

Functional roles of T3.37 and S5.46 in the activation mechanism of the dopamine D1 receptor

Hugo, Estefanía A.

Cassels, Bruce K.

Fierro, Angélica

© 2017, Springer-Verlag Berlin Heidelberg. The activation mechanism of dopamine receptors is unknown. The amino acids S5.42, S5.43, and S5.46 located in helix 5 appear to be crucial, but their specific roles in receptor activation have not been studied. We modeled the D1 dopamine receptor using the crystal structures of the D3 dopamine and β_2 adrenergic receptors. Molecular dynamics simulations show that the interaction of dopamine with the D1 receptor leads to the formation of a hydrogen-bond network with its catechol group and helices 3, 5, and 6, including water molecules. The para hydroxyl group of dopamine binds directly to S5.42 and N6.55, the latter also interacting with S5.43. Unexpectedly, S5.46 does not interact directly with the catechol; instead, it interacts through a water molecule with S5.42 and directly with T3.37. The formation of this hydrogen-bond network, part of which was previously observed in docking studies with dopamine agonists, triggers the opening of the E6.