Probing the structural determinants of the cyclic nucleotide binding sites of cGMP-dependent protein kinase Iα

The major serotonin transporter, SERT, modulates the amount of serotonin in the synaptic gap via reuptake into the presynaptic neuron. Serotonin reuptake inhibitors, SSRIs, are the dominant antidepressant prescribed to treat patients with major depressive disorder (MDD). Yet, 30% of those diagnosed have found the current modes of treatment ineffective. SERT is activated by the type Iα guanosine 3',-5' cyclic monophosphate (cGMP) dependent protein kinase (PKGIα). It is proposed that regulating SERT trafficking by modulating PKG activity in neurons may provide a novel therapeutic target for disorders affected by a deficiency of serotonin in the synapse. Unfortunately, the molecular mechanisms of PKG activation are poorly understood. This is partly due to the fact that the structure of full-length wild type PKG is unknown. Recently, however, the Dostmann lab solved the crystal structure of the regulatory domain of PKGIα. This allowed for the first high-resolution structural characterization of the cGMP binding sites of this protein. Unexpectedly, this structure revealed a tightly bound adenosine 3',-5' cyclic monophosphate (cAMP) molecule to one of the cyclic nucleotide binding (CNB) domains. This challenges the accepted model that cGMP preferentially binds to, and activates PKG. To further dissect differences in cyclic nucleotide binding events, additional biochemical and biophysical studies of the regulatory domain of PKG will be probed using analogs of cGMP and cAMP. This will lead to a more complete understanding of how this enzyme is regulated by different cyclic nucleotides and thus provide new platforms for drug research and development.