Supporting Information

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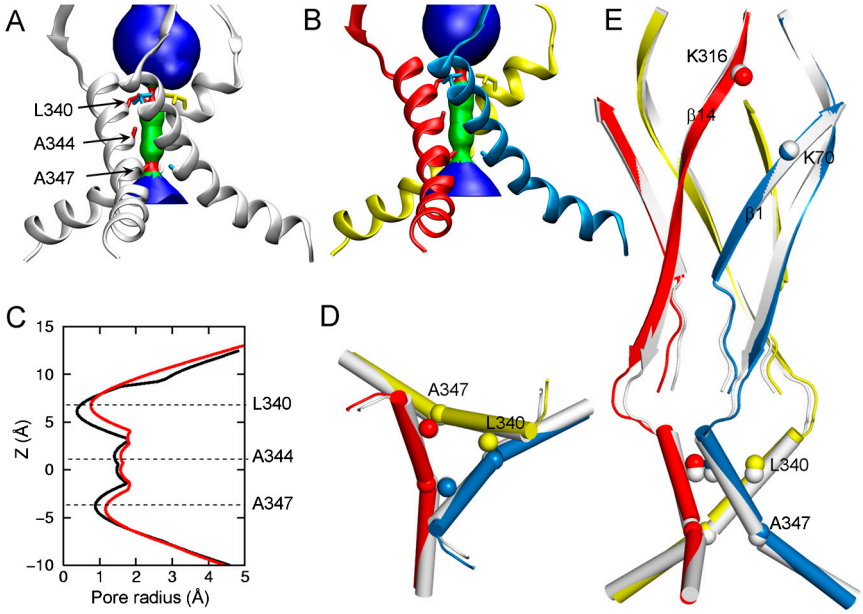

Fig. S1. Activated model generated by a second normal mode (mode 85). The five panels, (*A*)–(*E*), display the same information as in Fig. 2, except there the activated model was generated by mode 82. Note that the motional features putatively representing channel activation, as presented in the main text, are largely seen in this second mode. There are differences "tangential" to channel activation. In particular, in mode 82, the upper ends of β14 and β1 move slightly inward and outward, respectively; in mode 85, these motions reverse their directions. However, in both modes, the upper ends of β14 and β1 move toward each other, and it is this movement that is important for channel activation.

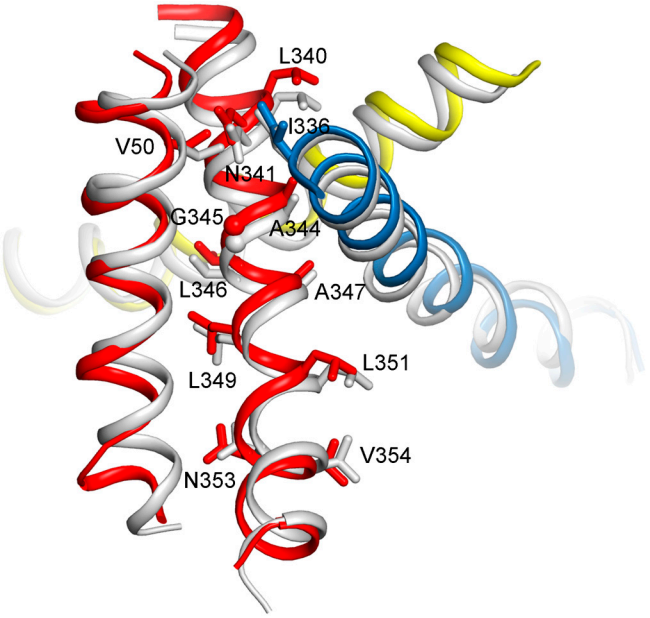

Fig. S2. Selected transmembrane domain residues in the resting (gray) and activated (red, blue, and yellow) states. Eleven of these residues have experimental data for substituted cysteine modification; I336 could cross-link with V50.

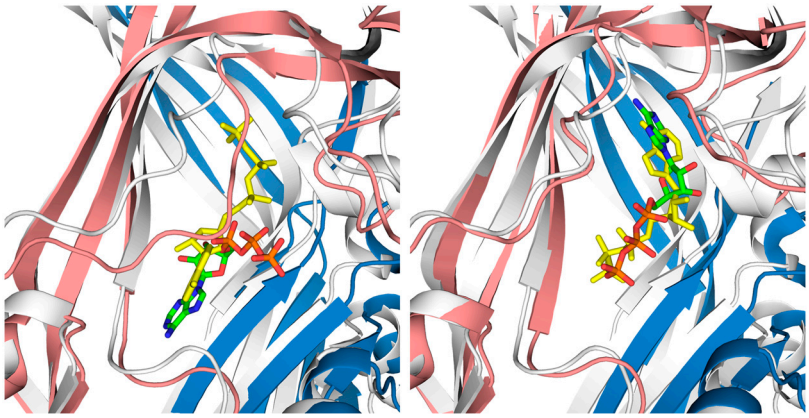

Fig. S3. Movement of ATP during molecular dynamics simulations. (*Left*) Proximal adenine. (*Right*) Distal adenine. In each case the initial ATP pose is in yellow; the final pose has C, N, O, and P atoms in green, blue, red, and orange, respectively. Two subunits of the receptor are shown in gray for the initial snapshot and in red and blue, respectively, for the final snapshot.

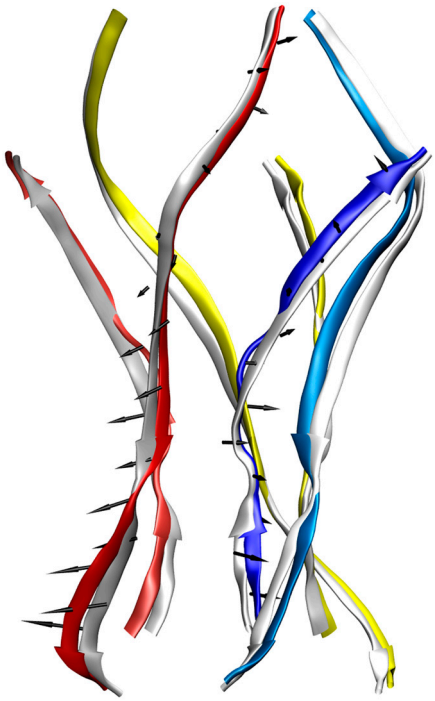

Fig. S4. Comparison of ectodomain motions leading to channel opening as suggested by the normal mode analysis and by the molecular dynamics simulations. β1 and β14 are shown in gray for the resting state and in red, blue, and yellow for the three subunits in the activated model generated by the normal mode analysis. Darker colors highlight one intersubunit β14-β1 pair. The activation motions of this β14-β1 pair in the molecular dynamics simulations are shown as arrows. Note that the arrows are largely consistent with the motional direction suggested by the normal mode analysis.

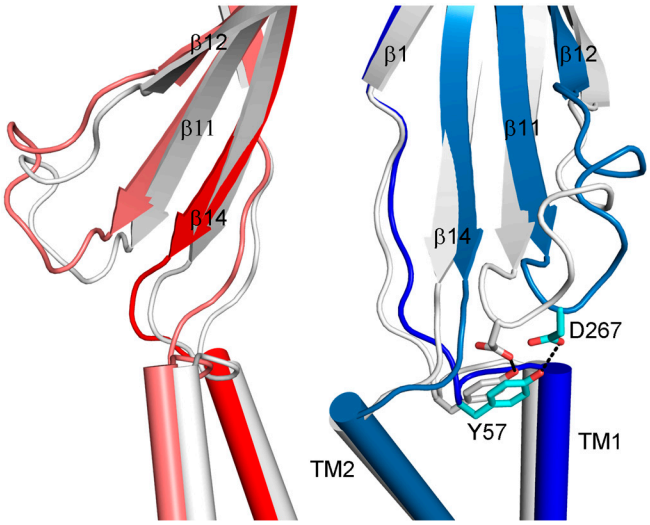

Fig. S5. Concerted motions of TM1 and TM2. Only two subunits are shown. The activated state is shown in red and blue; the resting state is shown in gray. A hydrogen bond between Y57 and D267 is preserved during activation.