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Editorial Open Access

Should We Assess the Effects of Investigational New Drugs on the Cardiovascular Relevant Serotonergic System?

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Editorial

Although serotonin (5-hydroxytryptamine, 5-HT) deficiency involves the neuroendocrine processes in the CNS, a growing body of evidence suggests that altered levels of 5-HT affects cardiovascular diseases. The complexity of effects that 5-HT has on the cardiovascular system is due to a broad tissue distribution of 5-HT receptors, which includes cardiomyocytes, pulmonary system, and vascular smooth muscle. Activation of distinct 5-HT receptors enhances the secretion of renin, the rate- limiting enzyme of the renin-angiotensin-system (RAS), suggesting that 5-HT may have a role in endothelium function under pathophysiological conditions. Several classes of drugs alter micro vascular contraction response to serotonin. Genetic evidence indicates that serotonin receptors are intimately involved in the control of cardiovascular homeostasis and complex regulation of cardiac structure and function. Emerging clinical evidence also suggests that serotonin reuptake inhibitors may be beneficial in secondary prevention of cardiovascular events. Additionally, serotonin deficiency is associated with incident cardiovascular disease, whereas normal levels of 5-HT tends to exert beneficial cardiovascular protective effects. Circulatory 5-HT decreases the risk of cardiomyopathy and 5-HT deficiency may adversely influence the cardiovascular system. However, it is not known whether correction of serotonin deficiency could contribute to the prevention of cardiovascular disease. More detailed insights are needed into the complex mechanisms of 5-HT in pathophysiologic mechanisms, such as inflammation, autonomic nervous system dysfunction, cardiac arrhythmias, renal dysfunction, and altered platelet function.

Introduction

Serotoninergic system (an amine system) is of importance both in sensory input and in behavioral output. The significance of serotonin-platelet, serotonin-endothelium, and serotonin-smooth muscle interactions as part of both coagulation and cardiovascular processes has been recognized for over a decade [1]. Thus, the serotonergic system's activity cannot be entirely ignored in the cardiovascular system, as previously suggested [2].

Whereas the mechanistic complexity of serotonin receptor functions varies considerably from receptor class to receptor class, it appears the underlying principles that dictate the cross-talk among the cardiovascular, endocrine (i.e., enteric) and nervous systems are the same. As such, several research directions are evident where the serotonergic system may likely be involved in either the beneficial or adverse effects of investigational new drugs (IND). Consequently, the mechanism of activation of the peripheral serotonin receptors in the cardiovascular system is a subject of considerable interest. To appreciate many of the mechanistic issues related to the serotonergic system and understand the significance of revisiting this system in relation to the cardiovascular system, it is useful to briefly elucidate cardiovascular effects of the serotonin receptors (Figure 1).

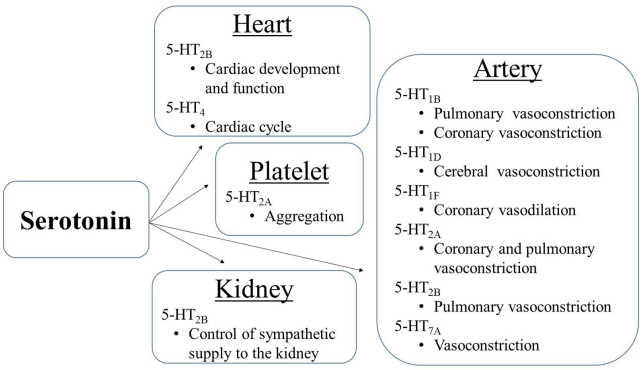

Figure 1: Putative physiological relevance of serotonin receptors in cardiovascular system. 5-HT: 5-hydroxtryptamine

The serotonergic system is composed of seven tissue nonspecific serotonin (5-hydroxytryptamine (5-HT)) receptor classes, denoted as 5-HT_1 through 5-HT_7, of which 5-HT_1, 5-HT_2, 5-HT_4, and 5-HT_7 have established cardiovascular involvement [3,4]. The serotonin receptor classes are further divided into subtypes based on differences in molecular structure, messenger coupling pathways and pharmacological responses, with 27 currently defined subtypes [3]. Of these seven classes all are G-protein-coupled receptors (GPCRs), with the exception of 5-HT_3 which is a ligand-gated cation-selective channel. The six serotonin GPCRs are characterized by the type of G-proteins they predominantly couple to when inducing signal transduction. Canonical G-protein signaling pathways can be used to broadly categorize the serotonin receptor classes, specifically: 5-HT_1 and 5-HT_5 primarily couple $G\alpha_i$, 5-HT_2 primarily couple $G\alpha_{q/11}$, and 5-HT_4, 5-HT_6, and 5-HT_7 primarily couple $G\alpha_s$ [5-8].

The 5-HT_1 class is divided into five receptor subtypes consisting of 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5- HT_{1E}, 5-HT_{1F}. Subtype 5-HT_{1C} was re-assigned as the 5-HT2C subtype following observed predominate $G\alpha_{q/11}$ functional coupling [7]. The 5-HT_1 class prominently couples to

$G\alpha_i$-proteins and generally inhibits adenylyl cyclase resulting in decreased conversion of ATP to cyclic AMP (cAMP) [9].

5-HT_{1A} couples to a broad range of secondary messengers (for overview and primary literature refer to Nichols and Nichols 2008) [8] and likely has diverse physiological roles. It is also, perhaps, the most extensively disseminated 5-HT receptor, with localization throughout the myenteric plexus, gastrointestinal tract, and central nervous system (CNS). There is currently no compelling evidence for 5- HT_{1A} receptor localization in either the blood vessels or the heart tissue [10]. However, there is continuing research towards the clinical enhancement of selective serotonin reuptake inhibitors (SSRIs) by co-administration of 5-HT_{1A} antagonists [11,12].

5-HT_{1B} receptors are widely distributed throughout both the cardiovascular system as well as the CNS. In the cardiovascular system 5-HT_{1B} receptors have been found localized in both endothelial cells and smooth muscle cells in both coronary arteries and pulmonary arteries (Figure 1) [7,11]. Additionally there is a prevalence of 5-HT_{1B} receptors in cerebral arteries which have been implicated in migraine pathogenesis and studied for therapeutic targeting by clinical 5-HT_{1B} agonists such as triptans [13].

5-HT_{1D} receptors share approximately a 63% structural homology with 5-HT_{1B}, but have a much lower expression and tissue distribution, being predominately located in the neural tissues [11]. Due to this low expression/dissemination the clinical significance is poorly understood. However, because of the high binding site similarities between 5-HT_{1D} and 5-HT_{1B} receptors there is often ligand-binding cross- affinity between the two receptors [9]. In particular, there is interest in the development 5-HT_{1D} specific agonists as use of many triptans in treatment of migraines target both 5-HT_{1D} and 5-HT_{1B} receptors, with the potential for 5-HT_{1B}-induced carotid vasoconstrictive side-effects which limits the utility of triptans in patients at risk for cerebrovascular or coronary disease (Figure 1) [14-16].

The final 5-HT_1 receptor subtype is 5-HT_{1F}, which shares a high degree of homology (approximately 70%) with the 5-HT1E subtype, has been found expressed in several areas of the brain and in coronary arteries [11,17,18]. Several studies have indicated that 5-HT_{1F} selective agonists are limited, or even devoid of, vasoconstrictor properties and may possess utility as clinical therapeutics for the treatment of migraines with reduced vasoconstrictive liabilities [17,19]. Correspondingly, the clinically relevant 5-HT_{1F} subtype-selective agonist LY334370 has been shown to be therapeutically effective while devoid of the negative coronary vasoconstriction observed in many 5-HT_{1B} agonists [9].

5-HT_2 class receptors have received the greatest attention due to their involvement in control of blood pressure and thrombocyte aggregation [20]. This class of receptor is also subdivided. 5-HT_{2A} receptors are widely distributed throughout the central and peripheral tissues. This receptor subtype plays a central role in cognitive processes; however, it also has roles in cardiovascular processes [9]. 5-HT_{2A} is expressed in both coronary and pulmonary arteries, mediating smooth muscle contraction and is involved in platelet aggregation [10,21]. 5-HT_{2A} antagonists have been shown to lower blood pressure and this subtype is being targeted for the development of clinically efficacious anti-hypertensive agents with reduced adrenergic side-effects [22].

5-HT_{2B} receptors have been observed to be expressed in high levels in liver, kidney, and throughout the CNS [7,23]. However, it is the expression of 5-HT_{2B} in heart valves that largely defines the clinical importance of this subtype [24,25]. The significance of this subtype was discovered in the early 1990's following a surge in patients exhibiting abnormal echocardiograms and cardiac valvulopathies, this was eventually correlated to off-target effects of fenfluramine at the 5-HT_{2B} receptors (Figure 1) [7]. Since then, the established negative cardiovascular effects exerted through this subtype, including cardiac hypertrophy and pulmonary hypertension, in addition to valvulopathies, have made this an important receptor at which to avoid pharmaceutical interactions with [24,25].

The 5-HT_4 class has at least eight different isoforms that have been detected, 5-HT_{4A}, 5-HT_{4B}, 5- HT_{4C}, 5-HT_{4D}, 5-HT_{4E}, 5-HT_{4F}, 5-HT_{4G}, and 5-HT_{4H}. However, due to the high level of homology between these splice variants any physiological differences remain unknown as they possess similar pharmacological responses [26]. Furthermore 5-HT_4 is another example of the G-protein coupling promiscuity observed with the serotonin receptors as 5-HT_4 has also been observed to couple $G\alpha_i$/O-proteins in addition to the expected Gαs-proteins [26]. 5-HT_4 receptors have been found localized in both the CNS and peripheral tissues [27]. However, the cardiovascular relevance of this receptor class is clear as it is expressed in all four chambers of the heart and has been shown to have involvement with the induction of arrhythmias [22,28].

The final serotonin class is 5-HT_7, of which three isoforms have been identified in humans: 5-HT_{7A}, 5-HT_{7B}, and 5-HT_{7D} [29,30]. However, due to the high level of homology between these splice variants the physiological significance of these different subtypes remains unknown as they possess similar pharmacological responses due to the lack of subtype selective agonistic ligands. 5-HT_7 receptors have been found expressed in CNS and cardiovascular tissues, in particular vascular smooth muscles and coronary arteries [31]. This cardiovascular presence has led to the idea that this receptor class may be a putative target for the treatment of migraines [32,33].

Much remains to be discovered before a complete picture of the physiological roles of the serotonergic system are elucidated. However, it is now appreciated that the serotonin receptors play significant physiological and pathophysiological roles in the tissue within the cardiovascular system [34]. Acute exposure to serotonin is associated with tachycardia and increased atrial contractility, whereas chronic exposure to serotonin can contribute to pulmonary hypertension via 5-HT_{1B} and proliferative 5- HT_{2B} receptors [10]. Activation of 5-HT_4 receptors increases heart rate in humans [1]. Evidence indicates that hyperactive platelet 5-HT_{2A} receptors and mutated 5-HT_{2B} receptors contribute to increased risk of thromboembolic events in patients with cardiovascular disease and cardiomyopathy respectively [35,36]. Tryptophan hydroxylase knockout mice display a dilated cardiomyopathy [37], highlighting reduced serotonin as a potential risk of developing heart disease. In addition, downregulation of serotonin transporter receptors in the periphery is implicated in increased risk of thromboembolic event among patients with cardiovascular disease [36]. Recent evidence suggests that there is cross-talk between beta-adrenergic and serotoninergic receptor pathways in the femoral artery [38]. The transient beta-adrenergic-serotoninergic receptor interaction and serotonin-induced transforming growth factor beta 1 (TGF-β1) activity [39] are clearly relevant to tissues within the cardiovascular system in clinical situation and require further study in this regard.

The implication in these observations on the serotonergic system is that serotonin has a vital effect on various tissues within the

cardiovascular system. Serotonin subtypes and serotonin transporter are diffusely distributed throughout the cardiovascular system. Subtle changes in the serotonergic system due to the presence of pharmacological agents may have pronounced physiological effects [40]. In vivo studies have shown pharmacological agents acting on serotonin-mediated pathways have resulted in numerous significant cardiovascular adverse effects. Select serotonin reuptake inhibitors influence both bleeding time and shear-induced platelet aggregation and thrombus propagation [41,42]. It has been proposed that an imbalance between serotonin interaction with serotonin receptors and the serotonin transporter may lead to the pathogenesis of the cardiac effects of serotonin [43]. Therefore, it is important to assess the effects of investigational new drugs against the cardiovascular relevant components of the serotonergic system during drug discovery and development so that the resulting clinical profile can be optimized early in the process.

The components of the serotonergic system represent an intricately regulated system that affect a variety of biological and behavioral functions. This system has been found to be influenced by a diverse array of compounds and pharmacological agents. The pattern that emerges from the studies of pharmacological agents that serve as stimulants, appetite suppressants, antidepressants and others, however, is that many of these compounds have surprisingly inherent serotonergic-modulatory capacity [44-48]. Perhaps even more important is the fact that these structurally diverse compounds can directly affect distinct tissues within the cardiovascular system. This should encourage health care providers, scientists and researchers involved in the development of new drugs to evaluate the effect of investigational new drugs on the serotonergic system. The task ahead is three-fold: 1) Re-evaluation of the clinical utility index of emerging drugs: 2) Development of effective high-throughput screening assays designed to identify molecules that may influence the serotonergic system: 3) Preclinical investigations into optimizing the selectivity of emerging compounds while minimizing, or eliminating, their potential interactions with peripheral serotonergic systems. These objectives are critical because they may provide a methodology to minimize, or avoid, adverse effects of investigational new drugs so often observed during Phase I clinical trials.

References

1. Villalon CM, Centurion D (2007) Cardiovascular responses produced by 5-hydroxytriptamine:a pharmacological update on the receptors/mechanisms involved and therapeutic implications. Naunyn Schmiedebergs Arch Pharmacol 376: 45-63.
2. Ramage AG, Villalón CM (2008) 5-hydroxytryptamine and cardiovascular regulation. Trends Pharmacol Sci 29: 472-481.
3. Kitson SL (2007) 5-hydroxytryptamine (5-HT) receptor ligands. Curr Pharm Des 13: 2621-2637.
4. Watts SW, Davis RP (2011) 5-hydroxtryptamine receptors in systemic hypertension: an arterial focus. Cardiovasc Ther 29: 54-67.
5. Gellynck E, Heyninck K, Andressen KW, Haegeman G, Levy FO, et al. (2013) The serotonin 5-HT7 receptors: two decades of research. Exp Brain Res 230: 555-568.
6. Neves SR, Ram PT, Iyengar R (2002) G protein pathways. Science 296: 1636-1639.
7. McCorvy JD, Roth BL (2015) Structure and function of serotonin G protein-coupled receptors. Pharmacol Ther 150: 129-142.
8. Raymond JR, Mukhin YV, Gelasco A, Turner J, Collinsworth G, et al. (2001) Multiplicity of mechanisms of serotonin receptor signal transduction. Pharmacol Ther 92: 179-212.
9. Nichols DE, Nichols CD (2008) Serotonin receptors. Chem Rev 108: 1614-1641.
10. Kaumann AJ, Levy FO (2006) 5-hydroxytryptamine receptors in the human cardiovascular system. Pharmacol Ther 111: 674-706.
11. Pytliak M, Vargova V, Mecharova V, Felšöci M (2011) Serotonin receptors - from molecular biology to clinical applications. Physiol Res 60: 15-25.
12. Portella MJ, de Diego-Adeliño J, Ballesteros J, Puigdemont D, Oller S, et al. (2011) Can we really accelerate and enhance the selective serotonin reuptake inhibitor antidepressant effect? A randomized clinical trial and a meta-analysis of pindolol in nonresistant depression. J Clin Psychiatry 72: 962-969.
13. Hall GC, Brown MM, Mo J, MacRae KD (2004) Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. Neurology 62: 563-568.
14. Mehrotra S, Gupta S, Chan KY, Villalón CM, Centurión D, et al. (2008) Current and prospective pharmacological targets in relation to antimigraine action. Naunyn Schmiedebergs Arch Pharmacol 378: 371-394.
15. Goadsby PJ, Lipton RB, Ferrari MD (2002) Migraine--current understanding and treatment. N Engl J Med 346: 257-270.
16. Goadsby PJ, Lipton RB, Ferrari MD (2002) Migraine--current understanding and treatment. N Engl J Med 346: 257-270.
17. Nilsson T, Longmore J, Shaw D, Pantev E, Bard JA, et al. (1999) Characterisation of 5-HT receptors in human coronary arteries by molecular and pharmacological techniques.Eur J Pharmacol 372: 49-56.
18. Adham N, Bard JA, Zgombick JM, Durkin MM, Kucharewicz S, et al. (1997) Cloning and characterization of the guinea pig 5-HT1F receptor subtype: a comparison of the pharmacological profile to the human species homolog. Neuropharmacology 36: 569-576.
19. Johnson KW, Schaus JM, Durkin MM, Audia JE, Kaldor SW, et al. (1997) 5-HT1F receptor agonists inhibit neurogenic dural inflammation in guinea pigs. Neuroreport 8: 2237-2240.
20. Aurup P, Højberg S (1990) [Serotonin and cardiovascular control]. Ugeskr Laeger 152: 2840-2843.
21. Saini HK, Takeda N, Goyal RK, Kumamoto H, Arneja AS, et al. (2004) Therapeutic potentials of sarpogrelate in cardiovascular disease. Cardiovasc Drug Rev 22: 27-54.
22. Kaumann AJ, Lynham JA, Brown AM (1996) Comparison of the densities of 5-HT4 receptors, beta 1- and beta 2-adrenoceptors in human atrium: functional implications.Naunyn Schmiedebergs Arch Pharmacol 353: 592-595.
23. Kursar JD, Nelson DL, Wainscott DB, Baez M (1994) Molecular cloning, functional expression, and mRNA tissue distribution of the human 5-hydroxytryptamine2B receptor.Mol Pharmacol 46: 227-234.
24. Nebigil CG, Choi DS, Dierich A, Hickel P, Le Meur M, et al. (2000) Serotonin 2B receptor is required for heart development. Proc Natl Acad Sci U S A 97: 9508-9513.
25. Nebigil CG, Etienne N, Messaddeq N, Maroteaux L (2003) Serotonin is a novel survival factor of cardiomyocytes: mitochondria as a target of 5-HT2B receptor signaling. FASEB J 17: 1373-1375.
26. Pindon A, van Hecke G, van Gompel P, Lesage AS, Leysen JE, et al. (2002) Differences in signal transduction of two 5-HT4 receptor splice variants: compound specificity and dual coupling with Galphas- and Galphai/o-proteins. Mol Pharmacol 61: 85-96.
27. Brattelid T, Kvingedal AM, Krobert KA, Andressen KW, Bach T, et al. (2004) Cloning, pharmacological characterisation and tissue distribution of a novel 5-HT4 receptor splice variant, 5-HT4(i). Naunyn Schmiedebergs Arch Pharmacol 369: 616-628.
28. Bach T, Syversveen T, Kvingedal AM, Krobert KA, Brattelid T, et al. (2001) 5HT4(a) and 5-HT4(b) receptors have nearly identical pharmacology and are both expressed in human atrium and ventricle. Naunyn Schmiedebergs Arch Pharmacol 363: 146-160.
29. Mahé C, Bernhard M, Bobirnac I, Keser C, Loetscher E, et al. (2004) Functional expression of the serotonin 5-HT7 receptor in human glioblastoma cell lines.Br J Pharmacol 143: 404-410.

30. Heidmann DE, Metcalf MA, Kohen R, Hamblin MW (1997) Four 5-hydroxytryptamine7 (5-HT7) receptor isoforms in human and rat produced by alternative splicing: species differences due to altered intron-exon organization. J Neurochem 68: 1372-1381.
31. Bard JA, Zgombick J, Adham N, Vaysse P, Branchek TA, et al. (1993) Cloning of a novel human serotonin receptor (5-HT7) positively linked to adenylate cyclase. J Biol Chem 268: 23422-23426.
32. Saakov BA, Khoruzhaia TA, Bardakhch'ian EA (1977) [Ultrastructural mechanisms of serotonin demyelination]. Biull Eksp Biol Med 83: 606-610.
33. Hedlund PB, Sutcliffe JG (2004) Functional, molecular and pharmacological advances in 5-HT7 receptor research. Trends Pharmacol Sci 25: 481-486.
34. Brudeli B, Moltzau LR, Andressen KW, Krobert KA, Klaveness J, et al. (2010) Synthesis and pharmacological properties of novel hydrophilic 5-HT4 receptor antagonists. Bioorg Med Chem 18: 8600-8613.
35. Nebigil CG, Hickel P, Messaddeq N, Vonesch JL, Douchet MP, et al. (2001) Ablation of serotonin 5-HT(2B) receptors in mice leads to abnormal cardiac structure and function. Circulation 103: 2973-2979.
36. Schins A, Honig A, Crijns H, Baur L, Hamulyák K (2003) Increased coronary events in depressed cardiovascular patients: 5-HT2A receptor as missing link? Psychosom Med 65: 729-737.
37. Côté F, Thévenot E, Fligny C, Fromes Y, Darmon M, et al. (2003) Disruption of the nonneuronal tph1 gene demonstrates the importance of peripheral serotonin in cardiac function. Proc Natl Acad Sci U S A 100: 13525-13530.
38. Delbin MA, Silva AS, Antunes E, Zanesco A (2012) Interaction between serotoninergic-and beta-adrenergic receptors signaling pathways in rat femoral artery. Arq Bras Cardiol 98: 29-34.
39. Jian B, Xu J, Connolly J, Savani RC, Narula N, et al. (2002) Serotonin mechanisms in heart valve disease I: serotonin-induced up-regulation of transforming growth factor-beta1 via G-protein signal transduction in aortic valve interstitial cells. Am J Pathol 161: 2111-2121.
40. Balachandran K, Bakay MA, Connolly JM, Zhang X, Yoganathan AP, et al. (2011) Aortic valve cyclic stretch causes increased remodeling activity and enhanced serotonin receptor responsiveness. Ann Thorac Surg 92: 147-153.
41. Halperin D, Reber G (2007) Influence of antidepressants on hemostasis. Dialogues Clin Neurosci 9: 47-59.
42. Belcher PR, Drake-Holland AJ, Noble MI (2006) The antiplatelet drug target in atherosclerotic diseases. Cardiovasc Hematol Disord Drug Targets 6: 43-55.
43. Levy RJ (2006) Serotonin transporter mechanisms and cardiac disease. Circulation 113: 2-4.
44. Hüfner K, Kandler C, Koudouovoh-Tripp P, Egeter J, Hochstrasser T, et al. (2014) Bioprofiling of platelets in medicated patients with depression. J Affect Disord 172C: 81-88.
45. Leino T, Viitamaa T, Haapalinna A, Lehtimäki J, Virtanen R (2009) Pharmacological profile of intrathecal fadolmidine, a alpha2-adrenoceptor agonist, in rodent models. Naunyn Schmiedebergs Arch Pharmacol 380: 539-550.
46. Perrine SA, Michaels MS, Ghoddoussi F, Hyde EM, Tancer ME, et al. (2009) Cardiac effects of MDMA on the metabolic profile determined with 1H-magnetic resonance spectroscopy in the rat. NMR Biomed 22: 419-425.
47. Pacher P, Kecskemeti V (2004) Cardiovascular side effects of new antidepressants and antipsychotics: new drugs, old concerns? Curr Pharm Des 10: 2463-2475.
48. van Zwieten PA, Blauw GJ, van Brummelen P (1990) Pharmacological profile of antihypertensive drugs with serotonin receptor and alpha-adrenoceptor activity. Drugs 40: 1-8.