# Receptors under flow: Mechanosensitive GPCRs

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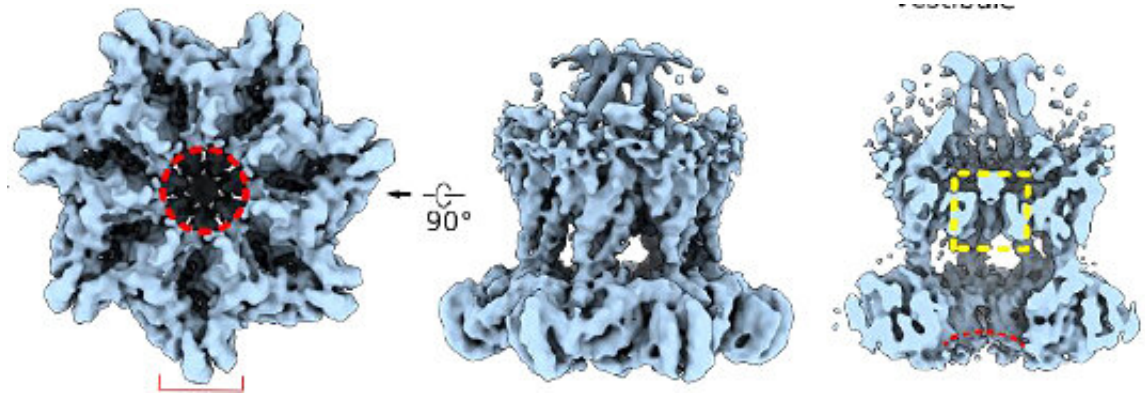


The flow of blood through the veins and arteries exerts a mechanical force on the blood-vessel wall and on the smooth musculature immediately beneath it. Credit: Ludwig Maximilian University of Munich

An LMU team has clarified how a receptor which is involved in the regulation of vital physiological processes senses the mechanical forces that act on blood vessels. The findings could suggest new therapies for diseases of the vasculature.

The flow of blood through the veins and arteries exerts a mechanical force on the blood-vessel wall and on the smooth musculature immediately beneath it. These forces also play a role in a number of crucial physiological processes, including the autoregulation of the blood supply to the various tissues in the body. Alterations in the ability of the vessel wall to respond appropriately to this shear stress also contribute to

the pathogenesis of disorders such as cardiac hypertrophy and pre-eclampsia, a condition that afflicts many women during pregnancy. Professor Michael Mederos y Schnitzler, Professor Thomas Gudermann and PD Dr. Ursula Storch at LMU's Walther Straub Institute of Pharmacology and Toxicology have now identified one of the sensor proteins involved in these processes and discovered how it responds to mechanical forces. The results of the study appear in the online journal *Nature Communications*.

Communication between cells and their environment is largely mediated by specialized receptor proteins that are embedded in the cell membrane. The family known as G-protein-coupled receptors (GPCRs) constitutes the largest class of these membrane-bound receptors. Most GPCRs serve as sensors for specific molecules (ligands). Binding of the ligand alters the protein's conformation, which initiates a response within the cell. However, some members of the group also react to mechanical stimulation. The new study focuses on a particular GPCR called the histamine H1 receptor (H1R). This protein is by far the most abundant GPCR found on the surface of the endothelial cells that line the blood vessels. "In the vasculature, this receptor is responsible for mediating the typical allergy-like reactions evoked by histamine. But we have previously shown that the protein also responds to mechanical stimuli," says Mederos.

He and his colleagues have now taken a closer look at the role of this receptor in the vascular system. Using isolated segments of the mesenteric artery of the mouse (which supplies much of the gastrointestinal tract with blood), they showed that, in the absence of histamine, H1R is indeed activated by the shear forces set up by the flow of blood over the surface of endothelial cells. Analogously to the binding of a molecular ligand, these mechanical forces activate the H1R receptor. This in turn triggers a cascade of reactions that eventually leads to dilation of the blood vessels, thus increasing the blood supply to the

tissues.

Having demonstrated that H1R mediates these physiological responses in response to shear stress, the LMU team investigated the molecular basis of the protein's mechanosensitivity. GPCRs are in part made up of helical segments that pass through the membrane and serve to connect their intra- and extracellular domains. Most GPCRs have seven of these transmembrane segments. However, H1R has eight helical domains, the last of which is intracellular. "When we removed this segment, helix 8, the mechanosensitivity of the receptor was lost," Mederos explains. "Conversely, insertion of this structural element into non-mechanosensitive receptors enabled them to react to mechanical stimuli."

The researchers therefore assume that shear stress alters the structure of helix 8. Thus, the H1R receptor is able to adopt distinct structural conformations—and trigger distinct signaling pathways—depending on whether it is activated by the binding of a chemical compound such as histamine or by mechanical forces. "Further work will be required to determine precisely how stretching of the membrane affects helix 8," says Mederos.

According to the authors, the new findings represent an important step forward. "A better understanding of the basis of mechanosensitivity will give us further insights into the origins of mechanically induced disorders, and could open up new approaches to the prevention and treatment of these diseases," Mederos concludes.

**More information:** Serap Erdogmus et al. Helix 8 is the essential structural motif of mechanosensitive GPCRs, *Nature Communications* (2019). DOI: 10.1038/s41467-019-13722-0