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Structure and function of serotonin G protein-coupled receptors

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ABSTRACT

Serotonin receptors are prevalent throughout the nervous system and the periphery, and remain one of the most lucrative and promising drug discovery targets for disorders ranging from migraine headaches to neuropsychiatric disorders such as schizophrenia and depression. There are 14 distinct serotonin receptors, of which 13 are G protein-coupled receptors (GPCRs), which are targets for approximately 40% of the approved medicines. Recent crystallographic and biochemical evidence has provided a converging understanding of the basic structure and functional mechanics of GPCR activation. Currently, two GPCR crystal structures exist for the serotonin family, the 5-HT_{1B} and 5-HT_{2B} receptor, with the antimigraine and valvulopathic drug ergotamine bound. The first serotonin crystal structures not only provide the first evidence of serotonin receptor topography but also provide mechanistic explanations into functional selectivity or biased agonism. This review will detail the findings of these crystal structures from a molecular and mutagenesis perspective for driving rational drug design for novel therapeutics incorporating biased signaling.

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1. Introduction

Serotonin or 5-hydroxytryptamine (5-HT) remains one of the most widely studied chemical messengers. Serotonin produces a myriad of physiological effects in humans, mediated through 14 distinct receptor subtypes, of which 13 are G protein-coupled receptors (GPCRs), and one ligand-gated cation channel (Hoyer et al., 1994; Berger et al., 2009). 5-HT receptors have evolved over the course of 700-800 million years (Peroutka & Howell, 1994; Kroeze & Roth, 1998). In the human central nervous system (CNS) alone, all the serotonin receptor subtypes, with the exception of 5-HT5b, are expressed, and they are involved in the modulation of sleep-wake cycles, emesis, appetite, mood, memory, breathing (Ray et al., 2011), cognition, and many other functions (Berger et al., 2009; Meltzer & Roth, 2013). Much of the serotonin in the body, however, is not found in the CNS, rather in the gastrointestinal (GI) tract, where it causes peristalsis through either smooth muscle contraction or enteric nerve depolarization (Gershon et al., 1990). Lesser known, but historically important, serotonin is found in the blood, isolated from platelets in the serum, where it is involved in blood coagulation and vasoconstriction, a function which led to its name "sero" (from serum) and "tonin" (to induce contraction)(Rapport et al., 1948b). Not surprisingly, more than 125,000 published articles as of 2014 (pubmed search) have been published on serotonin and its receptors.

Much research regarding serotonin has been in the area of neuropsychiatric drug discovery in treatment of affective disorders, where there continues to be an extreme interest in the design of more efficacious pharmaceuticals. Drugs either targeting serotonin receptors or serotonin

Abbreviations: 5-HT, 5-hydroxytryptamine, serotonin; GPCR, G protein-coupled receptor; CNS, central nervous system; GI, gastrointestinal; IP_3, inositol triphosphate; DAG, diacylglycerol; GRK, G protein receptor kinase; LSD, lysergic acid diethylamide; ERG, ergotamine; DHE, dihydroergotamine; TM, transmembrane; EL, extracellular loop; IL, intracellular loop

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itself represent a large share of the top selling pharmaceuticals in the past decade, with more being approved for future use. This is most evident with antidepressants such as SSRIs (serotonin-selective reuptake inhibitors) dominating the drug market, with over $11 billion in sales in 2008 alone, and Cymbalta (duloxetine), a dual serotonin-norepinephrine reuptake inhibitor (SNRI), being in the top 10 drugs sold in the US in 2012 (Lindsley, 2013). Additionally, newer antipsychotics, such as aripiprazole (Abilify) and quetiapine (Seroquel), which have partial agonist activity and/or antagonist activity at serotonin receptors, were also in the top 10 drugs sold in the US. Recently, newer SNRIs are being approved by the FDA with an indication to treat depression, including the approved levomilnacipran (Fetzima), and SSRIs with direct agonist activity at the 5-HT_{1A} receptor have been approved by the FDA including vilazodone (Viibryd) and vortioxetine (Brintellix) for treatment of major depressive disorder (Celada et al., 2013). There is, however, a need for the discovery of more efficacious CNS pharmaceuticals with reduced side effects associated with off-target activity. For example, agents for Parkinson's disease, such as pergolide and bromocriptine, were discontinued in the US because of their ability to induce cardiac valve hypertrophy, which has been linked to off-target agonist action at the 5-HT_{2B} receptor (Rothman et al., 2000; Setola et al., 2003; Horvath et al., 2004; Roth, 2007).

In addition to drug selectivity, the concept of functional selectivity (Urban et al., 2007) in pharmacology has revolutionized the drug discovery process with recent findings highlighting that functionally selective β-arrestin biased drugs can show efficacy in preclinical models of schizophrenia (Allen et al., 2011), and β-arrestin biased angiotensin II type 1 compounds are currently in Phase 2 clinical trials for treatment of congestive heart failure (Soergel et al., 2013). Thus, rational drug design of newer serotonin receptor drugs incorporating ligand bias appears to be a fruitful area of drug development that potentially could be facilitated by insights into the structure and function of their respective targets.

Recently, there has been a GPCR structural "renaissance" with crystal structures from several representative receptor classes being solved, including rhodopsin (Palczewski et al., 2000), β2 adrenergic (Cherezov et al., 2007), β1 adrenergic (Warne et al., 2008), A2A adenosine (Jaakola et al., 2008), H1 histamine (Shimamura et al., 2011), D_3 dopamine (Chien et al., 2010), smoothened (Wang et al., 2013b), CXCR4 (Wu et al., 2010), sphingosine 1-phosphate (Hanson et al., 2012), protease-activated receptor 1(Zhang et al., 2012), M2 muscarinic (Haga et al., 2012), M3 muscarinic (Kruse et al., 2012), mu opiate (Manglik et al., 2012), delta opiate (Granier et al., 2012), kappa opiate (Wu et al., 2012), nociceptin/orphanin (Thompson et al., 2012), and recently the 5-HT_{1B} and 5-HT_{2B} serotonin receptors (Wacker et al., 2013; Wang et al., 2013a). These receptor crystal structures provide a wealth of structural information for the design of more receptor subtype selective agents, and also provide insights into the chemo-mechanical processes involved in GPCR activatation (Mustafi & Palczewski, 2009). Thus, GPCR structures likely will serve medicinal chemists and pharmacologists to design new functionally selective drugs as potential therapies or pharmacological tools (Kenakin & Christopoulos, 2013).

The recent publications of two serotonin receptor crystal structures in complex with ergotamine (ERG), a former antimigraine agent, has opened up two major discussions relevant to the serotonin field, which concern the molecular basis for 1) serotonin receptor subtype recognition and 2) functional selectivity. The 5-HT_{1B} crystal structure illustrates the molecular basis for the selectivity of antimigraine triptan drugs that are devoid of 5-HT_{2B} receptor off-target activity, and the 5-HT_{2B} crystal structure provides clues into the functional mechanics of a receptor in a β-arrestin biased state. These crystal structures not only further our understanding into serotonin's therapeutic and off-target effects in the current drug discovery process, but also serve to refine our understanding of GPCRs in general.

This review will be divided into two major sections. The first part will provide a background and relevance of serotonin as it relates to our current understanding of its actions in the body and in medicine, with a particular emphasis on the 5-HT_{1B} and 5-HT_{2B} receptors. The second part will focus on the structural importance of the recently published serotonin receptor crystal structures, especially as it relates to our current understanding of GPCR structure and function. The final section will suggest future areas for the development of our understanding of functional selectivity and biased agonism.

2. Historic aspects and significance

2.1. Discovery of 5-HT and 5-HT receptors

Serotonin was actually discovered independently by two laboratories, Vittorio Erspamer's lab in Rome, Italy (Erspamer & Boretti, 1950) and Irvine Page's lab at the Cleveland Clinic (Rapport et al., 1948a, 1948b). Although the action of serotonin is usually associated with CNS function, the majority of serotonin actually resides in the gastrointestinal (GI) tract, produced by enterochromaffin cells lining the lumen of the gut, where it causes increased peristaltic activity (Beleslin & Varagic, 1958). It was from the GI tract that Vittorio Erspamer first isolated serotonin in 1938, a substance that he deduced was an indole amine, which he named enteramine (Erspamer & Asero, 1952). Years later in 1948, a substance in blood serum that produced vasoconstriction was isolated by Maurice Rapport, Arda Green, and Irvine Page of the Cleveland Clinic (Rapport et al., 1947, 1948a, 1948b), which was later named serotonin ("sero" serum, "tonin" constrict). It wasn't until 1953, however, when Betty Twarog in Irvine Page's lab analyzed brain extracts using a serotonin-sensitive mollusk bioassay (Twarog & Page, 1953), an assay initially discovered by Erspamer (Erspamer & Ghiretti, 1951), that the presence of serotonin in brain extract was recognized. Interestingly, Erspamer had initially posited an indole nucleus being contained in enteramine's structure, and later Rapport determined the structure of serotonin to be 5-hydroxytryptamine (Rapport, 1949) shown in Fig. 1.

Prior to the discovery of serotonin in the 1930's, Sandoz pharmaceuticals had been marketing ergotamine, a drug that produced uterine contractions and was used to induce labor (Hofmann, 1978). Ergotamine is part of a larger class of compounds called ergolines, which includes ergopeptines like ergotamine, lysergamides like lysergic acid diethylamide (LSD), and ergoclavines, all of which retain the indole nucleus in their structures (Fig. 1). By 1938, research into other ergolines at Sandoz by the Swiss chemist, Albert Hofmann, who under Arthur Stoll, synthesized several hundred analogs of ergotamine. Albert Hofmann is often famously noted for the discovery of LSD, which serendipitously had been discovered by him via synthesizing analogs of ergotamine and changing the amide substituent into simpler alkyl chains, a subclass of ergolines usually termed lysergamides. LSD, however, did not satisfy the pharmacological profile using rat uterus contraction assays, and interest in it as an obstetric drug waned. Hofmann, however, was compelled to re-synthesize LSD in 1943 based on the diethyl substitution found in a known analeptic drug coramine (nicotinic acid diethylamide, forming the D-ring of LSD, Fig. 1), which was known to induce CNS stimulation and increased respiration. On April 16th 1943, Hofmann experienced what he thought was a "mystical" experience around his newly synthesized LSD. Thinking he may have accidently ingested a small amount, three days later on April 19th, he ingested what he thought was a small test dose, 0.25 mg or 250 μg, which today is known to be a substantial dose of LSD, and the unexpected effects were far beyond any respiratory or CNS stimulant as seen with coramine. Instead, they were "kaleidoscopic, fantastic images" and "alterations that I perceived in myself, in my inner being" (Hofmann, 1980). From that time forward, the unique and powerful psychoactive properties that LSD can evoke became widely known.