BIOCHEMISTRY 640

(Biomembranes Discussion Group)

Wednesday, November 29, 2017

Room 4-70 Medical Sciences Building

4:00 PM

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"Molecular Understanding of Cannabinoid Receptor 1 Binding Modes"

For over 5,000 years *Cannabis sativa* has been used for medicinal and other purposes across many cultures. The cannabinoid receptor 1 (CB_1) is the major target of the psychoactive partial agonist Δ9-tetrahydrocannabinol (Δ9-THC), and the endocannabinoids anandamide (AEA) and 2-arachidonoyl glycerol (2-AG). CB_1 receptors are G-protein coupled receptors (GPCRs) abundant in neurons, where they modulate neurotransmission. The CB_1 receptor has been shown to influence memory and learning, and disease states associated with CB_1 receptors are observed in disorders ranging from addiction and anxiety disorders to motor dysfunction. CB_1 receptor function in liver and adipose tissues, vascular and cardiac tissue, reproductive tissues, and bone have also been displayed. Two agonist-bound crystal structures of human CB_1 in complex with the tetrahydrocannabinol (AM11542) and the hexahydrocannabinol (AM841) at 2.80 Å and 2.95 Å resolution respectively, are presented. These two CB_1 agonist complexes reveal conformational changes in the overall structure, such as a sizeable 53% reduction in the volume of the ligand-binding pocket and large increase in the surface area of the G-protein-binding region relative to the antagonist-bound state. A 'twin toggle switch' of Phe200 and Trp356 appears to be essential for receptor activation. These structures reveal important insights into the activation mechanism of CB_1 and provide a molecular basis for understanding the binding modes of natural, endogenous, and synthetic cannabinoids. Despite the diversity in cellular signaling by CB_1, the information presented suggests that agonists and allosteric modulators could be developed to specifically regulate unique cell type specific responses. These findings inspire the tailoring of ligands with distinct pharmacological properties to the CB_1 receptor.

Reference:
https://www.nature.com/articles/nature23272.pdf