cAMP Signaling

A review of the cAMP signaling system (Figure 3.23) begins with the resting state (non-signaling or basal level) of the pathway. In the resting state, a cAMP-dependent GPCR is associated with a guanyl nucleotide-binding protein, also referred to as a G-protein, on a the cytoplasmic side of the cell membrane. The G-protein is comprised of three subunits, the G_α, G_β, and G_γ subunits. In the absence of a ligand, the G_α subunit is bound to a guanosine diphosphate (GDP) molecule. When the natural ligand enters the extracellular binding site, conformational changes within the GPCR decreases its affinity for the G-protein assembly, and the G-protein assembly is released. This, in turn, initiates conformational changes in the G-protein assembly, causing it to release the GDP. At the same time, the G_α subunit separates from the G_β/G_γ complex. The G_α subunit then binds to guanosine triphosphate (GTP), and conformational changes within the G_α/GTP allow it to bind to the enzyme adenylyl cyclase. This enzyme is responsible for the conversion of adenosine-5′-triphosphate (ATP) into cAMP, the second messenger for this system. Binding of the G_α/GTP complex activates adenylyl cyclase, causing an increase in production of cAMP. Increased cAMP cellular concentrations then lead to changes in a targeted protein system. In the case of protein kinase A, cAMP binds to a regulator protein that is part of an enzyme/regulator complex that suppresses kinase activity. Binding of cAMP to the regulatory subunit, however, causes conformational changes in the regulatory protein, allowing it to disassociate from protein kinase A. Once it is released from the regulatory protein, protein kinase A becomes catalytically active, phosphorylating its substrate via an ATP-mediated pathway. Thus, ligand binding on the extracellular side of a GPCR is translated into kinase activity through a cascade of cellular signaling events.

Of course, once a signal is turned on, there needs to be a way to turn the signal off so that cellular activity can revert back to the way it was before the signal was initiated. Disassociation of the natural ligand from the binding site allows the GPCR to return to its inactive state and bind to a G-protein/GDP complex, but this will not release cAMP from the regulatory protein allowing it to suppress protein kinase A in the above example, nor will it separate the G_α/GTP complex from adenylyl cyclase, thereby halting the formation of additional cAMP. Fortunately, additional regulatory pathways exist to terminate the GPCR signal. cAMP levels, for example, are regulated by cAMP phosphodiesterase, which converts cAMP to AMP (adenosine monophosphate). Removal of cAMP by the action of cAMP phosphodiesterase, allows the regulatory protein to revert back to the configuration that suppresses protein kinase A activity, terminating the GPCR signal. Separately, the G_α protein is also a GTPase that slowly converts GTP to GDP. Once this occurs, the G_α protein is no longer able to bind to adenylyl cyclase, deactivating cAMP production and terminating the GPCR signal.