

## Chapter 25

# Molecular–Docking–Based Drug Design and Discovery: Rational Drug Design for the Subtype Selective GPCR Ligands

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### ABSTRACT

*Currently 30-50% of drug targets are G Protein-Coupled Receptors (GPCRs). However, the clinical use-ful drugs for targeting GPCR have been limited by the lack of subtype selectivity or efficacy, leading to undesirable side effects. To develop subtype-selective GPCR ligands with desired molecular properties, better understanding is needed of the pharmacophore elements and of the binding mechanism required for subtype selectivity. To illustrate these issues, we describe here three successful applications to un-derstand the binding mechanism associated with subtype selectivity: 5-HT<sub>2B</sub> (5-Hydroxytryptamine, 5-HT) serotonin receptor (HT<sub>2B</sub>R), H<sub>3</sub> histamine receptor (H<sub>3</sub>HR) and A<sub>3</sub> adenosine receptor (A<sub>3</sub>AR). The understanding of structure-function relationships among individual types and subtypes of GPCRs gained from such computational predictions combined with experimental validation and testing is expected the development of new highly selective and effective ligands to address such diseases while minimizing side-effects.*

### INTRODUCTION

G protein-coupled receptors (GPCRs) with >800 including 340 non-olfactory receptors are the largest superfamily in the human genome. These are customarily partitioned into 5 families: glutamate, rho-dopsin, adhesion, frizzled, and secretin (Fredriksson, Lagerstrom, Lundin, & Schioth, 2003). GPCRs regulate essential physiological processes (e.g. cellular metabolism, cell growth, secretion, immune

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defense, neurotransmission, and differentiation) through various endogenous ligands which include biogenic amines, peptides, lipids, nucleotides, and proteins, modulate (Lefkowitz, Pierce, & Luttrell, 2002). GPCRs also involves in various important cell recognition and communication processes (Ellis, 2004). Thus, GPCRs are important drug targets for all major disease areas, including neurodegenerative, psychiatric, metabolic, cardiovascular, cancer, and infectious diseases (Tang & Insel, 2005). Indeed, currently 30-50% of drug targets are GPCRs (Hopkins & Groom, 2002). The currently marked GPCR-targeting drugs with ~80 account for ~\$50 billion in annual sales, and many have annual sales > \$2 billion (Goddard III & Abrol, 2007). Identifying GPCR subtypes with specific cell and tissue has been accelerated for target evaluation, lead identification, and optimization of GPCRs. However, the clinical use as drugs for targeting GPCR have been limited by the lack of subtype selectivity or efficacy, leading to undesirable side effects.

## **BACKGROUND**

Endogenous ligands regulate multiple GPCR subtypes. Serotonin activates 15 serotonin (5-HT) receptors. With the exception of the 5-HT<sub>3</sub> receptor, a ligand-gated ion channel, all other 14 serotonin receptors are GPCRs. The 5-HT<sub>1</sub> (1A- 1F) and 5-HT<sub>5</sub> (5A, 5B) receptors decrease cellular level of cAMP through coupling with Gi/ Go protein, while 5HT<sub>4</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub> receptors increase cellular level of cAMP through coupling with Gs protein. 5-HT<sub>2</sub> (2A– 2C) receptors increase cellular level of inositol triphosphate (IP<sub>3</sub>) and diacylglycerol (DAG) through coupling with G<sub>q</sub>/ G<sub>11</sub> protein (Nichols & Nichols, 2008 ). Various biological and neurological processes were regulated through the serotonin receptors such as aggression, anxiety, appetite, cognition, learning, memory, mood, nausea, sleep, and thermoregulation. Thus, the serotonin receptors are the target of a variety of pharmaceutical drugs, including many antidepressants, antipsychotics, anorectics, antiemetics, gastroprokinetic agents, antimigraine agents, hallucinogens, and entactogens (Nichols & Nichols, 2008).

Histamine acts via four histamine receptors (HRs); H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub> and H<sub>4</sub>. Histamine has a critical role in immunomodulation and allergic diseases. Other biological activities include cell proliferation, differentiation, hematopoiesis, embryonic development, regeneration, wound healing, aminergic neurotransmission, secretion of pituitary hormones and regulation of gastrointestinal and circulatory functions (Jutel, Blaser, & Akdis, 2005). The H<sub>3</sub> and H<sub>4</sub> HRs inhibit the cellular level of cAMP through coupling with Gi/ Go protein, while the H<sub>2</sub>HR activates the cellular level of cAMP through coupling with Gs protein. The H<sub>1</sub>HR increases the cellular level of IP<sub>3</sub> and DAG through coupling with G<sub>q</sub>/ G<sub>11</sub> protein.

Adenosine binds all 4 subtypes of adenosine receptors (ARs), denoted A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub>, and A<sub>3</sub>, which coupled to G proteins. Activation of the A<sub>1</sub> and A<sub>3</sub> ARs inhibit the cellular level of cAMP via Gi/ Go protein, while the A<sub>2A</sub> and A<sub>2B</sub> ARs activate the cellular level of cAMP via Gs protein (Olah & Stiles, 1995). ARs are involved in many of the body's cytoprotective functions. Thus, ARs are important pharmacological targets in the treatment of a variety of diseases because of their key roles in controlling numerous physiological processes. For example, many therapeutic agents under development for treatment of central nervous system disorders, inflammatory diseases, asthma, kidney failure and ischemic injuries exert their effects via interactions with ARs.

To achieve high selectivity for specific GPCR subtype, an alternative approach is the development of selective allosteric modulators of the specific receptor subtypes. There are two marketed GPCR allosteric modulators, a positive allosteric modulator of the calcium sensing receptor used to treat hyperparathy-

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