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A Comparison of apo and Holoenzyme States of Phosphodiesterase 4D in Complex with (R)-Rolipram. J. Lomino, A. Burgin, R. Clark, D. Connor, M. Gurney, K. Hjerrild, H. Kim, R. Mishra, J. Singh, L. Stewart, E. Wallace, P. Witte, B. Staker. BioStructures Group, deCODE Genetics, 7869 NE Day Rd W. Bainbridge Island, WA 98110.

Phosphodiesterase (PDE) 4D is a type 4 cAMP specific PDE that catalyzes the hydrolysis of 3'5'-cAMP to AMP. PDEs are important enzymes involved in the regulatory control of a diverse spectrum of biological process; recent genetic studies argue that *PDE4D confers risk to ischemic stroke*. PDE4 inhibitors have been developed for the treatment of inflammatory diseases such as asthma and chronic obstructive pulmonary disease. These inhibitors have been shown to inhibit PDE4D in a conformational sensitive manner. The holoenzyme (enzyme bound to Mg^{2+}) binds to the conformational-sensitive inhibitor (R)-rolipram sixty times stronger than the apoenzyme (free enzyme). We present here a comparison of the crystal structures of (R)-rolipram bound to both the PDE4D apo- and holoenzymes. The pyrrolidone group of rolipram is partially disordered in the apoenzyme with electron density supporting a model in which the pyrrolidone group is oriented towards the empty putative Mg^{2+} binding site. The phenylmethoxy rings of rolipram are shifted one Å in the apoenzyme binding pocket. Likewise, Gln369 is shifted slightly in order to maintain two hydrogen bonds with the inhibitor. The apoenzyme crystallized in the same unit cell as the holoenzyme in space group $P2_12_12_1$ with the cell dimensions of $a=91.5$, $b=113.7$ and $c=161.3$. Four PDE molecules compose the asymmetric unit. X-ray data were collected at ALS beamline 5.0.1. to a resolution of 1.95 Å.