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Serotonin receptors and heart valve disease—It was meant 2B

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ABSTRACT

Carcinoid heart disease was one of the first valvular pathologies studied in molecular detail, and early research identified serotonin produced by oncogenic enterochromaffin cells as the likely culprit in causing changes in heart valve tissue. Researchers and physicians in the mid-1960s noted a connection between the use of several ergot-derived medications with structures similar to serotonin and the development of heart valve pathologies similar to those observed in carcinoid patients. The exact serotonergic target that mediated valvular pathogenesis remained a mystery for many years until similar cases were reported in patients using the popular diet drug Fen-Phen in the late 1990s. The Fen-Phen episode sparked renewed interest in serotonin-mediated valve disease, and studies led to the identification of the 5-HT_{2B} receptor as the likely molecular target leading to heart valve tissue fibrosis. Subsequent studies have identified numerous other activators of the 5-HT_{2B} receptor, and consequently, the use of many of these molecules has been linked to heart valve disease. Herein, we: review the molecular properties of the 5-HT_{2B} receptor including factors that differentiate the 5-HT_{2B} receptor from other 5-HT receptor subtypes, discuss the studies that led to the identification of the 5-HT_{2B} receptor as the mediator of heart valve disease, present current efforts to identify potential valvulopathogens by screening for 5-HT_{2B} receptor activity, and speculate on potential therapeutic benefits of 5-HT_{2B} receptor targeting.

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Contents

1. Serotonin and its receptors

1.1. Serotonin

Serotonin or 5-hydroxytryptamine (5-HT; Fig. 1) is enzymatically transformed from the essential amino acid tryptophan following hydroxylation and decarboxylation. Serotonin was discovered and isolated from serum 60 years ago (Rapport et al., 1948), and shortly after, the molecule was determined to originate from the enterochromaffin (or Kulchitsky) cells that are found throughout the gastrointestinal and bronchopulmonary system (Erspamer & Asero, 1952). High concentrations of 5-HT are found in blood platelets and enterochromaffin cells of the gut; lesser amounts are found around neurons located along the raphé nuclei of the brainstem. The human

Abbreviations: 5-HT, 5-hydroxytryptomine; AT_1R, angiotensin II type 1 receptor; CHD, carcinoid heart disease; ECM, extracellular matrix; GPCR, G protein-coupled receptor; GTP, guanosine triphosphate; HV, heart valve; HVD, heart valve disease; MAPK, mitogen activated protein kinase; MDA, 3,4-methylenedioxyamphetamine; MDMA, 3,4-methylenedioxymethamphetamine; TGF-β1, transforming growth factor-β1; VIC, valve interstitial cell.

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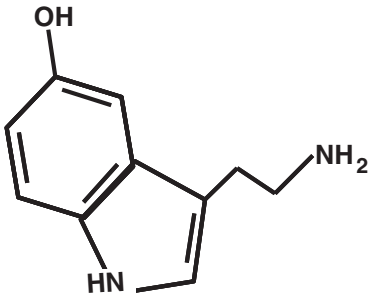

Fig. 1. Molecular structure of serotonin.

brain has evolved a sophisticated arrangement of axons stemming from the raphé nuclei to innervate nearly every brain region.

5-HT is involved in a diverse array of physiologic and biologic processes. In the brain, 5-HT has been found to affect sleep, mood, appetite, anxiety, aggression, perception, pain, and cognition (Roth et al., 1998; Edited by Roth, 2006; Berger et al., 2009). Systemically, 5-HT contributes to vascular and non-vascular smooth muscle contraction and platelet aggregation. Serotonin released from neurons is recaptured by an active reuptake pump (serotonin transporter), and is then inactivated by monoamine oxidase and converted to 5-hydroxyindoleacetic acid (Guyton & Hall, 1996). In vivo, the rate of urinary 5-hydroxyindoleacetic acid output is commonly used as an index of 5-HT metabolism.

1.2. Serotonin receptors

Signaling of 5-HT is mediated by receptors that are located on the cell membrane of neurons and most other cells in the body (Edited by Roth, 2006; Berger et al., 2009). There are six classes of G protein-coupled 5-HT receptors (5-$HT_{1,2,4,5,6,7}$) that can be subdivided into 14 unique subtypes. The 5-HT_3 receptor is unique among 5-HT receptors in that it is a ligand gated ion channel (Maricq et al., 1991; Edited by Roth, 2006). Heterotrimeric guanine nucleotide-binding protein G protein-coupled receptors (GPCRs) are well characterized and have been described extensively (Kroeze et al., 2002, 2003). Briefly, GPCRs are transmembrane proteins consisting of seven membrane-spanning α-helical segments with an extracellular N-terminus and an intracellular C-terminus. The binding of 5-HT to one of its receptors is thought to elicit a conformational change that activates associated heterotrimeric G proteins and recruits other downstream signaling/scaffolding molecules, such as GPCR kinases and β-arrestins (Armbruster & Roth, 2005; Allen & Roth, 2010). Upon activation by an agonist-occupied GPCR, G proteins release guanosine diphosphate, which is constitutively bound to the α subunit of the heterotrimer, and bind guanosine triphosphate (GTP). Binding of GTP to the α subunit causes it to dissociate from the βγ subunits (which remain associated to each other); free Gα then interacts with nearby, downstream effectors (e.g., adenylate cyclase for Gαs/olf- and Gαi/o/z-types or phospholipase C for Gαq/11-types), generating second messengers (e.g., cAMP produced by adenylate cyclase or inositol 1,4,5-trisphosphate and diacylglycerol produced by phospholipase C) that modulate downstream effectors inside the cell (e.g., protein kinases A and C activated by cAMP and diacylglycerol) [see Raymond et al., 2001 for review of 5-HT signaling pathways].

Because of the systemic presence of 5-HT and the multitude of receptor types found throughout the body that can elicit a myriad of cellular responses, drugs targeting 5-HT receptors are effective treatments for a variety of conditions. Each 5-HT receptor subtype contains at least one important therapeutic target. For instance, antimigraine medications (e.g., ergotamine and sumatriptan) activate 5-$HT_{1B/D}$ receptors. Clinically effective antipsychotics block the activation of 5-HT_{2A}, 5-HT_{2C} (Roth et al., 1992), 5-HT_6 (Roth et al., 1994), and 5-HT_7 (Roth et al., 1994; Abbas et al., 2009) receptors [see Roth & Xia, 2004 for review]. Antagonism of 5-HT_6 receptors has been postulated to enhance memory and learning in healthy individuals (Lindner et al., 2003). There are many pharmaceuticals used to target the multitude of serotonergic GPCRs; however the 5-HT_2 receptors are among the most frequently targeted, highlighting their important role in physiological and pathophysiological processes see [Roth, 2011 for recent review].

1.3. 5-HT_2 receptors

The 5-HT_2 family consists of three GPCRs: 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}. 5-HT induces an increase in inositol 1,4,5-trisphosphate (which leads to release of intracellular calcium stores and diacylglycerol production, Conn & Sanders-Bush, 1984; Roth et al., 1984; Kursar et al., 1994). In addition to these known signaling mechanisms, 5-HT_2 receptors also generate second messenger signaling that leads to cell-type specific responses depending on the organ under consideration. Some of the most notable effects of 5-HT_2 receptor-preferring drugs involve the brain, and these activities are exploited therapeutically. Two important, common examples are atypical antipsychotics and anorexigens. These drugs—and/or their metabolites—display activity at 5-HT_{2A} (viz: atypical antipsychotics are inverse agonists) (Meltzer et al., 1989; Weiner et al., 2001) and 5-HT_{2C} receptors (anorexigens and putative atypical antipsychotic drugs are agonists) (Kozikowski et al., 2010). 5-HT_{2A} and 5-HT_{2C} receptors are highly abundant in various human brain regions with 5-HT_{2A} being highly concentrated in cortical regions and 5-HT_{2C} more broadly distributed (Pazos et al., 1985; Abramowski et al., 1995). The 5-HT_{2B} receptor subtype displays a lower expression in the brain (Kursar et al., 1994), and thus, it plays a lesser role in the effects of psychoactive agents. Nevertheless, recent genetic and pharmacologic studies have implicated 5-HT_{2B} receptors in the biological activities of the recreational psychostimulant 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) (Doly et al., 2008; Doly et al., 2009) and the anorexigen fenfluramine (Banas et al., 2011).

The putative cardiovascular action of the 5-HT_{2A} and 5-HT_{2B} receptors may be similar. Both of these receptors have been shown to elicit mitogenic and secretory responses in ventricular and heart valve fibroblasts (Xu et al., 2002; Setola et al., 2003; Jaffre et al., 2004; Yabanoglu et al., 2009), indicating a possible role for each in cardiac development and disease. An issue in isolating functional differences between the 5-HT_2 receptors has been the lack of specificity in pharmacological agents used to target the receptors. In fact, many clinically used agents, particularly antipsychotics and anorexigens, display some activity at all three 5-HT_2 receptor subtypes. One reason for low selectivity among 5-HT_2 receptor-active compounds is the high degree of amino acid sequence homology among the three subtypes (Roth et al., 1998; Barnes & Sharp, 1999) with a structural similarity of 45–50% between the receptors (Pytliak et al., 2010). This homology is of significant consequence as drugs intended for the 5-HT_{2A} or 5-HT_{2C} receptors located in the brain may also bind to the 5-HT_{2B} receptors expressed in the brain or in other tissues. Therefore, special attention should be given to differential properties of these receptor subtypes to identify functional differences and enhance understanding of target specificity.

In 2005, we examined non-conserved residues in the transmembrane helices of the 5-HT_2 receptors to identify ones that might participate in the preferential binding of (+)-norfenfluramine to 5-HT_{2B} receptors. We generated a series of 5-HT_{2B} receptor point mutants that contained one 5-HT_{2A}- and/or 5-HT_{2C}-like putative ligand binding residue, and we determined whether any of the point mutations affected (+)-norfenfluramine binding affinity. Mutation of a valine in TM2, V2.53, to leucine (the analogous residue in the 5-HT_{2A} receptor), caused a 17-fold decrease in the K_i of (+)-norfenfluramine. Residue 2.53 in the 5-HT_{2C} receptor is also a valine, and the V2.53L point mutation caused a 12-fold decrease in the K_i of (+)-norfenfluramine. The

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