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Crystal Structure of Human Phosphodiesterase 3b: Atomic Basis for Substrate and Inhibitor Specificity. Scapin, G., Patel, S.B., Chung, C., Varnerin, J.P., Edmondson, S.D., Mastracchio, A., Parmee, E.R., Singh, S.B., Becker, J.W., Van der Ploeg, L.H.T., Tota, M.R. Depts. of Medicinal Chemistry and Metabolic Disorders Merck & Co., Rahway, NJ 07065, MRL San Diego Neuroscience Center, San Diego, CA 9212.

The PDE3 subfamily of phosphodiesterases consists of two closely related subtypes: PDE3A (mostly expressed in cardiac tissue, platelets and vascular smooth muscle cells) and PDE3B (prevalently expressed in hepatocytes and adipose tissue). PDE3 accommodates both cAMP and cGMP, and since the two nucleotides compete for the same catalytic site, the PDE3 family has been given the name of cGMP-inhibited PDE. PDE3 inhibitors increase lipolysis in adipocytes, and a specific PDE3B inhibitor would be a very useful tool to evaluate the effects of PDE3B inhibition on lipolysis and metabolic rate increase, and might represent a novel tool for treatment of obesity.

Although PDE3B is a membrane-associated protein, the catalytic domain can be independently expressed as a soluble, catalytically active enzyme. To facilitate the development of compounds specifically targeting the 3B isoform, we undertook structural studies of the PDE3B catalytic domain. We report here the three-dimensional structures of PDE3B in complex with a generic PDE inhibitor and a novel subtype-selective inhibitor. These structures provide insights into the enzyme's dual cAMP/cGMP affinity, and will allow for the design of more potent and selective PDE3B inhibitors.