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Many drugs are amphiphiles that, in addition to binding to a particular target protein, adsorb to cell membrane lipid bilayers and alter intrinsic bilayer physical properties (e.g., bilayer thickness, monolayer curvature, and elastic moduli). Such changes can modulate membrane protein function by altering the energetic cost (ΔG(bilayer)) of bilayer deformations associated with protein conformational changes that involve the protein-bilayer interface. But amphiphiles have complex effects on the physical properties of lipid bilayers, meaning that the net change in ΔG(bilayer) cannot be predicted from measurements of isolated changes in such properties. Thus, the bilayer contribution to the promiscuous regulation of membrane proteins by drugs and other amphiphiles remains unknown. To overcome this problem, we use gramicidin A (gA) channels as molecular force probes to measure the net effect of amphiphiles, at concentrations often used in biological research, on the bilayer elastic response to a change in the hydrophobic length of an embedded protein. The effects of structurally diverse amphiphiles can be described by changes in a phenomenological bilayer spring constant (H-B) that summarizes the bilayer elastic properties, as sensed by a bilayer-spanning protein. Amphiphile-induced changes in H-B, measured using gA channels of a particular length, quantitatively predict changes in lifetime for channels of a different length as well as changes in the inactivation of voltage-dependent sodium channels in living cells. The use of gA channels as molecular force probes provides a tool for quantitative, predictive studies of bilayer-mediated regulation of membrane protein function by amphiphiles.

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