Perturbation of bilayer surface tension differentially modulates mechanosensitive ion channels

N. Bavi,[1,2] C.D. Cox,[1,2] O. Bavi[3] and B. Martinac,[1,2] [1]Victor Chang Cardiac Research Institute, 405 Liverpool Street, Darlinghurst, NSW 2010, Australia, [2]St. Vincent's Clinical School, The University of New South Wales, NSW 2052, Australia and [3]Institute for Nanoscience and Nanotechnology, Sharif University of Technology, Tehran 1458889694, Iran.

The lipid composition of biological membranes modulates the activity of integral membrane proteins (Cantor, 1998; Andersen & Koeppe, 2007). This is particularly important for mechanosensitive channels, regardless of their gating paradigm. Here we use the surface active agent 2,2,2-trifluoroethanol (TFE) as a pharmacological tool to study the effect of surface tension perturbations on an array of bacterial and mammalian MS channels including MscL, Piezo1 and TREK-1. We chose TFE (a general anaesthetic) due to the fact that its effect on the bacterial channel MscS has already been studied. In particular TFE facilitates MscS activation from the periplasmic side, while it abolishes MscS current from the cytoplasmic side (Akitake *et al.*, 2007; Nomura *et al.*, 2015). Here, we demonstrate that 2 % v/v TFE can also facilitate the activation of: MscL if TFE is added to either bilayer leaflet, Piezo1 only if added to the cytoplasmic side and TREK-1 only from the extracellular side. Our molecular dynamics simulations revealed TFE increases the surface tension and the first moment of the pressure profile markedly and hence facilitates activation of MscL. Using our molecular dynamics, energetic analysis and collective experimental data, we postulate there is a close relationship between MS channel shape and its activation mechanism by surface tension perturbations. The activation curve of MscL, which is a cylindrical protein, was shifted to the left (activated easier) upon addition of TFE from either side. MscS and TREK on the other hand, which are conical, were only facilitated from the extracellular side. The activation curve of Piezo1 was also shifted to left only when TFE was added to the cytoplasmic side. Given surface active drugs are adsorbed onto cell membranes, these findings provide a mechanistic understanding of their non-specific impact on the function of different membrane proteins, particularly MS ion channels.

Akitake B, Spelbrink RE, Anishkin A, Killian JA, de Kruijff B, Sukharev S. (2007). 2,2,2-Trifluoroethanol changes the transition kinetics and subunit interactions in the small bacterial mechanosensitive channel MscS. *Biophys J* **92**, 2771-2784.

Andersen OS, Koeppe RE. (2007). Bilayer thickness and membrane protein function: an energetic perspective. *Annu Rev Biophys Biomol Struct* **36**, 107-130.

Cantor RS. (1998). The lateral pressure profile in membranes: a physical mechanism of general anesthesia. *Toxicol Lett* **100-101**, 451-458.

Nomura T, Cox CD, Bavi N, Sokabe M, Martinac B. (2015). Unidirectional incorporation of a bacterial mechanosensitive channel into liposomal membranes. *FASEB J* **29**, 4334-4345.