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Functional Mechanisms of GPCRs and Transporters Offer Insights for Targeted Drug Design

Harel Weinstein

Dept. Physiology and Biophysics, and Institute for Computational Biomedicine, Weill Cornell Medical College, Cornell University, New York, NY, 10065

The focus of the presentation is the molecular machinery involved in cell-cell communication and intracellular signal transduction, specifically GPCRs and Na^+-coupled neurotransmitter transporters (NSS). These molecular systems are modulated by the binding of endogenous ligands and pharmaceutical agents, and the presentation will illustrate the challenges encountered in the acquisition of the structure-based information that is required to understand these processes and to design new drugs that target them. The results from our studies are obtained from a combined experimental and computational approach that includes functional analysis, data-driven simulation and experimental validation that reveals how physiological function emerges from the activity of the membrane-associated proteins. Atomistic level formalisms in structural and computational molecular biophysics are employed to understand functional mechanisms triggered by the GPCRs and NSS transporters, and their allosteric modulation by ligands and by protein-protein interactions (e.g., with PDZ and BAR domains). The computational methods used to determine the mechanistic details, to design constructs with predetermined properties, and to guide novel experimental approaches, include (i) various forms of targeted molecular dynamics, (ii) mesoscale representations of protein and membrane dynamics and of lipid reorganization driven by interactions with proteins, based on free energy minimization methods and Monte Carlo sampling; and (iii) simulation of cell signaling pathways and networks.

ILLUSTRATIVE PUBLICATIONS

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2. Beuming T., et al., - The binding sites for cocaine and dopamine in the dopamine transporter are overlapping. *Nature Neurosci. 11*: 780-789 (2008) PMID: 18568020.
3. Ericksen S.S., et al.: Ligand selectivity of D2 dopamine receptors is modulated by changes in local dynamics produced by sodium binding. *J. Pharmacol. Exp. Ther. 328*: 40-54 (2009) PMID:18849360 .
4. Chang C.W., et al.: Towards a quantitative representation of the cell signaling mechanisms of hallucinogens: Measurement and mathematical modeling of 5-HT1A and 5-HT2A receptor-mediated ERK1/2 activation. *Neuropharmacology 56*: 213–225 (2009) PMID: 18762202
5. Han Y., et al. - Allosteric communication between protomers of dopamine class A GPCR dimers modulates activation. *Nature Chem. Biol. 5*: 688-695 (2009) PMID: 19648932
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7. Thorsen T.S., et al. : Identification of a small-molecule inhibitor of the PICK1 PDZ domain that inhibits hippocampal LTP and LTD. *Proc. Natl. Acad. Sci. USA 107*: 413-418 (2010) PMID: 20018661
8. Zhao Y., et al.: Substrate-dependent proton antiport in neurotransmitter:sodium symporters. *Nature Chem. Biol. 6*: 109-116 (2010) PMID: 20081826
9. Zhao Y., et al.: Single molecule studies of the allosteric modulation of intracellular gating in a neurotransmitter transporter homolog. *Nature* 2010 – (May 13 issue).
10. Claxton D.P., et al.: Ion/substrate-dependent conformational dynamics of a bacterial homolog of neurotransmitter:sodium symporters. Nature Struct. Mol. Bio 2010 – accepted April 2010.