Evidence for Possible Involvement of 5-HT$_{2B}$ Receptors in the Cardiac Valvulopathy Associated With Fenfluramine and Other Serotonergic Medications

Richard B. Rothman, MD, PhD; Michael H. Baumann, PhD; Jason E. Savage, BS; Laura Rauser, BS; Ace McBride, BS; Sandra J. Hufeisen, BS; Bryan L. Roth, MD, PhD

**Background**—Serotonergic medications with various mechanisms of action are used to treat psychiatric disorders and are being investigated as treatments for drug dependence. The occurrence of fenfluramine-associated valvular heart disease (VHD) has raised concerns that other serotonergic medications might also increase the risk of developing VHD. We hypothesized that fenfluramine or its metabolite norfenfluramine and other medications known to produce VHD have preferentially high affinities for a particular serotonin receptor subtype capable of stimulating mitogenesis.

**Methods and Results**—Medications known or suspected to cause VHD (positive controls) and medications not associated with VHD (negative controls) were screened for activity at 11 cloned serotonin receptor subtypes by use of ligand-binding methods and functional assays. The positive control drugs were (±)-fenfluramine; (+)-fenfluramine; (−)-fenfluramine; its metabolites (±)-norfenfluramine, (+)-norfenfluramine, and (−)-norfenfluramine; ergotamine; and methysergide and its metabolite methylergonovine. The negative control drugs were phentermine, fluoxetine, its metabolite norfluoxetine, and trazodone and its active metabolite m-chlorophenylpiperazine. (±)-, (+)-, and (−)-Norfenfluramine, ergotamine, and methylergonovine all had preferentially high affinities for the cloned human serotonin 5-HT$_{2B}$ receptor and were partial to full agonists at the 5-HT$_{2B}$ receptor.

**Conclusions**—Our data imply that activation of 5-HT$_{2B}$ receptors is necessary to produce VHD and that serotonergic medications that do not activate 5-HT$_{2B}$ receptors are unlikely to produce VHD. We suggest that all clinically available medications with serotonergic activity and their active metabolites be screened for agonist activity at 5-HT$_{2B}$ receptors and that clinicians should consider suspending their use of medications with significant activity at 5-HT$_{2B}$ receptors.

**Key Words:** valves ■ fenfluramine ■ norfenfluramine ■ receptors
intestinal disorders, and hypertension. Fenfluramine-associated VHD has led some to propose caution "in the long-term use of other agents that act on serotoninergic mechanisms, albeit by different pathways."

Uncritical acceptance of this proposal would significantly affect the treatment of psychiatric patients as well as hinder the development of new therapeutics. Thus, determining the mechanism of fenfluramine-associated VHD is likely to not only shed light on the adverse effects of this particular medication but also clarify whether this side effect might occur with other medications that act via serotoninergic mechanisms.

Perhaps by analogy with the ability of fenfluramine to increase synaptic levels of 5-HT, investigators proposed that fenfluramine produces VHD via a serotoninergic mechanism: increases in plasma 5-HT (see review13). However, as noted elsewhere, fenfluramine decreases platelet and plasma 5-HT in animals and humans, and phen/fen treatment lowers plasma 5-HT in humans.15 Therefore, another explanation must be sought to clarify how fenfluramine could cause VHD.

In light of the established role of 5-HT as a mitogen,14 we undertook the present study to determine whether fenfluramine [(±)-fenfluramine, (+)-fenfluramine, (−)-fenfluramine] or its metabolites [(±)-norfenfluramine, (+)-norfenfluramine, (−)-norfenfluramine] might activate mitogenic 5-HT receptors. Several other drugs were included in the study to provide both positive and negative controls. Additional "positive controls" included methysergide, its active metabolite methylergonovine,15 and ergotamine. Methysergide and ergotamine are well known to produce primarily left-sided VHD affecting the mitral valve,16,17 Negative controls included phentermine, fluoxetine, and its metabolite norfluoxetine, which have not been associated with VHD. We included the antidepressant trazodone and its active metabolite m-chlorophenylpiperazine (mCPP) as an additional negative control. In addition to having activity at a wide range of 5-HT receptors,18 mCPP shares with fenfluramine the ability to release brain 5-HT via a carrier-mediated exchange mechanism.19 Trazodone is not associated with VHD. Our working hypothesis was that the "positive control" drugs would share in common the ability to activate a particular 5-HT receptor expressed in heart valves that is mitogenic, and that the "negative control" drugs would not. We called this the commonly activated serotonin receptor, or CASR.

Methods

Materials

The National Institute of Mental Health's Chemical Synthesis and Drug Supply Program provided the following compounds: (±)-norfenfluramine, (+)-norfenfluramine, and (−)-norfenfluramine. (±)-Fenfluramine and (+)-fenfluramine were obtained from the NIDA Drug Supply Program (Rockville, Md). (−)-Fenfluramine, fluoxetine, and norfluoxetine were purchased from Research Biochemicals Inc. Phentermine, mCPP, methysergide, and methylergonovine were purchased from Sigma Chemical Co. Trazodone was supplied by the NIH Psychoactive Drug Screening Program.

Radioligand Binding Assays and Sources of cDNA Clones

Radioligand binding assays for 5-HT receptors were performed as previously detailed with cloned human (5-HT1A, 5-HT1B, 5-HT1D, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3A, 5-HT3B, 5-HT3D, 5-HT5A, 5-HT5B, 5-HT5C) or rat (5-HT1A, 5-HT1D, 5-HT2B, 5-HT2C) cDNAs expressed in COS-7 cells.20 The h5HT1A cDNA was obtained from John Raymond (Medical University of South Carolina), the h5-HT1B, h5HT1D, h5-HT2A, and h5-HT2C cDNAs were from Mark Hamblin (University of Washington), the rat 5HT2A and rat 5HT2C cDNAs were from David Julius (University of California San Francisco), and the h5HT3A cDNA was from Rene Hen (Columbia University).

The h5-HT2B cDNA was obtained by amplification from human brain cDNA (Quickclone cDNA; Clonetech) with Pfu polymerase and subcloned in-frame into the pTag2A eukaryotic expression vector (Stratagene). The h5HT3B cDNA was obtained by amplification of human genomic DNA (Clonetech) with Pfu polymerase and subcloned into the pcDNA3.0 eukaryotic expression vector. The sequences of the h5-HT2B and h5HT3B cDNAs were verified by automated DNA sequencing (Cleveland Genomics, Inc). Detailed protocols for transfection, using FUGENE6, as well as complete details of all the radioligand binding assays, are available.20,21a

For initial screening, compounds were tested at concentrations of 10 μmol/L; Kᵢ determinations using 7 concentrations of unlabel ligand spanning 4 orders of magnitude were obtained on compounds that gave >50% inhibition at 10 μmol/L. Kᵢ values were calculated with the LIGAND program as previously detailed.20–23

Functional Assays: Phosphoinositide Hydrolysis

Phosphoinositide hydrolysis assays were performed with stably (5-HT2A, 5-HT3B) or transiently (5-HT2B) expressed receptors plated in 24-well culture plates as previously detailed.21b,22 In brief, transfected cells were loaded with [H]inositol (15 Ci/mmol; 1 μCi/ml) overnight in inositol-free DMEM without serum. The next day, [H]-inositol phosphate accumulation assays were performed in a modified Krebs-bicarbonate buffer as previously detailed. Kᵢ (nmol/L) and percent Vₘₐₓ (relative to 5-HT) values were calculated as previously described.21b–23

Results

Figure 1 reports the results of the initial screen of compounds in the ligand-binding assays. On the basis of these results, Kᵢ values were determined for selected compounds. The fenfluramines and norfenfluramines had Kᵢ values ranging from 673 to 1950 nmol/L and lacked agonist activity at the 5-HT1A receptor (data not shown). The other positive control drugs (methysergide, ergotamine, and methylergonovine) had high affinities for the 5-HT1B site and were full potent agonists (data not shown). This pattern of results, along with the fact that clinically used 5-HT1A agonists, such as buspirone, are not associated with VHD, suggests that the 5-HT1A receptor is not the CASR.

The fenfluramines and norfenfluramines had low affinity for the 5-HT1D, 5-HT1B, and 5-HT1E receptors (data not shown), and the other positive-control compounds had high affinities for these sites. Because of the low affinity of the fenfluramines for these sites, we did not conduct functional activity studies. The low affinities of the fenfluramines for the h5-HT1D/1E receptors, coupled with the observation that sumatriptan, a potent 5-HT1D/1E agonist24 widely used for treating migraine headaches, is not associated with VHD, suggests that the 5-HT1D/1E receptors do not mediate fenfluramine-associated VHD.

The ergot compounds had high affinity for the 5-HT2A, 5-HT2B, and 5-HT3B receptors (Table 1). With regard to the 5-HT3A receptor, ergotamine was a full agonist, methysergide was a weak partial agonist, and methylergonovine was a potent, full agonist (Table 2). The fenfluramines had micro-
molar affinity for the 5-HT$_{2A}$ receptor. Although the fenfluramines were weak partial agonists, the norfenfluramines were somewhat more potent partial agonists. The relatively low affinity of the norfenfluramines at the 5-HT$_{2A}$ receptor suggests that this site is not the CASR.

The norfenfluramines were moderately potent at the 5-HT$_{2C}$ receptor and were full agonists. The fenfluramines were also full agonists but were significantly less potent than the norfenfluramines. Among the other positive-control test drugs, methysergide and methylergonovine had high affinity for the 5-HT$_{2C}$ receptor, with methysergide being a weak partial agonist and methylergonovine being a potent full agonist. Ergotamine, conversely, was a potent partial agonist, and methysergide was a very-low-efficacy partial agonist at the 5-HT$_{2B}$ receptor. Methylergonovine was a high-affinity partial agonist. Among the negative control drugs, mCPP was a moderate-potency partial agonist with the same efficacy as methylergonovine. With the exception of the findings with mCPP, these findings suggest that the 5-HT$_{2B}$ receptor may be the CASR. Trazodone, which binds with high affinity to the 5-HT$_{2B}$ receptor (Table 1), is a potent 5-HT$_{2B}$ antagonist (data not shown).

The fenfluramines and norfenfluramines were inactive at the 5-HT$_{5}$ and 5-HT$_{6}$ receptors (data not shown), indicating that these receptors are most likely not the CASR. Although the norfenfluramines have moderate affinity at the 5-HT$_{7}$ receptor, ergotamine had low affinity for this site, suggesting that the 5-HT$_{7}$ receptor is not the CASR (data not shown).

Functional studies demonstrated that the norfenfluramines were full agonists at the 5-HT$_{2A}$ site (Figure 2). The fenfluramines, in contrast, bound to the 5-HT$_{2A}$ receptor with $K_i$ values of $\approx 5$ µmol/L. Ergotamine was a potent partial agonist, and methysergide was a very-low-efficacy partial agonist at the 5-HT$_{2B}$ receptor. Methylergonovine was a high-affinity partial agonist. Among the negative control drugs, mCPP was a moderate-potency partial agonist with the same efficacy as methylergonovine. With the exception of the findings with mCPP, these findings suggest that the 5-HT$_{2B}$ receptor may be the CASR. Trazodone, which binds with high affinity to the 5-HT$_{2B}$ receptor (Table 1), is a potent 5-HT$_{2B}$ antagonist (data not shown).

The fenfluramines and norfenfluramines were inactive at the 5-HT$_{5}$ and 5-HT$_{6}$ receptors (data not shown), indicating that these receptors are most likely not the CASR. Although the norfenfluramines have moderate affinity at the 5-HT$_{7}$ receptor, ergotamine had low affinity for this site, suggesting that the 5-HT$_{7}$ receptor is not the CASR (data not shown).

Phentemine was inactive at all 5-HT receptors assayed here.

---

Figure 1. 3D representation of initial screen of compounds in ligand-binding assays. Data show mean percent inhibition of specific binding (along z axis) at all tested neurotransmitter receptors and channels (along x axis) by 10 µmol/L concentration of test agents (along y axis). Left arrow shows location of 5-HT$_2$-family receptors and fenfluramine analogues; right arrow shows location of phentermine and adrenergic receptors. Human clones were used except where noted: 5-HT1A indicates 5HT$_{1A}$ serotonin receptor; 5-HT1Da, 5HT$_{1D}$a serotonin receptor; 5-HT1Db, 5HT$_{1D}$b serotonin receptor; 5-HT1E, 5HT$_{1E}$ serotonin receptor; r5HT2A, rat 5HT$_{2A}$ serotonin receptor; 5-HT2B, 5HT$_{2B}$ serotonin receptor; r5HT2C, rat 5HT$_{2C}$ serotonin receptor; 5-HT3, mouse 5HT$_{3}$ receptor; 5-HT5A, 5HT$_{5A}$ serotonin receptor; 5-HT6, 5HT$_{6}$ serotonin receptor; 5-HT7, 5HT$_{7}$ serotonin receptor; H1, histamine H1 receptor; NMDA, NMDA glutamate receptor; VMAT2, vesicular monoamine transporter type II; SERT, serotonin transporter; NET, norepinephrine transporter; bDAT, bovine dopamine transporter; GABA-A, rat GABA-A receptor; rBZP, rat benzodiazepine binding site; Alpha2A, $\alpha_{2A}$-adrenergic receptor; Alpha2B, $\alpha_{2B}$-adrenergic receptor; Alpha2C, $\alpha_{2C}$-adrenergic receptor; rBeta1, rat $\beta_1$-adrenergic receptor; rBeta2, rat $\beta_2$-adrenergic receptor; alpha1A, rat $\alpha_{1A}$-adrenergic receptor; V1, vasopressin-1 receptor; V2, vasopressin-2 receptor; and V3, vasopressin-3 receptor.
in the CASR mediates fenfluramine-associated VHD. Among the receptors assayed, the 5-HT₃A receptor has 5 characteristics consistent with its being the CASR: (1) it is located on both mitral and aortic valves; (2) it mediates mitogenesis; (3) the norfenfluramines have high affinity and efficacy at the 5-HT₂ receptor; (4) ergotamine and methysergide, the active metabolite of methysergide, are high-affinity partial agonists for the 5-HT₂ receptor; and (5) with the exception of mCPP (see below), the negative control drugs (fluoxetine, norfluoxetine, phentermine) have very low affinity for this site and lack agonist effects at this receptor. The 5-HT₃C receptor is ruled out as the CASR, primarily because few of these receptors are expressed in heart valves.

There are several observations that, at first glance, are difficult to reconcile with the hypothesis that the 5-HT₂ receptor mediated the valvulopathy associated with administration of fenfluramine, ergotamine, and methysergide. First, whereas (+)-fenfluramine produces primarily aortic regurgitation, ergotamine and methysergide produce primarily mitral regurgitation. Given that 5-HT₃ receptors are found on both valves, the mechanism underlying the anatomic specificity of the valvulopathy associated with these 2 classes of drugs is enigmatic. Second, methysergide appears to produce a more severe form of VHD than fenfluramine. Patients with fenfluramine-associated VHD are clinically asymptomatic and typically do not have audible heart murmurs. The best estimate of the incidence of clinically significant fenfluramine-associated VHD is 0.07% per year. In contrast, patients treated with methysergide developed clinically significant VHD, including new heart murmurs, with an incidence of 3%. Thus, although methylergonovine is a less effective agonist at the 5-HT₃ receptor than norfenfluramine, it produces a more severe form of VHD in a greater number of patients. Third, methysergide administration is associated with fibrosis of other anatomic sites in addition to heart valves. In contrast, fenfluramine-associated fibrosis appears to be localized to heart valves.

Fourth, the finding that mCPP has activity at 5-HT₂ receptors must be reconciled with observations that traz.

### Table 1. $K_i$ Values of Test Drugs at 5-HT₂ Receptors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rat $K_i$ (nM)</th>
<th>Human $K_i$ (nM)</th>
<th>Rat $K_i$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(±)-Fenfluramine</td>
<td>216.2 ± 2.5</td>
<td>4134 ± 753</td>
<td>3183 ± 374</td>
</tr>
<tr>
<td>(+)-Fenfluramine</td>
<td>1107 ± 1354</td>
<td>5099 ± 690</td>
<td>6245 ± 514</td>
</tr>
<tr>
<td>(-)-Fenfluramine</td>
<td>5463 ± 352</td>
<td>5713 ± 1344</td>
<td>3415 ± 542</td>
</tr>
<tr>
<td>(±)-Norfenfluramine</td>
<td>2316 ± 163</td>
<td>52.1 ± 12.3</td>
<td>557 ± 36</td>
</tr>
<tr>
<td>(+)-Norfenfluramine</td>
<td>1516 ± 88</td>
<td>11.2 ± 4.3</td>
<td>324 ± 7.1</td>
</tr>
<tr>
<td>(−)-Norfenfluramine</td>
<td>3841 ± 361</td>
<td>47.8 ± 18.0</td>
<td>814 ± 58</td>
</tr>
<tr>
<td>Ergotamine</td>
<td>9.0 ± 0.6</td>
<td>3.0 ± 0.2</td>
<td>12.0 ± 0.9</td>
</tr>
<tr>
<td>Methysergide</td>
<td>15.0 ± 2.4</td>
<td>9.1 ± 2.9</td>
<td>1.8 ± 1.0</td>
</tr>
<tr>
<td>Methylergonovine</td>
<td>12.6 ± 0.6</td>
<td>0.49 ± 0.09</td>
<td>12.4 ± 0.6</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>299 ± 31</td>
<td>5030 ± 1152</td>
<td>50.0 ± 5.9</td>
</tr>
<tr>
<td>Norfluoxetine</td>
<td>638 ± 63</td>
<td>5063 ± 1161</td>
<td>286 ± 35</td>
</tr>
<tr>
<td>Trazodone</td>
<td>19.8 ± 1.4</td>
<td>73.6 ± 21.17</td>
<td>402 ± 26</td>
</tr>
<tr>
<td>mCPP</td>
<td>39 ± 27</td>
<td>3.2 ± 0.6</td>
<td>59 ± 6.5</td>
</tr>
<tr>
<td>5-HT</td>
<td>614 ± 43</td>
<td>4.0 ± 1.1</td>
<td>12.2 ± 0.8</td>
</tr>
<tr>
<td>Phentermine</td>
<td>&gt;10 000</td>
<td>&gt;10 000</td>
<td>&gt;10 000</td>
</tr>
</tbody>
</table>

Values are mean ± SEM (n = 3). Units are nanomolar.

### Table 2. Functional Activity of Test Drugs at 5-HT₂ Receptors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Human $K_{act}$ (nM)</th>
<th>Human $V_{max}$ (nM)</th>
<th>Human $K_{act}$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(±)-Fenfluramine</td>
<td>4131 ± 14 400</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>(+)-Fenfluramine</td>
<td>&gt;10 000</td>
<td>379 ± 70</td>
<td>362 ± 64</td>
</tr>
<tr>
<td>Ergotamine</td>
<td>ND</td>
<td>38 ± 8.2</td>
<td>80 ± 5.9</td>
</tr>
<tr>
<td>Methysergide</td>
<td>ND</td>
<td>88 ± 5.3</td>
<td>100 ± 6.5</td>
</tr>
<tr>
<td>Methylergonovine</td>
<td>ND</td>
<td>18.4 ± 5.3</td>
<td>13 ± 2.4</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>93 ± 5.3</td>
<td>71 ± 8.8</td>
<td>80 ± 10</td>
</tr>
<tr>
<td>Norfluoxetine</td>
<td>ND</td>
<td>150 ± 25</td>
<td>2.9 ± 0.9</td>
</tr>
<tr>
<td>Trazodone</td>
<td>ND</td>
<td>18 ± 2.4</td>
<td>33 ± 2.0</td>
</tr>
<tr>
<td>mCPP</td>
<td>ND</td>
<td>18 ± 2.4</td>
<td>33 ± 2.0</td>
</tr>
<tr>
<td>5-HT</td>
<td>ND</td>
<td>30 ± 1.8</td>
<td>103 ± 4.1</td>
</tr>
<tr>
<td>Phentermine</td>
<td>ND</td>
<td>56 ± 1.8</td>
<td>75 ± 8.8</td>
</tr>
</tbody>
</table>

Values are mean ± SEM (n = 3). $K_a$ values are nmol/L ± SEM; $V_{max}$ values are % of 5-HT₂. ND indicates not done.
trazodone, from which it is metabolically derived, is not associated with VHD. Therapeutic doses of trazodone generate plasma levels of mCPP from 150 to 550 nmol/L, which are in the range needed to activate 5-HT₂B receptors. However, trazodone is a potent 5-HT₂B receptor antagonist, and its plasma levels are ∼5-fold higher than that of mCPP. Thus, trazodone would act to block activation of 5-HT₂B receptors by mCPP.

Thus, a possible explanation for the differing degrees of VHD prevalence seen among the 5-HT₂B agonists is the degree of 5-HT₂B antagonism produced by either parent drug or metabolites. Methysergide, as a very-low-efficacy 5-HT₂B agonist, would act to antagonize the agonist effects of methylergonovine (Table 2). However, methysergide is rapidly metabolized to methylergonovine, is more rapidly eliminated, and achieves blood levels 10-fold lower than methylergonovine. Because the agonist actions of methylergonovine are most likely not significantly blocked by its parent drug, methysergide administration would probably cause a higher prevalence of VHD. In the case of fenfluramine, (+)-fenfluramine and (−)-fenfluramine have lower efficacy (∼40%) at the 5-HT₂B receptor than (+)-norfenfluramine (75%) and achieve blood levels twice that of norfenfluramine. This indicates that the parent drugs would partially antagonize activation of 5-HT₂B receptors by (+)-norfenfluramine. This may explain why the fenfluramines appear to produce a less severe form of VHD than methysergide (see above).

Taken at face value, the 5-HT₂B hypothesis predicts that elevations of plasma 5-HT should produce valvulopathy in both the aortic and mitral valves. Indeed, 5-HT is the most potent and efficacious agonist at the 5-HT₂B receptor. Medications such as lithium and monoamine oxidase inhibitors produce sustained 2-fold increases in plasma 5-HT and are not associated with VHD. This suggests that modest elevations of plasma 5-HT are unlikely to produce this adverse effect. Patients with carcinoid syndrome develop extremely high levels of plasma 5-HT (>500 nmol/L), and fibrotic valve lesions occur exclusively on the right side of the heart. Although some attribute the lack of left-sided VHD in carcinoid syndrome to the almost complete removal of plasma 5-HT by the lung before the blood empties into the left atrium, this hypothesis fails to take into account the fact that the blood samples taken for analysis of 5-HT are withdrawn from the antecubital vein in the arm, the blood of which is derived most directly from the left side of the heart. Although the right side of the heart is undoubtedly bathed in higher concentrations of 5-HT than the left side, the left side is clearly exposed to 5-HT concentrations well in excess of that necessary to completely activate the 5-HT₂B receptor. Thus, it is not clear why carcinoid syndrome produces fibrotic lesions on the valves of the right side of the heart, whereas fenfluramine, methysergide and ergotamine affect primarily the valves of the left side.

Viewed collectively, these considerations suggest that activation of 5-HT₂B receptors may be necessary to produce VHD. Clearly, other factors also determine the susceptibility of an individual to develop the lesion, its anatomic location, and its severity. Despite our lack of knowledge of what these factors might be, these data suggest that serotonergic medications, which do not activate 5-HT₂B receptors, are unlikely to produce VHD. These findings further suggest that the simplest pathogenic mechanism to explain anorexigen-associated VHD is a direct activation of 5-HT₂B receptors by norfenfluramine. This mechanism does not necessitate the formulation of unlikely synergistic mechanisms between phentermine and fenfluramine or a role for plasma 5-HT to explain the occurrence of VHD. Finally, on the basis of these results and those recently reported by Fitzgerald et al, we suggest that all clinically available medications with serotonergic activity and their metabolites should be screened for agonist activity at 5-HT₂B receptors.

Note Added in Proof
Dr Roth’s laboratory has begun to measure the efficacies of clinically used serotonergic compounds at the h5-HT₂B receptor and have not yet found any that are agonists.

Acknowledgments
The authors gratefully acknowledge the support of the NIMH Psychoactive Drug Screening Program (N01MH80005) and the National Institute of Mental Health’s Chemical Synthesis and Drug Supply Program. Dr Roth was supported by K02MH01367.

References

![Figure 2. Dose-response curves for selected agents in 5-HT₂B functional assay: (+)-norfenfluramine, (−)-norfenfluramine, ergotamine, methylergonovine, and mCPP. Data represent mean±SD of [³H]IP accumulation in counts per minute from HEK-293 cells transiently transfected with h5HT₂B receptor from a typical experiment. Curves were generated with GraphPad Prizm and represent theoretical fits of data using parameter estimates obtained from fits.](image-url)


Evidence for Possible Involvement of 5-HT2B Receptors in the Cardiac Valvulopathy Associated With Fenfluramine and Other Serotonergic Medications
Richard B. Rothman, Michael H. Baumann, Jason E. Savage, Laura Rauser, Ace McBride, Sandra J. Hufeisen and Bryan L. Roth

Circulation. 2000;102:2836-2841
doi: 10.1161/01.CIR.102.23.2836

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/102/23/2836

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/