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Itching for Answers: How Histamine Relaxes Lymphatic Vessels

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Abstract

In the current issue of *Microcirculation*, studies by Kurtz et al. [12] and Nizamutdinova et al. [18] together provide new evidence supporting a role for histamine as an endothelial-derived molecule that inhibits lymphatic muscle contraction. In particular, Nizamutdinova et al. show that the effects of flow-induced shear stress on lymphatic endothelium are mediated by both nitric oxide and histamine, since only blockade of both prevents contraction strength and frequency from being altered by flow. Separately, Kurtz et al. used confocal microscopy to determine a preferential expression of histamine receptors on the lymphatic endothelium and demonstrated that histamine applied to spontaneously contracting collecting lymphatics inhibits contractions. Previous studies disagreed on whether histamine stimulates or inhibits lymphatic contractions, but also used differing concentrations, species, and preparations. Together these new reports shed light on how histamine acts within the lymphatic vasculature, but also raise important questions about the cell type on which histamine exerts its effects and the signaling pathways involved. This editorial briefly discusses the contribution of each study and its relevance to lymphatic biology.

Keywords

lymphatic smooth muscle; spontaneous contractions; histamine; nitric oxide; shear stress

Active lymph pumping is a large component of lymph transport and is critical for interstitial fluid balance as well as immune status. The “lymph pump” in each tissue consists of a series of lymphangions—segments of a collecting lymphatic vessel flanked by one-way valves and covered by a layer of smooth muscle cells (LM) that contract spontaneously, rapidly, and synchronously [5,27]. Lymph pumps are modulated by physical factors, various hormones, and metabolites. Importantly, lymphatic pumping is inhibited during acute and chronic inflammation [14,24]. One potential mediator of lymph pump inhibition is histamine, a product of mast cell degranulation. In the blood vasculature, it is well established that histamine increases blood flow and vascular permeability in acute inflammation [3]; however, its effects on lymphatic function are not as defined. The literature paints a perplexing picture of how histamine affects lymphatic vessels, with histamine enhancing or inhibiting pump function depending on the concentration applied [20,26]. Various studies also point to a possible involvement of LECs, roles for H1 and/or H2 receptors, and an unclear role for NO—the primary endothelial-derived inhibitor of the lymphatic pump identified to date [8,20,26]. The use of lymphatic vessels from different species and tissues,

with in vivo and in vitro methods, as well as pressurized and wire-mounted vessels adds to the confusion in synthesizing the results of the various lymphatic vessel responses to histamine.

Two new papers in this issue of *Microcirculation* advance our understanding of the role of histamine in the control of lymphatic vessel pumping. Both use collecting lymphatic vessels that are isolated from the rat mesentery, cannulated, and pressurized for in vitro study. Kurtz et al. [12] studied the lymphatic response to exogenous histamine acutely after vessel isolation, at constant pressure in the absence of flow; Nizamutdinova et al. [18] placed the pressurized vessels in serum-free culture for 24 hours, permitting inhibition of HDC and histamine turnover using either a pharmacologic inhibitor or morpholino oligomers, prior to evaluation of the release of endogenous histamine as intraluminal flow was varied.

Collecting lymphatic vessels are quite sensitive to changes in shear stress [1,9,10,16,17], such that luminal flow created by the imposition of an axial pressure gradient leads to decreases in tone AMP and CF, as well as decreases in indices of net pumping calculated from these parameters. These effects of shear stress are mediated in large part by NO, produced from eNOS in LECs [2], but in some previous studies, a significant component of flow-induced lymphatic inhibition is not prevented by eNOS blockade, suggesting the contribution of another mediator. Nizamutdinova et al. [18] now present evidence that this additional mediator is histamine. Luminal flow evoked by a 5 cmH₂O pressure gradient elicited ~30% reductions in CF and AMP. In the presence of the eNOS inhibitor, L-NAME, these effects were substantially blunted but not abolished; however, they were completely abrogated with combined inhibition of eNOS and HDC (Figure 1 in Nizamutdinova et al. [18]) suggesting that the aggregate response is mediated by a combination of NO and histamine. Previous work on arteries provides strong precedent that histamine production by HDC can be modulated by shear stress [6,7]. Kurtz et al. [12] measured the lymphatic contractile response to varying concentrations of externally applied histamine and found that clear inhibition of CF and tone did not occur until histamine concentrations exceeded 10 μ M. This finding is consistent with at least one previous report that the inhibitory effects of histamine on pumping do not occur until higher concentrations are achieved [20]. In combination, these results suggest that histamine evoked by shear stress in collecting lymphatic vessels may accumulate to high local concentrations; alternatively, a higher dose of histamine may need to be added abluminally to cross the vessel wall and stimulate luminal receptors.

A number of important questions about the effects of histamine remain unresolved, but these recent studies provide several clues to their answers. On which cell type(s) does histamine act? What receptors are required? Are its effects on lymphatic muscle direct or mediated by another molecule? Using confocal analysis Nizamutdinova et al. [18] showed that HDC is present only on the endothelium (Figure 2 in [18]), whereas Kurtz et al. [12] identified H1 and H2 receptors on both LM and LECs (Figures 3, 4 in [12]), but concluded that they were primarily expressed on LECs. Both H1 and H2 receptors appear to be required as blockade of either alone abolished the inhibitory effect of histamine on CF and tone (Figure 5 in Kurtz et al. [12]). However, high concentrations of each antagonist were used, which warrant a more detailed dose–response study to help resolve the relative importance of each receptor

and the downstream second messenger pathways involved. Importantly, Kurtz et al. [12] showed that the effects of 100 μ M histamine were not blocked by eNOS inhibition, excluding NO as an intermediate signal. Other potential second messengers remain to be tested, including metabolites of arachidonic acid, which are known to be powerful modulators of lymphatic pumping [11,16,19,22]. Similar to NO, sGC appears to be a downstream target of histamine derived products (Figures 7, 8 in Kurtz et al. [12]). The differential effects of histamine on tone vs CF (Figures 6, 7 in Kurtz et al. [12]) suggest that there are multiple targets of these products on LM, e.g., ion channels controlling pacemaking and contractile proteins.

Taken together, one can speculate that shear stress induces histamine production by HDC on LECs, which then acts in an autocrine manner to stimulate the production of NO and at least one other molecule that together target sGC on LM. Alternatively, histamine released from LECs may act, along with NO, in a paracrine fashion on H receptors expressed by LM to activate sGC and downstream targets to inhibit pumping. It will be interesting to determine which of these scenarios explains the actions of histamine on lymphatic pumping in vivo.

What are the pathophysiological implications of histamine-mediated inhibition of lymphatic pumping? Mast cells are attracted by chemotactic cues to the adventitial layer of the lymphatic vessel wall, where they accumulate in relatively high density [4]. In that location, they may be poised to trigger the massive release of other vasoactive products in response to immune cell activation, analogous to enhanced NO production from iNOS after an inflammatory insult [13]. Another example may be found in models of inflammatory bowel disease, where lymphatic dysfunction may precede edema formation [25] and in which strong K_{ATP} channel activation downstream of sGC results in hyperpolarization of LM to reduce or completely inhibit lymphatic pumping [15]. Under such conditions, there may be a sufficient luminal pressure gradient for forward lymph flow that pumping becomes relatively energetically inefficient [21]. Thus, mast cell degranulation and histamine release may serve to enhance lymph transport to deliver antigen to the lymph node, similar to the enhancement in indices of lymph transport that occurs following alcohol exposure [23].

In conclusion, the two new studies in this issue of *Microcirculation* [12,18] provide new information about the role of histamine in the regulation of lymphatic pumping and raise a number of important questions related to the interaction of immune function and lymphatic transport—an exciting topic of current research.

PERSPECTIVE

Histamine is usually thought of as a component of mast cell degranulation that mediates vascular responses to inflammatory stimuli. The effects of histamine on the lymphatic vasculature have been confounded by inconsistencies between various experiments performed in the past, thus a definitive role has been elusive. The two studies discussed in this editorial show that not only does histamine inhibit lymphatic contractions that are important for pumping lymph and antigen to downstream lymph nodes, but that it can also be released by lymphatic endothelial cells to do so.

Abbreviations used:

AMP	contraction amplitude
CF	contraction frequency
eNOS	endothelial nitric oxide synthase
HDC	histidine decarboxylase
iNOS	inducible nitric oxide synthase
LECs	lymphatic endothelial cells
LM	lymphatic muscle
NO	nitric oxide
sGC	soluble guanylate cyclase

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