Tapping the translation potential of cAMP-signaling: molecular basis for selectivity in cAMP agonism and antagonism as revealed by NMR

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Eukaryotic cAMP-binding domains (CBDs) control multiple cellular functions (e.g. phosphorylation, guanine exchange and ion channel gating). Hence, the manipulation of cAMP-dependent signaling pathways has a high translational potential. However, the ubiquity of eukaryotic CBDs also poses a challenge in terms of selectivity. Before the full translational potential of cAMP-signalling can be tapped, it is critical to understand the structural basis for selective cAMP agonism and antagonism. Here, we show how recent NMR approaches developed in our laboratory [1, 2, 3] reveal that structurally homologous CBDs respond differently to several CBD ligands, i.e. cAMP-analogs and other small molecules selected through library screening. These unexpected differences arise either at the level of binding (i.e. affinity) or allostery (i.e. modulation of the auto-inhibitory equilibria). We will discuss several examples pertaining to PKA and EPAC. We will also show how the comparative NMR analyses of eukaryotic CBDs assist the development of selective CBD effectors that may serve as drug leads for the treatment of cardiovascular diseases.

