Shear force responsiveness of arteries depends on an interdependent activity of the epithelial Na^+ channel and the endothelial glycocalyx

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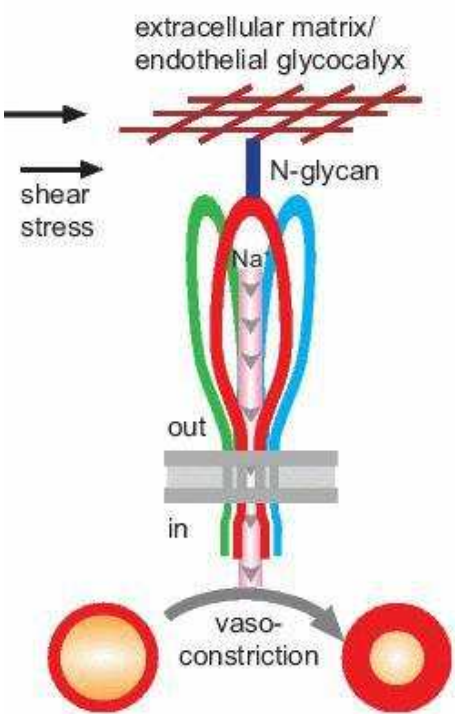
The endothelial glycocalyx (EG) is important for vascular shear stress sensation and vascular responsiveness. The mechanisms and targets for the transduction of shear stress into cellular signals are poorly understood. The epithelial Na^+ channel (ENaC) is an emerging candidate, since its activity is regulated by shear stress and there is growing evidence of ENaC expression in arteries. The aim of our work is to reveal if and how ENaC and the EG interact to mediate vascular responsiveness.

Pressure myography experiments were performed to assess shear stress responses of isolated murine arteries and electrophysiological experiments of expressed ENaC were performed to gain insights into the mechanism involved in shear stress sensation. Hyaluronidase was used to degrade hyaluronic acid (HA, an essential component of extracellular matrices) and ENaC's contribution was addressed by application of amiloride.

Mouse carotid arteries dilated in response to increased intraluminal flow/shear stress. This response was augmented by amiloride confirming ENaC's role as vasoconstrictor. Hyaluronidase mimicked the amiloride response and the subsequent amiloride application was ineffective, indicating an interdependent activity of ENaC and the EG in arteries. This observation was confirmed in *Xenopus* oocytes – hyaluronidase treatment also decreased the shear-dependent ENaC activation. Site-directed mutagenesis revealed that *N*-glycosylated asparagines of ENaC are important for SF activation, suggesting that the attached glycans provide a connection to the extracellular matrix.



These experiments confirm an interdependent activity of ENaC and the EG that mediates shear stress sensation and vascular responsiveness (Figure). The interdependent activity relies on *N*-glycosylated asparagines of ENaC. Future studies may reveal whether impaired vascular responsiveness is caused by changes of the interdependent ENaC/EG activity.