REVIEW OF CLINICAL PHARMACOLOGY AND
PHARMACOKINETICS INTERNATIONAL
EDITION 24: 74 (2010)

Appication of Classic Pharmacological Principles to Modern Drug Didcovery

Dimitri E. Grigoriadis, Ph.D.

Neurocrine Biosciences Inc., San Diego, CA 92130 USA

SUMMARY

Various pharmacological, biochemical and structural methodologies have defined specific mechanisms that have enabled the discovery of novel therapeutics in a variety of disease states. The superfamily of GPCRs (G-Protein Coupled Receptors) is the largest cell membrane-bound protein family encompassing more than 1000 different and distinct proteins. These membrane-bound proteins are responsible for translating extracellular stimuli into intracellular signals. Many decades of research have been focused on the identification of small molecules that interact with these proteins to be used as potential therapeutics in disease. While the experimental methodologies used in modern drug discovery have greatly evolved, the basic underlying pharmacological principles that these are based upon are still being utilized in our understanding of these complex cellular systems. The superfamily of GPCRs has been subdivided into 5 distinct classes. This presentation will use examples from two of these classes (Class A; GnRH and Class B; CRF_1 and CRF_2) to describe our current understanding of the discrete molecular interactions of the endogenous ligands and novel small molecules. These differences have been elucidated through a detailed examination of the binding, activation and regulation characteristics of peptide and non-peptide antagonists and will demonstrate key features of the signaling properties of these ligands that have been exploited for the discovery of unique chemical compounds. The results of these efforts over the past decade has enabled us to discover and identify small molecule drug candidates that are currently undergoing Phase 2 Clinical trials in diseases such as endometriosis (GnRH receptor antagonists), major depressive disorder (CRF_1 receptor antagonists) and acute decompensated heart failure (CRF_2 receptor agonists). These molecules all represent unique approaches in their interaction with their respective GPCRs and hold tremendous potential as novel therapeutics in the treatment of these diseases and disorders.