modulation of glycocalyx accessibility for circulating blood may constitute a physiologically relevant mechanism to regulate functionally perfused volume and exchange area at the microvascular level. Both aspects are discussed in the current review. (Trends Cardiovasc Med 2007;17:101–105) © 2007, Elsevier Inc.

• Endothelial Glycocalyx: from Sugars to Volume

The in vivo glycocalyx is considered to be a negatively charged, gel-like mesh at the

luminal side of the endothelium. Its structural composition has well been described in previous reviews (Pries et al. 2000; Tarbell and Pahakis 2006). In brief, glycoproteins (eg, selectins, adhesion

molecules), proteoglycans, and glycosaminoglycans comprise the anionic polysaccharide structures of the layer and are in vivo associated with numerous molecules from the circulating blood, and water¹ (Figure 1, top panel). Heparan sulfate proteoglycans are prominently present on endothelial cells, contain abundant binding sites for plasma proteins by virtue of specific patterns of sulfation, and have the ability to function as signal transduction molecules via their core proteins, the syndecans and glypicans. Hyaluronan is not attached to a core protein but binds to surface receptors (eg, CD44). This glycosaminoglycan is not sulfated and lacks binding sites for plasma proteins, yet because of its possible length of several microns and its ability to bind water up to ~10,000 times its own weight, it is considered to contribute significantly to the volume of the endothelial glycocalyx (Figure 1).

Intravital microscopic studies of the microcirculation in cremaster tissue of rodents indicate that the glycocalyx excludes flowing red blood cells and greatly retards plasma flow under control conditions (Smith et al. 2003; Vink and Duling 1996; Vink and Duling 2000). In contrast, neutral 40-kDa dextrans were observed to rapidly equilibrate with the glycocalyx, whereas flowing leukocytes seem to compress the glycocalyx during passage in a capillary (Vink and Duling 1996). Based on these observations, methodologies were recently developed to determine systemic glycocalyx volume and sublingual capillary glycocalyx dimensions in humans (Nieuwdorp et al. 2006a, 2006b). Comparison of the dilution of fluorescently labeled red blood cells to the extrapolated dilution of 40-kDa dextrans at the time of injection revealed that in healthy subjects the dextrans distributed in an ~1.5-L larger volume than circulating plasma volume, which was determined from the red blood

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¹ In the literature, the term endothelial glycocalyx is sometimes ascribed solely to the endothelial membrane-bound polysaccharide structures, whereas association of these structures with molecules from the blood has also been termed the endothelial surface layer. In the current review, no distinction is made between the endothelial glycocalyx (or simply glycocalyx) and the endothelial surface layer.

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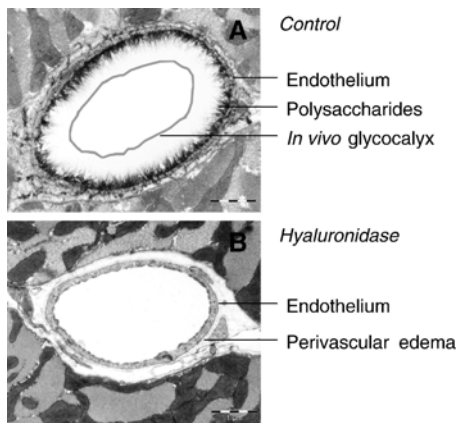


Figure 1. *Top:* electron microscopic cross section of rat myocardial capillary showing alcian blue-stained polysaccharide structures at the luminal side of endothelial cell, and estimated glycocalyx dimension in vivo. Reprinted with permission from van der Berg et al. (2003). The endothelial glycocalyx protects against myocardial edema. *Circ Res* 92(6):592–594. Glycoproteins, proteoglycans, and glycosaminoglycans comprise the anionic polysaccharide structures of the glycocalyx and are in vivo associated with plasma proteins (eg, albumin, fibrinogen), growth factors (eg, vascular endothelial growth factor), enzymes (eg, lipoprotein lipase, superoxide dismutase), and water, resulting in a hydrated gel-like layer (see text). *Bottom:* cross section of capillary after 1 hour perfusion with hyaluronidase, resulting in a loss of polysaccharide staining and the development of perivascular edema (Reprinted with permission from van der Berg et al. (2003). The endothelial glycocalyx protects against myocardial edema. *Circ Res* 92(6):592–594. Used with permission from Lippincott Williams & Wilkins [http://www.lww.com]).

cell volume and systemic hematocrit. In contrast, systemic glycocalyx volume was estimated to be only ~ 0.5 L in patients with type 1 diabetes mellitus (Nieuwdorp et al. 2006a). The decrease in these patients was predominantly the result of a reduction in distribution volume of the dextrans, arguing against a significant contribution of rapid 40-kDa dextran leakage to the estimation of anatomic vascular volume. Sublingual capillaries were visualized by using orthogonal polarization spectral microscopy, and glycocalyx thickness was estimated from the difference between capillary red blood cell column width during baseline, reflecting functionally perfused capillary diameter, and after passage of a leukocyte, reflecting the anatomic capillary diameter, and was ~ 0.9 μm in healthy subjects. In line with the observed decrease in systemic glycocalyx volume, estimated glycocalyx thickness in sublin-

gual capillaries was smaller in patients with type 1 diabetes mellitus, ~ 0.5 μm (Nieuwdorp et al. 2006a).

• Role for Glycocalyx in Microvascular Perfusion and Exchange

The vast majority of glycocalyx volume is residing in the capillaries, because capillary endothelial surface area accounts for most of the total surface area of the vascular system. Indeed, systemic glycocalyx volume was found to correlate with microvascular glycocalyx thickness in control subjects and diabetic patients (Nieuwdorp et al. 2006a). Original intravital microscopic studies of Klitzman and Duling (1979) already pointed to the presence of a 1.2- μm -thick, slow-moving plasma layer to explain the low instantaneous volume fraction of red blood cells within cremaster muscle capillaries (ie, capillary tube hematocrit $\approx 10\%$). Ten years later, it was indicated that this layer represented the endothelial glycocalyx, as evidenced by the more than 2-fold increase in capillary tube hematocrit after local microperfusion of capillaries with the enzyme heparinase (Desjardins and Duling 1990).

A more comprehensive understanding of the barrier properties of the endothelial glycocalyx originated when Vink and Duling (1996, 2000) measured the intraluminal distribution of various fluorescently labeled molecules compared to the endothelial wall inside capillaries. Accessibility of inert macromolecules to the glycocalyx domain with a thickness of ~ 0.5 μm was found to be a function of their charge and size, such that large (≥ 70 kDa) dextrans were partially excluded from the domain, and smaller, neutral dextrans had unimpaired access to it. In contrast, permeation of proteins into the glycocalyx did not follow a simple charge and size dependency. Thus, fibrinogen and albumin, despite substantially differing sizes (340 and 70 kDa, respectively), were observed to move into the glycocalyx at a similar slow rate, indicating specific interactions between these proteins and glycocalyx structures (Vink and Duling 2000).

A role for the glycocalyx in vascular wall permeability and selectivity is suggested by experimental studies in which the glycocalyx was treated with glycosaminoglycan-degrading enzymes. Enzymatic degradation has been associated with a reduction in exclusion of anionic

dextrans (Henry and Duling 1999), increases in hydraulic conductivity (Adamson 1990) and protein permeability (Huxley and Williams 2000), and an increased glomerular clearance of albumin (Jeansson and Haraldsson 2003). Although the precise role of the glycocalyx in regulation of water and solute transport remains to be determined, important contributions have been made by Curry and coworkers, who have proposed the so-called glycocalyx-junction-break model in which the glycocalyx forms the principal molecular sieve at the capillary wall: the size of the small pores is determined by the spacing between the fibers in the glycocalyx on the endothelial surface, whereas the number of pores is determined by the length and frequency of breaks in the junction strand (Curry 2005; Michel and Curry 1999). According to this model, the colloid osmotic forces opposing filtration across continuous capillaries are developed across the glycocalyx rather than the interstitial space, resulting in the advancement of the so-called revised Starling principle (Adamson et al. 2004; Hu et al. 2000; Zhang et al. 2006).

• Role for the Glycocalyx in Vascular Protection

An important role for the endothelial glycocalyx in preserving endothelial function is derived from enzyme treatment studies, in which glycocalyx degradation was shown to result in an increased adhesion of leukocytes in venules (Constantinescu et al. 2003), the formation of perivascular edema (Van den Berg et al. 2003), and an impairment of shear stress-dependent nitric oxide (NO) production in arteries and cultured endothelial cells (Florian et al. 2003; Mochizuki et al. 2003). On the other hand, increasing experimental evidence indicates that the glycocalyx is early vulnerable upon exposure to cardiovascular risk factors (for reviews, see Gouverneur et al. 2006; Nieuwdorp et al. 2005). Thus, as evidenced by an increased accessibility of dextrans or red blood cells into the glycocalyx domain or an increased tube hematocrit in cremaster capillaries, degradation of glycocalyx structures was found to occur after provocation with inflammatory and atherogenic stimuli, such as tumor necrosis factor- α administration (Henry

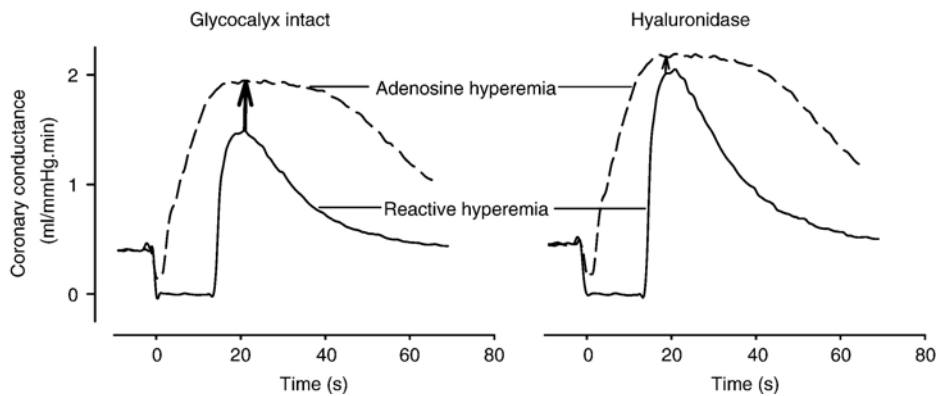


Figure 2. Schematic illustration of coronary conductance response in open-chest anesthetized dogs during reactive hyperemia (maximum response, 15 seconds occlusion) and adenosine hyperemia (maximum response, intracoronary bolus of 650 μg) with intact glycocalyx (*left*) and after hyaluronidase treatment (*right*). Figure data from VanTeeffelen et al. (2005). With intact glycocalyx, adenosine is able to functionally recruit coronary microvascular glycocalyx volume and increase coronary conductance more than reactive hyperemia (*left, thick arrow*). With glycocalyx degradation, peak coronary conductance during reactive hyperemia increases without a significant change in the peak conductance during adenosine (*right*). As a consequence, the capability of adenosine to recruit coronary microvascular glycocalyx volume and coronary conductance compared to reactive hyperemia is reduced during glycocalyx degradation (*right, thin arrow*). For details, see VanTeeffelen et al. (2005).

and Duling 2000), ischemia/reperfusion (Rubio-Gayosso et al. 2006), and infusion of oxidized low-density lipoprotein (Constantinescu et al. 2001; Vink et al. 2000). Furthermore, a recent electron microscopic study of the mouse carotid artery demonstrated that the endothelial glycocalyx at an atherosclerosis-prone site (internal carotid sinus region) was considerably thinner (~100 nm) than at a site with a low risk for atherosclerosis development (common carotid region, ~400 nm) (Van den Berg et al. 2006). In addition to a loss of protection against fluid and solute leakage and adhesion of platelets and leukocytes, the presence of a thinner glycocalyx at atherosclerosis-prone sites might contribute to their increased susceptibility by impairing NO production, because substantial evidence in support of the endothelial glycocalyx acting as shear stress mechanotransducer has been provided the past 2 years, as recently reviewed (Tarbell and Pahakis 2006).

Recent studies on humans seem to exemplify a generalized nature of a gradual glycocalyx perturbation in the development of diabetes-related microvascular disease. As evidenced by smaller systemic glycocalyx volumes and sublingual capillary glycocalyx thicknesses, patients who have type 1 diabetes mellitus with microalbuminuria were demonstrated to exhibit more severe signs of glycocalyx degradation compared to their

normalbuminuric counterparts (Nieuwedorp et al. 2006a). A 6-hour normoinsulinemic hyperglycemic clamp in healthy subjects decreased the systemic glycocalyx volume to about 50% of that in control (Nieuwedorp et al. 2006b). The decrease in systemic glycocalyx volume could be prevented by infusion of the antioxidant *N*-acetylcysteine, which supports the hypothesis that hyperglycemia-induced overproduction of superoxide anions might be the common element in hyperglycemia-induced vascular damage (Brownlee 2001). The reduction in systemic glycocalyx volume was associated with an impaired flow-dependent dilation of the brachial artery and rapid increases in circulating levels of hyaluronan, perhaps as a result of shedding of this glycosaminoglycan from the glycocalyx into the blood. Actual glycocalyx dimensions are the ultimate result of biosynthesis of polysaccharide structures and association with blood-borne substances on one hand and shedding or release of components on the other hand (Gouverneur et al. 2006; Mulivor and Lipowsky 2004; Tarbell and Pahakis 2006). With respect to the synthesis of glycosaminoglycans, studies on isolated endothelial cells indicate a pivotal role for shear stress. Exposure to shear stress stimulates the incorporation of hyaluronan into the glycocalyx and can affect both synthesis and size distribution of sulfated glycosaminoglycans (Gouverneur

et al. 2006). On the other hand, shear stress may also contribute to the shedding, for example, during reperfusion after ischemia (Mulivor and Lipowsky 2004). Shedding is predominantly a result of the activation or release of intracellular or membrane-bound proteases or lyases (Mulivor and Lipowsky 2004), and appears to be required for leukocyte adherence to the vessel wall, because under normal conditions leukocytes are supposed to be shielded from contact with their adhesion molecules by the glycocalyx (Constantinescu et al. 2003; Mulivor and Lipowsky 2002).

• Degradation vs Agonist-induced Glycocalyx Modulation

In line with the role of the endothelial glycocalyx as determinant of perfused capillary volume, acute removal of heparan sulfate structures from the glycocalyx was originally found to result in a 14% to 21% decrease in microvascular

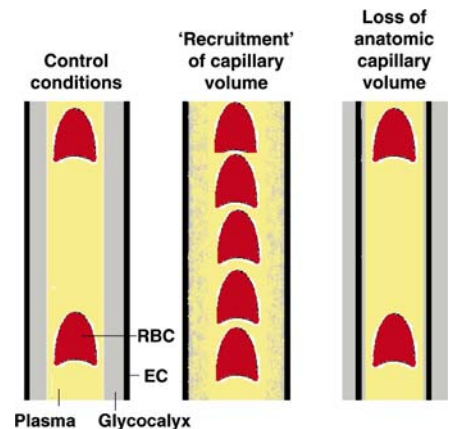


Figure 3. Schematic diagram depicting proposed relations between functionally perfused volume, glycocalyx exclusion, tube hematocrit, and anatomic diameter in capillaries in control (*left*), during agonist-induced modulation of glycocalyx (*middle*) and during pathologic loss of glycocalyx (*right*). Under control conditions, a thick blood-excluding glycocalyx lines the endothelium (EC) and causes capillary tube hematocrit to be low (*left*). Metabolic stimuli and vasoactive substances can increase functionally perfused capillary volume and capillary tube hematocrit by effectively recruiting blood-excluding glycocalyx volume (*middle*). Conditions of glycocalyx degradation are associated with reductions in anatomic capillary diameter (*right*), and it is hypothesized that fluid is translocated from the glycocalyx toward the perivascular space. The ability of metabolic stimuli and vasoactive substances to recruit glycocalyx volume is impaired under these conditions.

resistance in the vasodilated rat mesentery bed (Pries et al. 1997). Similarly, hyaluronidase treatment of the coronary bed was recently shown to result in an ~40% increase in coronary conductance during reactive hyperemia (Figure 2, left panel) (VanTeeffelen et al. 2005). On the other hand, hyaluronidase infusion has also been associated with the formation of perivascular edema and reductions in anatomic capillary diameter in isolated rat hearts (Figure 1, bottom) (Van den Berg et al. 2003), and neuraminidase administration in the rat mesentery doubled flow resistance because of the accumulation of platelets on the endothelium (Pries et al. 1997). These data suggest that, although loss of glycocalyx at first sight might appear favorable for nutrient supply and exchange, the microvascular changes associated with an impaired vascular protection ultimately prevail over the increase in perfused capillary volume.

In contrast to true degradation of glycocalyx structures by inflammatory and atherogenic stimuli, intravital microscopic observations by Duling and coworkers in the cremaster muscle suggest that metabolic stimuli and agonists can increase functionally perfused capillary volume by modulation of blood-excluding glycocalyx volume. Capillary tube hematocrit was demonstrated to be about 4-fold higher during muscle activity and adenosine superfusion compared to the resting condition (Klitzman and Duling 1979); in contrast, after treatment of the glycocalyx with heparinase, adenosine did not provoke a significant change in the already elevated capillary tube hematocrit anymore (Desjardins and Duling 1990). More recently, the same group showed a reduction in glycocalyx exclusion of anionic dextrans during superfusion of the cremaster muscle with adenosine (Platts and Duling 2004). Red blood cell exclusion was impaired to a considerably lesser extent and only at pharmacologic doses (Platts and Duling 2004). These observations have prompted us to propose a concept in which agonists such as adenosine can “recruit” capillary volume for perfusion by increasing accessibility of the glycocalyx for flowing plasma without necessarily changing the accessibility for red blood cells. This concept is depicted in Figure 3. Under control conditions (left panel), a thick blood-excluding glycocalyx lines the endothelium of capillaries and causes

tube hematocrit in these vessels to be low. During conditions of adenosine, glycocalyx accessibility for plasma flow is increased, resulting in an increase in capillary tube hematocrit and functionally perfused capillary volume (middle). According to this concept, modulation of blood-excluding glycocalyx volume might provide a mechanism by which vasoactive substances can increase functionally perfused capillary volume and surface area for exchange, in addition to vasodilation of resistance vessels.

The potency of adenosine to “recruit” glycocalyx volume in the coronary bed was recently estimated by comparing increases in coronary conductance during adenosine hyperemia and reactive hyperemia (VanTeeffelen et al. 2005). Under control conditions, adenosine was able to functionally recruit coronary microvascular glycocalyx volume and increase coronary conductance up to 40% more than reactive hyperemia (Figure 2, left panel, thick arrow). This capability was substantially lost after hyaluronidase treatment (Figure 2, right panel, thin arrow). In patients with type 1 diabetes mellitus, the loss of systemic glycocalyx volume was associated with a reduction in sublingual anatomic capillary diameter (Nieuwdorp et al. 2006a). Similar to the rapid effects of hyaluronidase infusion in nonbeating, isolated hearts (Figure 1, bottom), we hypothesize that long-term conditions of perturbed glycocalyx are associated with fluid leakage from the intravascular to extravascular space, and that this fluid shift might underlie reductions in anatomic capillary diameter and/or functional capillary density, such as found in type 1 diabetes mellitus (Kindig et al. 1998). As depicted in the right panel of Figure 3, the ability of metabolic stimuli and vasoactive substances to recruit glycocalyx volume is expected to be impaired under these conditions.

• Summary

Current evidence indicates that the endothelial glycocalyx is a dynamic layer that plays a role in vascular homeostasis throughout the circulation. Besides its traditional role in regulation of microvascular perfusion and exchange, the glycocalyx is shown to mediate shear stress-dependent NO production, to inhibit the adhesion of blood cells, and

to maintain the vascular permeability barrier. In experimental animal models, and recently also in human subjects, loss of glycocalyx has been shown during exposure to atherogenic risk factors, yet future studies are needed to determine whether invoked loss of glycocalyx increases the risk of cardiovascular disease and whether restoration of the glycocalyx can delay the progression of atherosclerosis or diabetes-associated microvascular disease. Although potential increases in perfused microvascular volume resulting from loss of glycocalyx volume seem to be counteracted by reductions in anatomic diameter, agonist-induced modulation of the glycocalyx might provide a way by which vasoactive substances can augment microvascular perfusion and exchange. This aspect seems to be overlooked at the moment, but definitely deserves further study in the future.

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TCM

NR4A Nuclear Receptors in Atherosclerosis and Vein-Graft Disease

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Nur77, Nurr1, and NOR-1 form the NR4A subfamily of the nuclear hormone receptor superfamily of transcription factors and have been described in the regulation of differentiation, proliferation, apoptosis, and survival of many different cell types. The expression of NR4A nuclear receptors in vascular pathologies has only recently been revealed, after which studies on the functional involvement of NR4A receptors in vascular disease were initiated. This review summarizes our current view on involvement of Nur77, Nurr1, and NOR-1 in atherosclerotic vascular disease and discusses NR4A function in vascular response to injury. (Trends Cardiovasc Med 2007;17:105-111) © 2007, Elsevier Inc.

• General Introduction

Atherosclerosis is a pathological process in the arterial vessel wall, which evolves over decades during human life and is characterized by the accumulation of neointimal macrophages, foam cells, and activated smooth muscle cells (SMCs). Eventually, atherosclerosis may result in local obstruction of normal blood flow and may cause diseases such as angina pectoris, myocardial infar-

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