BIOCHEMISTRY 640

(Biomembranes Discussion Group)

Wednesday, March 21, 2018

Room 4-70 Medical Sciences Building

4:00 PM

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"Spotlight on GPCRs: Engineering a Photoswitchable Dopamine Receptor Agonist"

G protein-coupled receptors (GPCRs) constitute the largest superfamily of membrane proteins, and lie upstream of a multitude of biological processes. Ligands of GPCRs include light-sensitive compounds, pheromones, hormones, and neurotransmitters. Ligand binding results in second messenger production through the activity of associated G proteins, and can activate multiple signal transduction pathways. Within this large protein family, GPCR subfamilies can differ in stimuli, cell-specific expression, associated G proteins, downstream effector proteins, and accessory proteins, creating a complicated and intricate system. Better understanding of the mechanisms and modes of action of the GPCR family has implications for mechanistic models of various disorders, including schizophrenia and addiction. However, due to their high prevalence, the presence of multiple GPCRs, and high degree of similarity in binding sites, classical pharmacological studies of individual receptors and their G protein partners has proved difficult. Targeting specific GPCRs, and elucidating their function and properties *in vivo,* is essential for better understanding of GPCR function and future therapeutic development.

In this study, a tethered, photoswitchable dopamine analogue was developed to produce light-gated dopamine receptors D1R and D2R. Engineered cysteine sites within these receptors enables covalent modification and tethering of a synthetic dopamine analogue, whose access to the BINDING site and thus agonist action is tightly and efficiently controlled by light. This attachment results in the ability to control distinct receptors in a receptor subtype-specific, cell-type-specific, and spatiotemporally precise manner, paving the way for highly specific investigations using *in vivo* systems.

Reference: Donthamsetti P.C., Winter N., Schonberger M., Levitz J., Stanley C., Javitch J.A., Isacoff E.Y., and Trauner D. (2017) Optical Control of Dopamine Receptors Using a Photoswitchable Tethered Inverse Agonist. J Am Chem Soc 139, 18522-18535.