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EDITORIAL

# Dimerization of G-Protein-Coupled Receptors: Implications for Drug Design and Signaling

The articles in this special supplement to *Neuropsychopharmacology* are collected from research presented at a symposium entitled "Dimerization of G-Protein-Coupled Receptors: Implications for Drug Design and Signaling." They describe current research into this rapidly evolving area that the Editors thought would be of interest to members of the ACNP and other investigators. In a small overview, we wish to emphasize several important implications of this research for our readership.

At the most obvious level, we wish to indicate to the readership that the types of interactions described in these articles were only hinted at in the older literature. Most of the research that has been conducted in the G protein-coupled receptor (GPCR) area has been directed toward the identification of individual genes coding for different members of the superfamily. Many thought that diversity of subtypes would account for diversity of pharmacology and cellular response to drugs. Beyond this, how these individual receptor subtypes couple to the large group of individual heterotrimeric $G\alpha\beta\gamma$ complexes was thought to provide an even greater diversity in response. This is an active research area that is still being explored through co-expression of G proteins with individual receptor subtypes and through investigation of signaling domains with chimeric receptors. These complexities alone account for great diversity in signaling and its control, but the story does not stop here.

Studies with normal receptors have also indicated that dimerization of the GPCR can occur when GPCRs are expressed in artificial systems and studies with chimeras indicate what part of the receptors participate in these interactions. Cross-linking experiments indicate that dimerization also occurs in natural systems. The fact that individual members of the family, e.g., GABAb receptors, must exist as dimers in order to signal is something that would not have been anticipated early in the 1990s. Dimerization and its extension to other receptor subtypes, including the opiate receptors, open a whole vista of possibilities for subtle changes in the pharmacology of GPCRs that may be due to dimerized receptors that may not always signal as either a monomer or as dimers. These observations of heterogeneously dimerized opiate receptors also clear up a number of anomalies in the pharmacology of the opiates that pointed to the existence of additional opiate receptor subtypes that could not be subsequently isolated. Dimerization of one family (e.g., dopamine) of receptors with another (adenosine receptors) can lead to even greater diversity in response of a single complex to more than one transmitter.

More generally, the fact that dimerization of receptors can occur also points out the possibility that the same receptor may function differently within the same cell depending on the cellular environment and relative density of the receptors. These differences may ultimately result in subtle changes in rates of receptor desensitization, activation of different signaling cascades, multiple agonists, and heightened sensitivity to the concentration of the agonist. Whether these differences can be captured systematically in drug design remains to be seen. For example, it is quite conceivable that synthetic partial agonists affecting rates of dimerization and desensitization, different from full agonists, may be of great importance where desensitization of the response is a clinical limitation of existing drugs.

While the observations of this symposium have focused on GPCRs, such receptor-receptor interactions may be of greater generality than we might suspect. Although homo- and hetero-dimerization within the cytokine superfamily is also well-documented, other cell surface markers and adhesion molecules may also have similar types of interactions. Within the more conventional neurotransmitter signaling systems, interactions

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between members of different receptor superfamilies, such as ligand-gated (GABAa) and GPCRs (D5), while not strictly speaking dimerization, may regulate the strength of synaptic responses independent of classical second messengers (Liu et al. 2000). Most radically, receptors may signal in ways that are entirely distinct from the use of second messengers. Indeed, this type of signaling may be a general rule, rather than an isolated phenomenon. Multiple receptors and effectors may exist in tightly linked scaffolds with very controlled and stereotyped responses, rather than fluidly moving in the membrane as was initially conceptualized in the 1980s.

The post-genomic era of biological research is upon us. As the full-length sequences of genes expressed in various brain cells are identified, we can start along the path toward an understanding of how these cells develop and function. To do this, we must develop a sense of the complete set of proteins expressed by a cell at any one time — the proteome. The ultimate picture of the cell, painted by proteomics, can allow us to discover how changes in a single signaling pathway can affect other pathways and how one signaling pathway interacts with another. These cascades, starting with a GPCR, either in monomeric or dimeric form, are highly orchestrated responses mediated through a scaffold of preformed protein-protein interactions. Interactions utilizing second messengers, kinases, and phosphorylated substrates form one "more traditional" mode (slower) of signaling, while protein-protein interactions can form a non-traditional set of interactions that can occur on a timescale more reminiscent of fast ion channel modes of signaling. Certainly the variations in expression and localization from neuron to neuron, and intracellularly, can yield all shades of gray in terms of neuronal function.

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## REFERENCES

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