Serotonin Transporter Mechanisms and Cardiac Disease

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Serotonin (5-HT)–related mechanisms have been explored extensively for pharmaceutical development, especially with regard to antidepressants and appetite suppressants. However, pharmacological agents acting through 5-HT–related pathways have been associated with a number of significant cardiovascular adverse effects, including pulmonary hypertension, cardiac arrhythmias, and cardiac valve abnormalities. Evidence for a 5-HT valvulopathy has arisen from a variety of observations, including clinical, animal model, and cell culture investigations. Patients with carcinoid syndrome tumors, others treated with the diet drug combination fenfluramine-phentermine (Fen/Phen), and individuals treated with ergot derivatives have been observed to develop what is most likely a 5-HT valvulopathy with comparable heart valve pathology between these different clinical groupings. In patients with carcinoid syndrome tumors, high 5-HT levels were observed to be associated with fibrodsplasia affecting predominantly the right-side cardiac valves; a comparable pattern of valve disease was observed in a number of reported patients treated with ergot derivatives. The reason for this right-side valvulopathy distribution (tricuspid and pulmonary valves) has been hypothetically attributed to pulmonary monoamine oxidase inhibition by Phen, resulting in increased 5-HT exposure for these right side cardiac valves being exposed to relatively lower 5-HT levels despite elevated systemic 5-HT. However, a recent animal study involving daily injection of 5-HT in rats demonstrated both elevated 5-HT levels and right- and left-side valve abnormalities.

The Fen/Phen valvulopathy has been reported to affect both right- and left-side cardiac valves, and this was hypothesized to be due in part to pulmonary monoamine oxidase inhibition by Phen, resulting in increased 5-HT exposure for left-side cardiac valves. However, the mechanisms responsible for the pathogenesis of the cardiac effects of 5-HT are likely linked to interactions involving both 5-HT receptors and the 5-HT transmembrane transporter (5-HTT). This issue of Circulation contains an important study of 5-HTT–knockout mice with cardiac valvulopathy and myocardial fibrosis that provides novel insights into 5-HT–related heart disease and the importance of 5-HTT in its pathogenesis.

5-HT Receptor and Transporter Mechanisms

5-HT signaling takes place via a plasma membrane receptor system that has at this time at least 15 cognate receptors divided into 7 families, and all but 1 of these are G-protein–coupled receptor superfamilies. 5-HTT facilitates intracellular processing of 5-HT after receptor interactions. In non-neuronal tissues, 5-HT production is rate limited by tryptophan hydroxylase (Tph1). Interestingly, Tph1-knockout mice demonstrate a diluted cardiomyopathy. Although 5-HTT is present in embryonic myocardium and cardiac valves, it is not present in mature myocardium but persists in valvular cells. Because the Fen/Phen diet drug combination was demonstrated to be associated with a cardiac valvulopathy with valve cusp pathology comparable to the carcinoid valvulopathy, it is important to consider the potential contributions of each of these components (Fen/Phen) to the pathogenesis, especially in view of the potential role of 5-HTT in 5-HT valvulopathy. Fen is known to be both a 5-HT receptor agonist and a substrate for 5-HTT. However, Phen is a monoamine oxidase inhibitor and thus would be expected to delay the breakdown of 5-HT. No patients treated with Phen alone have been observed to develop a cardiac valvulopathy; however, both Fen/Phen and Fen-alone patients were reported to have developed valve disease. Furthermore, although it was hypothesized that Fen/Phen administration would result in elevation of 5-HT levels, this was never observed in Fen/Phen- or Fen-treated patients. In fact, Fen/Phen lowers 5-HT levels in human subjects. Thus, these prior results suggest that Fen, its metabolites, or 5-HT alone may have contributing mitogenic effects resulting in valvulopathy, and importantly, the processing of 5-HT or Fen via 5-HTT may play a major mechanistic role in 5-HT valvulopathy. Interference with 5-HT processing via knocking out 5-HTT resulted in valvulopathy in mice; thus, it is possible that because of an absence of transmembrane processing (via knocking out 5-HTT), there are increased and persistent 5-HT receptor interactions in the mice in these studies. This could result in the increased valvular mitogenic activity and extracellular matrix production noted in the 5-HTT–knockout mice.

5-HT Processing, Cardiac Valvulopathy, and Cardiomyopathy

The 5-HT type 2B receptor (5-HT2B) has been demonstrated to be present in aortic valve tissue and has been hypothesized to be the key target of the 5-HT agonists such as Fen and its analogues that have been implicated in the anorexigen valvulopathy cases. However, other 5-HT receptor types...
have been demonstrated to be present in heart valve cells; thus, the impact of 5-HT on cardiac valve tissue may be both extensive and complex.

It is also of interest that 5-HT-mediated G-protein receptor signal transduction has been shown to result in upregulation of the cytokine TGFβ1 in sheep heart valve interstitial cells in culture, followed by both increased production of collagen and glycosaminoglycans. 5-HT–knockout mice demonstrated increased collagen accumulation in heart valve leaflets compared with controls, and human cardiac valve myofibroblasts demonstrated increased collagen production in response to 5-HT administration that was specifically inhibited by a 5-HT type IB/ID receptor inhibitor. However, 5-HTT–knockout mice also deficient in the 5-HT type IB receptor demonstrated no differences from the 5-HTT–knockout mice in terms of cardiac valve phenotype; both had equivalent valvulopathy, indicating that 5-HT type IB/ID receptor signaling is not critical in these mice.

Although valvular calcification typically has not been seen clinically with 5-HT valvulopathy, chondroid metaplasia was present in a number of the cardiac valves from the 5-HTT–knockout mice. It is possible that the cardiac valve disease observed in these mice may be associated with cellular phenotype changes related to bonelike activity observed by others in pathology studies of human calcific valve disease. Other research has demonstrated that TGFβ1-related mechanisms are strongly associated with calcific valve disease; thus, TGFβ1 mechanisms may be operative in 5-HT–knockout mice via increased TGFβ1 production resulting from sustained increased 5-HT receptor interactions because of 5-HTT deficiency.

5-HT has been demonstrated in transgenic mouse studies to act on the myocardium via specific receptor pathways. 5-HT3R–knockout mice demonstrated diminished numbers of mitochondria and dilated cardiomyopathy. In contrast, mice overexpressing 5-HT3R specifically in heart demonstrated mitochondrial proliferation and myocardial hypertrophy. The observations of cardiac fibrosis in the 5-HTT–knockout mice are difficult to interpret in light of the 5-HT3R mouse studies. The 5-HTT–knockout results may reflect myocardial fibrosis in the setting of heart failure associated with either cardiomyopathy, as a secondary result of significant cardiac valve dysfunction, or both.

**Clinical Implications**

The impact of 5-HT–related mechanisms on heart disease may be of concern at this time in light of the anorexigen-related clinical reports and related experimental observations. However, clinical studies since the initial Fen/Phen reports have not completely revealed the potential scope of 5-HT–related mechanisms on heart valve disease. A study of 292 patients receiving selective 5-HT–reuptake inhibitors (SSRIs) failed to show an association between use of these agents and cardiac valve abnormalities assessed with echocardiography. Furthermore, estimates of the incidence of valvulopathy in patients receiving Fen/Phen have varied widely, which most likely is due to the limitations of cardiac ultrasound evaluation of valvular function and study design issues. A meta-analysis of the published studies of patients treated with Fen/Phen estimated that 1 in 8 patients receiving these agents for >90 days had valvular disease. However, this investigation also acknowledged a number of limitations, including publication bias, that could have resulted in an overestimation of incidence.

It is important to note that 5-HTT polymorphisms have been associated with variable pharmacological responsiveness to SSRIs in patients with psychiatric disorders, and 5-HTT polymorphisms have also been observed to be associated with the penetrance of clinical manifestation in a number of neurological diseases. The 5-HTT–knockout mouse results indicate that 5-HTT polymorphisms may be of potential interest for investigations of SSRIs and other agents that affect 5-HT metabolism with regard to susceptibility to 5-HT valvulopathy, myocardial disorders, and pulmonary hypertension. Furthermore, the unique responsiveness of heart valve interstitial cells to 5-HT and 5-HT agonists indicates that 5-HT receptor antagonists, agents targeting 5-HTT, and related specific inhibitors of G-protein signaling may merit investigation for treating selected types of heart valve disease.

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**Disclosures**

None.

**References**


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