PKA: Assembly of Isoform-specific Macromolecular Signaling Complexes in the Brain

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cAMP-dependent kinase (PKA) is a tetrameric complex of two catalytic (C) subunits and a dimeric regulatory (R) subunits. The activity of the C-subunit is unleashed by cAMP binding to the R-subunits. cAMP activation is important for many neuronal functions such as synaptic plasticity, including hippocampal long term potentioation. Specificity of PKA signaling is achieved in part by the four functionally non-redundant R-subunits that are localized in close proximity to channels, transporters, and receptors as well as organelles. This specific localization is achieved through assembly of the regulatory subunits to scaffold proteins referred to as A Kinase Anchoring Proteins (AKAPs). In spite of shared domain organization the four holoenzymes show distinct quaternary structures that each define an allosterically regulated signaling complex. While structures of the individual R- and C-subunits define the catalytic and signaling properties of each protein it is only the tetrameric X-ray structure that reveals the in vivo functional signaling complex. High resolution large scale mosaic imaging of a sliced brain demonstrates the unique distribution of the isoforms within the brain while correlated light and electron microscopy methods are used to demonstrate unique sub-cellular localization to organelles such as the inner mitochondrial membrane. These diverse interdisciplinary tools are defining physiological PKA signaling as highly localized complexes that are targeted to specific sites in the cell in close proximity to other signaling molecules where activity is then regulated by cAMP and calcium, kinases and phosphatases, and cyclases and phosphatases.