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Atypical Activation of Endogenous Piezo1 Channels by Shear Stress in Endothelial Cells

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Abstact: The sensing of blood flow-evoked shear stress is critical in vascular development and maintenance of a healthy vasculature in the adult [1,2]. The identity of molecules which sense and transduce this force into appropriate vascular anatomy and function is therefore keenly sought. A central question is whether there is a force sensor protein ("receptor") which directly detects the force, acting either alone or in complex with other proteins. Piezo1 channels are Ca^{2+}-permeable non-selective cationic channels which are activated by membrane stretch. These channels are important for shear stress-sensing and vascular function in embryonic and adult mice. Through whole-cell perforated patch recordings from endothelial fragments, we observed that a resting membrane potential of -43 mV was depolarized by fluid flow. When Piezo1 was conditionally deleted in endothelium the resting potential was hyperpolarized and fluid flow-evoked depolarization was absent. Outside-out patches were then excised from endothelium and found to contain constitutive single channel activity with the expected 25-pS unitary conductance of Piezo1 channels; the channel activity could be further enhanced by fluid flow and inhibited by the non-selective Piezo1 channel inhibitor, Gd^{3+}, and was absent in Piezo1 knockout mice. Furthermore, Piezo1 channels activated by shear stress in endothelial cells have unique characteristics which confer them to respond to the physiological flow. The data suggest Piezo1 channels expressed in the endothelium can be activated by shear stress in a direct and unique way which satisfies the physiological requirements.

Keywords: Shear stress; Piezo1; activation; endothelial cells.

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