

Functional Selectivity and Classical Concepts of Quantitative Pharmacology

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ABSTRACT

The concept of intrinsic efficacy has been enshrined in pharmacology for half of a century, yet recent data have revealed that many ligands can differentially activate signaling pathways mediated via a single G protein-coupled receptor in a manner that challenges the traditional definition of intrinsic efficacy. Some terms for this phenomenon include functional selectivity, agonist-directed trafficking, and biased agonism. At the extreme, functionally selective ligands may be both agonists and antagonists at different functions mediated by the same receptor. Data illustrating this phenomenon are presented from serotonin, opioid, dopamine, vasopressin, and adrenergic receptor systems. A variety of mechanisms may influence this apparently ubiquitous phenomenon. It may be initiated by differences in ligand-induced intermediate conformational states, as shown for the β_2 -adrenergic receptor. Subsequent mecha-

nisms that may play a role include diversity of G proteins, scaffolding and signaling partners, and receptor oligomers. Clearly, expanded research is needed to elucidate the proximal (e.g., how functionally selective ligands cause conformational changes that initiate differential signaling), intermediate (mechanisms that translate conformation changes into differential signaling), and distal mechanisms (differential effects on target tissue or organism). Besides the heuristically interesting nature of functional selectivity, there is a clear impact on drug discovery, because this mechanism raises the possibility of selecting or designing novel ligands that differentially activate only a subset of functions of a single receptor, thereby optimizing therapeutic action. It also may be timely to revise classic concepts in quantitative pharmacology and relevant pharmacological conventions to incorporate these new concepts.