Chapter 17
Hallucinogen Actions on 5-HT Receptors
Reveal Distinct Mechanisms of Activation
and Signaling by G Protein-Coupled Receptors

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Abstract We review the effect of some key advances in the characterization of molecular mechanisms of signaling by G protein-coupled receptors (GPCRs) on our current understanding of mechanisms of drugs of abuse. These advances are illustrated by results from our ongoing work on the actions of hallucinogens on serotonin (5-HT) receptors. We show how a combined computational and experimental approach can reveal specific modes of receptor activation underlying the difference in properties of hallucinogens compared with nonhallucinogenic congeners. These modes of activation—that can produce distinct ligand-dependent receptor states—are identified in terms of structural motifs (SM) in molecular models of the receptors, which were shown to constitute conserved functional microdomains (FM). The role of several SM/FMs in the activation mechanism of the GPCRs is presented in detail to illustrate how this mechanism can lead to ligand-dependent modes of signaling by the receptors. Novel bioinformatics tools are described that were designed to support the quantitative mathematical modeling of ligand-specific signaling pathways activated by the 5-HT receptors targeted by hallucinogens. The approaches for mathematical modeling of signaling pathways activated by 5-HT receptors are described briefly in the context of ongoing work on detailed biochemical models of 5-HT2A, and combined 5-HT2A/5-HT1A, receptor-mediated activation of the MAPK 1,2 pathway. The continuing need for increasingly more realistic representation of signaling in dynamic compartments within the cell, endowed with spatio-temporal characteristics obtained from experiment, is emphasized. Such developments are essential for attaining a quantitative understanding of how the multiple functions of a cell are coordinated and regulated, and to evaluate the specifics of the perturbations caused by the drugs of abuse that target GPCRs.

Keywords molecular modeling, molecular dynamics simulations, membrane proteins, signaling, mathematical modeling, bioinformatics tools

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Introduction

The rapid advances in the characterization of molecular mechanisms of signaling by G protein-coupled receptors (GPCRs) have enhanced the understanding of mechanisms of drugs of abuse. In particular, the recognition that the translation of intra-receptor mechanisms of activation into intracellular signaling through protein-protein interactions can take diverse forms that are ligand–dependent, is beginning to explain the special properties exhibited by drugs of abuse targeting this type of receptors. This relation is illustrated here by recent results from our ongoing work on the actions of hallucinogens on serotonin receptors, which are members of the rhodopsin-like GPCR family. The findings are reviewed briefly in the context of broader advances in understanding GPCR signaling to clarify the effect on the emerging understanding of cellular mechanisms of the hallucinogenic drugs of abuse that target these receptors.

A very recent review of the structures, pharmacology, and neurophysiology of hallucinogens provides a thorough and thoughtful analysis of the current information and understanding regarding the mechanisms underlying hallucinogen action.1 The review illustrates as well how many of the fundamental questions regarding these mechanisms remain unanswered, despite the abundance of information available in the literature from work at all the levels accessible to physiological, pharmacological, and behavioral approaches. The understanding of the involvement of the 5-HT2 receptors targeted by the hallucinogens in these mechanisms, and the molecular and structural requirements for the function of these GPCRs in cellular signaling, are equally incomplete.

To change this situation, we have undertaken a coordinated collaborative effort that brings together experimental and computational approaches. The research effort is supported by the National Institute on Drug Abuse (Bethesda, MD) and combines quantitative computational and experimental approaches in the mechanistic investigation of hallucinogenic drug action of compounds in various structural classes including (1) indolealkylamines (eg, the hallucinogenic N,N-dimethyltryptamine); (2) ergolines (eg, D-LSD); and (3) phenylethylamines and phenylisopropylamines (eg, mescaline, DOI) (for reviews see Nichols,1 Gresch et al,2 and Aghajanian and Marek3) In the portion of this multifaceted work that is reviewed briefly below, we emphasize the information elicited from the computational modeling and simulations of mechanisms that can discriminate the actions of hallucinogens on the GPCRs in comparison to activation by nonhallucinogenic congeners. The aim of this quantitative modeling is to reveal the molecular details of the manner in which the hallucinogens trigger the mechanistically related subcellular elements that are responsible for their special properties. This type of information is tested, validated, and enhanced by the experimental component of the complete research program, and the insights are directed as well to the design of appropriate therapeutic measures.

The computational structure-function studies and simulation approaches use 3-dimensional (3-D) models of the receptor molecules and their interactions with ligands. Specific structure-based approaches have evolved for this purpose.4,5 To enable the study of downstream signaling following ligand-receptor interaction,