Cryo-EM Uncovers How Lysophosphatidic Acid (LPA) Cooperatively and Allosterically Activates the Inflammatory Pain Receptor Transient Receptor Potential Vanilloid 1 (TRPV1)

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TRPV1 is an excitatory cation channel that mediates pain sensation in primary sensory afferent neurons, including heat and inflammatory pain. Several endogenous lipid agonists, such as LPA, have shown to activate and mediate inflammatory pain via TRPV1 both in cell culture and in animal models. Therefore, understanding how these lipids bind to TRPV1 to induce an open state is important for understanding their role in the TRPV1 pain axis and for developing pharmaceutical strategies for targeting this receptor. Using single-particle cryo-EM analysis, we have been able to capture sub-saturating states of LPA binding to TRPV1 from a single sample. We determine how LPA binds stepwise to tetrameric TRPV1 in 6 distinct LPA-bound states: LPAx0, LPAx1, LPAx2 distal, LPAx2 vicinal, LPAx3, and LPAx4.

These substates show that LPA binds in a cooperative mechanism that transduces conformational changes to the adjacent monomer, rather than to the monomer in which it binds. Furthermore, we demonstrate that the binding site is at a key regulatory site were phosphoinositide lipids and drugs have shown to bind TRPV1. These data reveal new mechanistic insight into how ligands communicate open transitions throughout the TRPV1 tetramer.