Ablation of Serotonin 5-HT$_{2B}$ Receptors in Mice Leads to Abnormal Cardiac Structure and Function

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**Background**—Identification of factors regulating myocardial structure and function is important to understand the pathogenesis of heart disease. Because little is known about the molecular mechanism of cardiac functions triggered by serotonin, the link between downstream signaling circuitry of its receptors and the heart physiology is of widespread interest. None of the serotonin receptor (5-HT$_{1A}$, 5-HT$_{1B}$, or 5-HT$_{2C}$) disruptions in mice have resulted in cardiovascular defects. In this study, we examined 5-HT$_{2B}$ receptor–mutant mice to assess the putative role of serotonin in heart structure and function.

**Methods and Results**—We have generated G$_q$-coupled 5-HT$_{2B}$ receptor–null mice by homologous recombination. Surviving 5-HT$_{2B}$ receptor–mutant mice exhibit cardiomyopathy with a loss of ventricular mass due to a reduction in number and size of cardiomyocytes. This phenotype is intrinsic to cardiac myocytes. 5-HT$_{2B}$ receptor–mutant ventricles exhibit dilation and abnormal organization of contractile elements, including Z-stripe enlargement and N-cadherin downregulation. Echocardiography and ECG both confirm the presence of left ventricular dilatation and decreased systolic function in the adult 5-HT$_{2B}$ receptor–mutant mice.

**Conclusions**—Mutation of 5-HT$_{2B}$ receptor leads to a cardiomyopathy without hypertrophy and a disruption of intercalated disks. 5-HT$_{2B}$ receptor is required for cytoskeleton assembly to membrane structures by its regulation of N-cadherin expression. These results constitute, for the first time, strong genetic evidence that serotonin, via the 5-HT$_{2B}$ receptor, regulates cardiac structure and function. (Circulation. 2001;103:2973-2979.)

Key Words: cardiomyopathy ■ cell adhesion molecules ■ genetics ■ serotonin
Methods
Generation of 5-HT_{2B} Receptor–Knockout Mice
Targeted mutagenesis by homologous recombination was described previously. All animal experimentation was performed in accordance with institutional guidelines, and protocols were approved by the French Animal Care Committee in accordance with European regulations.

Morphological Analysis of Mouse Embryos
Transmission electron microscopy and histological techniques were performed as previously described. Immunochemistry was performed on heart cryosections with the anti–sarcomeric myosin heavy chain (MHC) antibody (MF-20). Anti-tropomyosin and N-cadherin antibody reactions were performed on paraffin sections as described. Signal intensity was quantified with a fluorescent imaging system and the product of counted pixel intensity per area.

Cardiomyocyte Density Determination and Confocal Microscopic Analysis
Confocal microscope images of the sections were taken on a Leica TCS4D. Total numbers of nuclei per field were calculated by counting propidium stained–nucleated cells. Nonmyocytes were tabulated as described. The total number of myocytes was calculated as the product of averaged pixel intensity per area.

Analysis of Hypertrophic Cardiac Genes by RT-PCR
Semiquantitative reverse transcription–polymerase chain reaction (RT-PCR) was performed on 1 μg of total RNA extracted from age-matched control and knockout mice with the ribosomal elongation factor 1A used as an internal control as previously described. The following primers were used: atrial natriuretic factor (ANF), 5'-CCAGGCTATTTGAGCAA-3' and 5'-GAAGCTTGTGCACTCC-3'; GATA4, 5'-GAAGCTGTTGCAGC-3' and 5'-TTGGGACTGGGCGCCAGTCATGTC-3'; α-MHC, 5'-CTGCCGAGAAGGTATTTCTCCTG-3' and 5'-GGGAAAGTIGACGGCGCCGATCAAGG-3'; and β-MHC, 5'-TGCAAAAGGCTCAGGTCTAGGCCC-3' and 5'-GCAACCACACCCCTGCAAGTTC-3'. The PCR products were quantified with an image analyzer (Bio-Rad, GS700) and calculated as arbitrary units.

Cardiomyocyte Isolation and Video Imaging
Ventricular cardiomyocytes from newborn mice were isolated as previously described. Beating rate in response to dobutamine was determined by video recording of isolated cardiomyocytes. The analysis was performed on the stage of an inverted microscope (Leica DMRB) with software developed by J.-L.V.

Echocardiographic Methods
Animals (19-week-old mice) anesthetized with sodium pentobarbital (30 mg/kg IP) were observed with 2D-guided M-mode echocardiograms with a short-focal-length, 12-MHz (Hewlett-Packard Medical Systems) transducer. LV end-systolic and end-diastolic diameters (LVESD and LVEDD, respectively) were measured. The percentage of LV fractional shortening was then calculated.

Blood Pressure Measurements
Systolic arterial pressure and heart rate were recorded by the tail-cuff technique with the LE5002 Storage Pressure [System (Lietica)] in awake 19-week-old mutant and control mice.

Electrocardiogram
Nineteen-week-old mice anesthetized with tribromoethanol (2.5% solution, 13 μL/g body wt SC) were recorded with the 4 arms of the ECG leads attached at the origin of each paur and bipolar lead derivations. The signal was recorded by an ECG (EKG-Burdick, Siemens) connected to a data acquisition system (MP100 and Acknowledge Software, Biopac Systems Inc).

Isolated Perfused Heart Preparation
Hearts from mice (12 to 19 weeks old, 23 to 25 g) anesthetized with sodium pentobarbital (60 mg/kg IP) and heparinized (500 U/kg IP) were cannulated and perfused according to Langendorff at 37°C and pH 7.4 with modified Krebs–Henseleit solution containing (mmol/L) NaCl 118, NaHCO_{3} 24, KCl 4.7, KH_{2}PO_{4} 1.2, MgSO_{4} 1.2, CaCl_{2} 2.5, disodium EDTA 0.5, and glucose 10, gassed with 95% O_{2}/5% CO_{2}. Perfusion pressure was constant and equivalent to 100 cm H_{2}O. The diastolic tension of the suture was adjusted to 1 g during the stabilization period of the heart.

Measurement of Markers for Cardiac Failure and Myocardial Damage
Enzyme immunoassay for creatine kinase-MB isoenzyme and for cardiac troponin I was determined from samples of serum from adult mice.

Data Analysis and Statistics
All values represent the average of independent experiments±SEM (n = number of experiments as indicated in the text). Comparisons between groups were performed with Student’s unpaired t test or ANOVA and a Fischer test. Significance was set at P<0.05.

Results
Heart Morphology
5-HT_{2B} receptor inactivation leads to partial embryonic death due to trabecular defects in the heart leading to midgestation lethality (30%, n =120). The 5-HT_{2B} receptor–mutant mice that reached birth displayed no obvious defects, although 30% (n =120) of newborn mice developed signs of fatigue and dyspnea between postnatal days 2 and 5 and died within 24 hours from the onset of these symptoms. A likely cause of neonatal death is inadequate cardiac output due to hypoplasia of the LV, despite the lack of evidence for pulmonary edema. All 5-HT_{2B} receptor–mutant mice that survived the first postnatal week developed to adulthood with cardiac problems. This variation in severity of the phenotype could not be attributed to variability in the genetic background of the mice (all the findings were obtained from 129/PAS pure background mice, and similar mortality was also observed on a C57/Black6J-129/PAS mixed background).

Newborn 5-HT_{2B} receptor–mutant hearts display a striking decrease in the ratio of heart to body weight (28%). This difference was 24% in 6-week-old mutants (Table 1). Histological analysis demonstrated that the decrease in heart mass was restricted to the ventricles (as shown in Figure 1A).

Cardiomyocyte Number and Size
The ratio of cardiomyocytes to total cells (stained with MF-20 antibody, myocyte-specific MHC, and propidium iodide, respectively) revealed 15% fewer cardiomyocytes in the newborn mutants, as shown in Figure 1B. Isolated mutant cardiomyocytes are 12% shorter than wild-type (n >15) (Figure 1C). The decrease in ventricular mass observed in 5-HT_{2B} receptor–mutant mice results, therefore, from decrease in both cell density and size of cardiomyocytes.
Hypertrophic Gene Expression in Heart

To determine whether the loss of ventricular mass creates compensatory hypertrophic growth associated with altered expression of hypertrophic markers, ANF, α-MHC, β-MHC, and GATA4 expression was evaluated in 12-week-old mutant hearts. Semiquantitative RT-PCR analysis of mutant heart mRNA demonstrated that none of these mRNAs showed significant variation in expression level (≤5% variation compared with control, n=5 different individuals). Similar results were obtained in newborn mutants (data not shown).

Cardiomyocyte Function

To determine whether the cardiac phenotype of 5-HT<sub>2B</sub> receptor–mutant mice was cell-intrinsic, the function of spontaneously beating isolated cardiomyocytes from newborns was investigated. The β-adrenergic receptor agonist dobutamine increased the beating rate of wild-type cardiomyocytes in a dose-dependent manner. Mutant cardiomyocytes, however, exhibited an impaired response to dobutamine in the absence of sympathetic innervation (Figure 2), indicating cell autonomous defects.

Ultrastructural Analysis

A loss of myocardial organization, a scattered area of degenerated cardiomyocytes, and myofibrillar disarray were apparent in newborn mutant hearts. Wavy myofibrils were identified by anti-tropomyosin staining (Figure 3A). In this area, myofilaments appeared misaligned, I bands were not detectable, abnormally wide Z bands were seen, and mitochondria were rounded and irregular (Figure 3B). The sarcomere length in mutants is 33% smaller than that in control mice (n=25). Notably, no evidence for myocardial apoptosis, fibrosis, or significant inflammatory cell infiltrates was found. Nearly identical histopathological findings were observed in all adult mutant hearts.

Furthermore, 5-HT<sub>2B</sub> receptor–mutant cardiomyocytes had reduced numbers of adherens junctions (Table 1), and the intercalated disks were consistently disorganized (Figure 4A). Z line–associated protein expression was investigated. Vinculin staining in mutant newborn ventricles was unaltered (not shown). N-cadherin expression, however, was reduced by 38.8% in mutant myocardium (Figure 4B, Table 1).

Hemodynamic Measurements

Transthoracic echocardiograms (Figure 5A, Table 2) show LV dilation and reduced systolic performance of the adult mutant mice. In male mutants, the LVEDD was 25% higher than wild-type. Extreme LV dilation (increased LVEDD) was observed, and the LVESD was increased by 50% in male 5-HT<sub>2B</sub> receptor mutants (n=4). The percent of LV fractional

| TABLE 1. Morphometry of 5-HT<sub>2B</sub> Receptor–Mutant Mouse Cardiac Parameters |
|-----------------------------|-----------------------------|
|                             | +/+                         | −/−                        |
| Heart-to–body weight ratio  |                            |                            |
| Newborn                     | 1.06±0.12                   | 0.76±0.07                  |
| 6 weeks                     | 0.67±0.40                   | 0.51±0.03                  |
| Sarcomere length            |                            |                            |
| Newborn                     | 2.04±0.02                   | 1.38±0.05                  |
| N-Cadherin expression       |                            |                            |
| Newborn                     | 73.4±12.4                   | 44.0±8.2                   |
| Intercalated disk size      |                            |                            |
| Newborn                     | 2.54±0.08                   | 0.64±0.09                  |

Heart-to–body weight ratio is in % (n=5 per group); sarcomere length in μm (n=25 per group, 2 individuals each); N-cadherin expression in arbitrary units (n=10 per group, 4 individuals each); intercalated disk size in μm assessed by direct measurement on electron micrograph per unit picture (n=5 per group, 2 individuals each). Values are expressed as mean±SEM.

*P<0.05: difference between mutant (−/−) and wild-type (+/+) mice.

Figure 1. 5-HT<sub>2B</sub> receptor–mutant mice exhibit decreased ventricular mass due to decreased cell number and size. A, Representative sagittal section from paraffin-embedded adult hearts (12 weeks old). rv indicates right ventricle. B, Cardiomyocytes (MHC-positive cells) and total cells (propidium iodide (PI)–stained nucleus) per field were counted (n=100 from 4 independent stainings). Numbers are expressed as mean±SD for n=8 sections. C, Ventricular myocytes from newborn mice were isolated, and their size was measured. Values are expressed as mean±SEM for n=100. Bars: A, 200 μm; B, 50 μm; C, 100 μm. D, Markers known to be expressed in hypertrophic growth (ANF, α-MHC, and GATA4) were analyzed by RT-PCR in adult mice (12 weeks). 5-HT<sub>2B</sub> receptor–mutant (−/−) and wild-type (+/+) mice.
shortening, as an indicator of systolic cardiac function, was significantly decreased in male (20%) (Figure 5A, Table 2) but not in female mutants (not shown). When myocardial function was measured by Langendorff’s heart preparation in vitro, however, the developed force in response to adrenergic stimuli (isoproterenol) was also significantly reduced in female mutants (Table 2, Figure 5B). A slight decrease in mutant female coronary flow was also observed, whereas no apparent change in basal blood pressure or heart rate was detected (Table 2).

**ECG Analysis**

ECG analysis in mutants revealed neither atrioventricular nor intraventricular conduction defects (similar PR intervals, QRS duration, and amplitude). The resting heart rate was significantly decreased in the anesthetized female mutants. The P duration, but not P amplitude, was significantly increased in female (47%) and to a lesser extent in male (17%) mutants. The most striking difference between wild-type and 5-HT$_{2B}$ receptor mutants (both female and male) was dramatically elevated T-wave amplitude, which is an indicator of abnormalities in repolarization of ventricles (Figure 5C, Table 2). Serum potassium levels, however, were not altered (not shown).

**Biochemical Markers of Heart Failure**

Clinical indications of human acute myocardial infarction and injury are revealed by serum levels of the cardiac-specific biochemical markers troponin I and creatine kinase-MB. Strikingly elevated markers were observed in the serum of 5-HT$_{2B}$ receptor mutants (6 weeks old) (Figure 5D). Interestingly, male 5-HT$_{2B}$ receptor mutants exhibited more pronounced biological changes than females.

**Discussion**

In this study, we provide the first evidence that G$_q$-coupled 5-HT$_{2B}$ receptor ablation in mice leads to cardiomyopathy with LV dysfunction, dilation, and an abnormal structure within the Z band correlated with a deficiency in N-cadherin expression.

5-HT$_{2B}$ receptor–mutant mice exhibit thinning of the ventricular wall and a reduction in ventricular mass that appears

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**Figure 2.** Cardiac phenotype in 5-HT$_{2B}$ receptor–mutant mice is intrinsic to cardiomyocytes. A, Beating rate of isolated cardiomyocytes from newborn hearts in response to different concentrations of dobutamine. B, Beating rate in isolated single cardiomyocytes was deduced from these digital video recordings. Beating rate is expressed as mean myocyte contractions/min ± SEM. Mutant (−/−, n=5) and wild-type (+/+, n=3) mice.

**Figure 3.** 5-HT$_{2B}$ receptor–mutant mice display dramatic disruption of cardiomyocyte cytoarchitecture with myofibrillar disarray. A, Representative sections from paraffin-embedded adult hearts stained with tropomyosin antibody. B, High magnification of sarcomeres from LVs of newborn mice. Actin fibers (F), desmosomes (D), mitochondria (M), nexus (N), and Z bands (Z) are shown. Bars: A, 50 μm; B, 1 μm. 5-HT$_{2B}$ receptor–mutant (−/−) and control (+/+) mice.

**Figure 4.** Intracellular junctional structures are perturbed in 5-HT$_{2B}$ receptor–mutant mice. A, High magnification of intercalated disk (ID) structures from LVs of newborn mice. Actin fibers (F), desmosomes (D), mitochondria (M), nexus (N), and Z bands (Z) are shown. B, Immunohistochemistry for intercalated disk protein N-cadherin in newborn hearts. DAPI staining shows distribution of cells (right). Bars: B, 50 μm; A, 0.5 μm. 5-HT$_{2B}$ receptor–mutant (−/−) and control (+/+) mice.
Have a hypertrophic response remains to be investigated. 5-HT2B receptor–mutant mice, there were no morphological signs of hypertrophy. Unlike the expression of hypertrophic markers was not elevated, and despite increased preload conditions (increased LVEDD), the reexpression. In the 5-HT2B receptor–mutant heart, however, could be due to impaired growth during postnatal development (unpublished observations). Together, these data suggest that the 5-HT2B receptor affect the organization of myofibrils and related cardiomyocyte cytoarchitecture? 5-HT2B receptor–mutant cardiomyocytes exhibit abnormal organization of contractile elements, including Z-stripe enlargement (Figure 5). Interestingly, most of the mutations leading to dilated cardiomyopathy in humans affect structural proteins involved in cytoskeleton–extracellular matrix interaction at the Z stripe.23 The altered intercalated disk structures observed in the hearts of 5-HT2B receptor–mutant mice could be a molecular mechanism leading to impaired contractility and myofibrillar degeneration. Z line–associated structures are responsible for the lateral alignment of myofilaments, and their anchorage is at N-cadherin– and vinculin-containing costameres along the cell membrane. The 5-HT2B receptor–mutant mice exhibit decreased N-cadherin levels. N-Cadherin plays an important role in maintaining myofibril integrity,24 in cardiomyocyte interaction, and in myofibrillogenesis.25 Downregulation of N-cadherin and disruption of intercellular adhesion have also been reported in failing guinea pig hearts.26 Addition of antibodies against N-cadherin to cardiomyocyte cultures also induces myofibrillar and cytoskeletal disorganization.27 Furthermore, mutation of the Drosophila 5-HT2Dro receptor (a pharmacological orthologue to 5-HT2B receptor) results in embryos that do not gastrulate properly due to impaired proliferation, not apoptosis. Mutation of the thin-filament protein troponin T in mice also results in cardiomyopathy due to a primary loss of cardiomyocytes and decrease in cell size.13 Myofibrillar loss is the most obvious structural change in human cardiomyopathy,17 and sarcomeric disarray is characteristic of failing hearts.18 Actually, the decrease in cardiomyocyte size could be due to impaired growth during postnatal development. The loss of ventricular mass increases biomechanical stress on the remaining viable heart muscle, which typically triggers a hypertrophic response by inducing embryonic gene reexpression. In the 5-HT2B receptor–mutant heart, however, despite increased preload conditions (increased LVEDD), the expression of hypertrophic markers was not elevated, and there were no morphological signs of hypertrophy. Unlike the 5-HT2B receptor–mutant mice, α-MHC– and myf5-mutant mice develop hypertrophy, and interstitial fibrosis accompanied cardiomyopathy.19 Why 5-HT2B receptor mutants fail to have a hypertrophic response remains to be investigated.

Combined myofibrillar breakdown and inhibited myofibrillogenesis may account for loss of ventricular mass without substantial hypertrophy. Mice overexpressing tropomodulin20 or mutated troponin T are models of dilated cardiomyopathy with inhibited myofibrillogenesis without a hypertrophic response.13

Other neurotransmitters and hormones that use Gq protein signaling are also involved in cardiomyopathies. In vitro and in vivo studies have indicated a role for hormones such as angiotensin II, bradykinin B2,21 endothelin 1, norepinephrine, and prostaglandin E2, not only in stimulation of cardiac hypertrophy but also in compensation of the hypertrophied heart through induction of cardiomyocyte apoptosis.22 Targeted expression of the carboxy-terminus of the α-subunit of Gq or overexpression of the Gq protein in the heart causes cardiomyopathy. The regulation of cardiomyocyte cytoarchitecture through the Gq-coupled pathway, however, is poorly understood.

Our data suggest that alteration in cardiomyocyte cytoarchitecture results from 5-HT2B receptor mutation. How does the 5-HT2B receptor affect the organization of myofilaments and related cardiomyocyte cytoarchitecture? 5-HT2B receptor–mutant cardiomyocytes exhibit abnormal organization of contractile elements, including Z-stripe enlargement (Figure 5). Interestingly, most of the mutations leading to dilated cardiomyopathy in humans affect structural proteins involved in cytoskeleton–extracellular matrix interaction at the Z stripe.23 The altered intercalated disk structures observed in the hearts of 5-HT2B receptor–mutant mice could be a molecular mechanism leading to impaired contractility and myofibrillar degeneration. Z line–associated structures are responsible for the lateral alignment of myofilaments, and their anchorage is at N-cadherin– and vinculin-containing costameres along the cell membrane. The 5-HT2B receptor–mutant mice exhibit decreased N-cadherin levels. N-Cadherin plays an important role in maintaining myofibril integrity,24 in cardiomyocyte interaction, and in myofibrillogenesis.25 Downregulation of N-cadherin and disruption of intercellular adhesion have also been reported in failing guinea pig hearts.26 Addition of antibodies against N-cadherin to cardiomyocyte cultures also induces myofibrillar and cytoskeletal disorganization.27 Furthermore, mutation of the Drosophila 5-HT2Dro receptor (a pharmacological orthologue to 5-HT2B receptor) results in embryos that do not gastrulate properly because of changes in E-cadherin–dependent cell adhesiveness.28 Our data suggest that the 5-HT2B receptor in mammals is required for proper myofibrillar integrity and myofibrillogenesis by regulating N-cadherin expression. The 5-HT2B receptor–mutant mouse phenotype has similarity to the natural history of patients with dilated cardiopathy. LV dilatation and depressed LV systolic performance in the mutant mice are typical features used to diagnose dilated cardiomyopathy in humans. Moreover, serum biochemical indicators of myocardial infarction are increased in the 5-HT2B receptor–mutant mice. No apparent changes in basal blood pressure and heart rate are detected (Table 2), suggesting that either the 5-HT2B receptor is not involved in basal blood pressure control or systemic vascular flow redistribu-
tion compensates at least partially for this impaired contractility.

5-HT<sub>2B</sub> receptor–mutant mice exhibit sex differences: Consistent with the idea that the morphological lesions detected in male mutant mice underlie abnormal functions, female mutant mice with less severe histopathological findings did not reveal significant functional changes under steady-state conditions. Similar sex differences occur in other cardiomyopathy models, such as in the X-linked cardiomyopathy in humans, heart failure occurs rapidly after onset of symptoms in males but is delayed in its onset and progression in females. Cardioprotective effects in females have been attributed to estrogen action.

The 5-HT<sub>2B</sub> receptor–specific agonist norfenfluramine, ergot drugs, and 5-HT released from carcinoid tumors contribute to valvular fibroplasia in humans. The lack of detectable valvular defects in mutant mice, however, indicates that the 5-HT<sub>2B</sub> receptor is not required for heart valve development.

Mutation of a noncytoskeletal molecule, the 5-HT<sub>2B</sub> receptor, provides the first genetic evidence that 5-HT, via this receptor, regulates cardiomyocyte function and structure. These findings should facilitate a genetic approach and new avenues of drug design in fighting cardiovascular disease.

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**References**


**TABLE 2. 5-HT<sub>2B</sub> Receptor–Mutant Adult Mouse Cardiovascular Parameters**

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<th>Female (+/+)</th>
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SAP (systolic arterial pressure) and heart rate were assessed by tail-cuff method on awake animals (n=5 per group); basal heart rate and developed force values were obtained from isolated perfused heart (n=8 per group). ECG was performed on anesthetized animals; QTc=QT/V, RR, n=5 per group. Values are expressed as mean±SEM. *P<0.05: difference between mutant (+/−) and wild-type (+/+) mice.
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