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RIa Subunit of PKA: A cAMP-free Structure Reveals a Hydrophobic Capping Mechanism for Docking cAMP into Site B. Jian Wu, Simon Brown, Nguyen-Huu Xuong, Susan Taylor, Chemistry and Biochemistry, Univ. of California, San Diego, 9500 Gilman Dr. #0654, La Jolla, CA 92093 USA.

In eukaryotes the primary target for cAMP, a ubiquitous second messenger, is cAMP-dependent protein kinase (PKA). Understanding how binding and release of cAMP changes the cAMP-binding domains and then triggers long-range allosteric responses is an important challenge. This conformational switching requires structure solution of cAMP-binding domains in both their cAMP-bound and cAMP-free states. We describe for the first time a crystal structure of the cAMP-binding domains of the PKA Type I α regulatory subunit where site A is occupied by cGMP and site B is unoccupied. The structure reveals that the carboxyl terminus of cAMP-binding domain B serves as a hydrophobic cap to lock the cyclic nucleotide via its adenine ring into the β -barrel. In the absence of cAMP, the “cap” is released via an extension of the C-terminal helix, and exposed to solvent. This simple hinge mechanism for binding and release of cAMP also provides a mechanism for allosteric communication between sites A and B.