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To cite this version:

Canan G Nebigil, Luc Maroteaux. Functional consequence of serotonin/5-HT2B receptor signaling in heart: A role of mitochondria for transition between hypertrophy and heart failure?. Trends in Cardiovascular Medicine, 2001, 11 (8), pp.329-335. 10.1016/s1050-1738(01)00135-9 . hal-03721187

HAL Id: hal-03721187

https://hal.science/hal-03721187v1

Submitted on 12 Jul 2022

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Functional consequence of serotonin/5-HT_{2B} receptor signaling in heart: A role of mitochondria for transition between hypertrophy and heart failure?

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Short title. serotonin and 5-HT_{2B} receptor in heart

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Journal Subject Heads:

Basic Science Research [130] Animal models of human disease
[138] Cell signaling/signal transduction
[145] Genetically altered mice

Word count: 4600

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Key words: Cardiomyopathy; genetics; hypertrophy; receptors; signal transduction

Para- and/or autocrine factors that interact with receptors coupled to G-proteins of the Gq/11 families are implicated in the development of myocardial hypertrophy and apoptosis. Whether hypertrophy renders cardiac myocytes more sensitive or resistant to apoptosis is still controversial. A delicate balance may exist among hypertrophy, apoptosis, and heart failure. However, the factors involved in the transition from compensatory hypertrophy to heart failure have not been elucidated yet in the context of Gq-coupled pathways. Overexpressing serotonin Gq-coupled 5-HT_{2B} receptor in the mice heart induces mitochondrial proliferation associated with hypertrophy, while ablation of this receptor leads to mitochondrial structural and functional impairments associated with myofibrillar breakdown and dilated cardiomyopathy. In this review, we discuss a novel role of mitochondria in the transition from hypertrophic to dilated cardiomyopathy that involves the Gq coupled 5-HT_{2B}R signaling pathway.

The role of serotonin in heart

Serotonin (5-hydroxytryptamine, 5-HT) was first isolated from blood and found to function as a vasoconstrictor. 5-HT is found in three main areas of the body: the intestinal wall (where it causes increased gastrointestinal motility), blood vessels (where it causes constriction of large vessels) and the central nervous system. Several lines of evidence suggest that 5-HT regulates cardiovascular function during embryogenesis and adulthood. 5-HT is secreted from enterochromaffin cells into the blood and stored in the platelets. Circulating 5-HT can also be taken up by sympathetic neurons and vascular endothelial cells and can be co-released. The effects of 5-HT in the cardiovascular system are complex: for example, 5-HT has been associated with bradycardia or tachycardia, hypotension or hypertension and vasodilatation or vasoconstriction. Recent pharmacological studies suggested that compounds acting on 5-HT receptors could be of therapeutic use in treatment of migraine, hypertension, heart and vascular diseases [1,2].

The various biological actions of 5-HT are mediated by numerous cognate receptors. It now appears that there are at least 15 receptor subtypes that belong to four classes of receptors: 5-$HT_{1/5}$, 5-HT_2, 5-HT_3 and 5-$HT_{4/6/7}$ [3]. Binding of 5-HT to the Gq/11-coupled, 5-$HT_{2\ (A,\ B,\ C)}$ receptors activates phospholipase C (PLC), which initiates a rapid release of inositol trisphosphate and increases intracellular calcium levels. The 5-HT_{2B} receptor (5-HT_{2B}R) is expressed in the adult cardiovascular system, as well as in the gut and brain. 5-HT_{2B}R mediates 5-HT-induced mitogenesis in transfected fibroblasts by recruiting c-Src for cell cycle progression *via* the Mitogen Activated Protein Kinase (MAPK ERK1/2) pathway [4]. Stimulation of the 5-HT_{2B}R results in cross talk with the 5-$HT_{1B/1D}$R subtype *via* activation of PLA_2 and nitric oxide synthesis *via* a PDZ recognition motif [5].

In clinical disorders associated with increased 5-HT plasma levels such as carcinoid tumors, valvular heart disease has been commonly observed. This valvulopathy is characterized by hyperplasic valvular and endocardial lesions with increased extracellular matrix. The 5-HT mitogenic signaling has been proposed to trigger the valvular hyperplasia observed in carcinoid patients [6]. Antidepressant drugs that selectively inhibit the membrane 5-HT transporter (increasing the availability of 5-HT) have also been shown to produce arrhythmia including atrial fibrillation, bradycardia and heart block [7]. Antidepressants might contribute to cardiac damage in patients with coronary heart disease by amplifying the platelet aggregation, thus continuing vasoconstriction through increasing 5-HT levels. The prevalence of major depression in individuals with coronary artery disease is estimated to range from 15% to 23% [8]. Another drug that causes the efflux of 5-HT, 3,4-methylenedioxymethamphetamine (MDMA) can produce significant cardiovascular toxicity [9]. Some patients taking appetite-suppressants such as fenfluramine or ergot derivatives also experience valvular hyperplasia [10]. Fenfluramine is a potent 5-HT releaser acting at the 5-HT transporter. However, its main metabolite, norfenfluramine has preferentially high affinity for human 5-HT_2Rs acting as an agonist [10].

Norfenfluramine -mediated valvular disease was recently reported to be mediated predominantly by 5-HT_{2A}Rs via ERK1/2 activation trough both a protein kinase C and a Src stimulation [11]. In addition, use of fenfluramine resulted in a recent outbreak of pulmonary hypertension in humans. It has also been reported that activation by 5-HT or fenfluramine of the 5-HT_{2B}R is a limiting step that controls lung vascular proliferation and remodeling including the elastase activity and TGF-beta release associated with pulmonary hypertension [12].

The diversity of 5-HT receptors and the lack of 5-HT receptor isotype specific pharmacological agents have complicated attempts to identify the specific receptors involved in 5-HT-induced cardiac functions. As an alternative to classical pharmacological approaches, mice lacking or overexpressing 5-HT receptors are useful tools for defining the specific 5-HT receptor subtypes involved in 5-HT responses.

5-HT_{2B}R is required for myocardial trabeculation during embryogenesis.

We have created 5-HT_{2B}R gene knockout (KO) mice to address the roles of 5-HT_{2B}R during development and in the adult. Genetic ablation of 5-HT_{2B}R induces trabeculation defects in the developing heart, causing partial lethality at mid-gestation [13]. KO mice undergo two periods of lethality, one before embryonic day embryonic day 11.5 and the other shortly after birth. Histological analysis of hearts from 5-HT_{2B}R KO embryos revealed defects of the subepicardial layer and lack of trabeculation of the ventricular myocardium. The myocardial abnormalities of the 5-HT_{2B}R embryo mice correlate with 5-HT_{2B}R expression in the compact zone and in the myocardial trabeculae. Since the Gq-coupled 5-HT_{2B}R transduces mitogenic signals in fibroblasts [4], impaired differentiation and proliferation in the heart of 5-HT_{2B}R KO embryos probably accounts for the mid-gestation lethality. Interestingly, analysis of the mutant mice for Gq/G11 protein demonstrated a strict dependence on Gq/G11 dosage. Mice lacking both G-proteins $Gq^{-/-}$ / $G11^{-/-}$ died at embryonic day 11 due to ventricular hypoplasia. In addition, $Gq^{-/-}$ / $G11^{+/-}$ newborn mutants exhibit craniofacial defects. Thus, two active Gq and G11 alleles are necessary for postnatal life and at least one intact Gq or G11 allele is required to bring the embryo to term [14]. G11 seems to be preferentially required for 5-HT_{2B}R-dependent heart developmental events, since the skeletal abnormalities observed in $Gq^{-/-}$/$G11^{+/-}$ embryos could not be detected in the 5-HT_{2B}R KO mice

5-HT_{2B}R mutations alter cardiomyocyte function and structure.

Newborn 5-HT_{2B}R KO mice developed cardiac dilation at 100% penetrancy. The thinning of the ventricular wall and the reduction in ventricular mass observed in the 5-HT_{2B}R KO mice result from both a reduction in the number of myocardial cells and a decrease in cell size. The decrease in cardiomyocyte size could be due to impaired growth during postnatal development [15]. Cardiomyocytes from KO mice also exhibit impaired contractility and beating rates in response to dobutamine (a β-adrenergic receptor agonist) in the absence of sympathetic innervation, indicating cell

autonomous defects. The impaired contractility and myofibrillar degeneration could be related to the altered intercalated disc structures observed ultrastructurally in 5-HT_{2B}R KO hearts [15]. Myofibril loss is the most obvious structural change in human cardiomyopathy and sarcomeric disarray is characteristic of failing hearts [16]. Interestingly, most mutations leading to dilated cardiomyopathy in humans affect structural proteins involved in cytoskeleton-extracellular matrix interactions at the Z-stripe [17]. Z line-associated structures are responsible for the lateral alignment of myofibrils, and their anchorage to N-cadherin- and vinculin- containing costameres along the cell membrane. N-cadherin plays an important role in maintaining myofibril integrity, in cardiomyocyte interaction and in myofibrilogenesis [18]. The 5-HT_{2B}R KO mice exhibit decreased N-cadherin levels [15]. Downregulation of N-cadherin and disruption of intercellular adhesion have also been reported in failing guinea pig hearts [19]. Myofibrillar organization and intercellular junction structures are impaired in the absence of 5-HT_{2B}R, suggesting that its activation plays a crucial and specific role in the organization and expression of cytoskeletal structures in cardiomyocytes [15].

The 5-HT_{2B}R KO heart phenotype is reminiscent of the natural history of patients with dilated cardiomyopathy.

All 5-HT_{2B}R KO mice that survived until the first postnatal week reached adulthood and exhibited dilated cardiomyopathy-like symptoms. Dilated cardiomyopathy in human is diagnosed with two typical features, left ventricular (LV) dilatation and depressed LV systolic performance. Both features were observed in adult 5-HT_{2B}R KO mice hearts. Echographic analysis showed that the LV end-diastolic diameter and the LV end-systolic diameter were significantly increased in 5-HT_{2B}R KO male mice [15]. Moreover, serum biochemical indicators of myocardial infarction (creatine kinase-MB mass, troponin I-C) are increased in the 5-HT_{2B}R KO mice. 5-HT_{2B}R KO mice therefore, provide a novel model of mouse cardiomyopathy, characterized by a phenotype of dilation with a “failed” hypertrophic response (figure 1).

Heart-specific overexpression of 5-HT_{2B}R leads to cardiac hypertrophy. Overexpression of 5-HT_{2B}R in the heart using a MHC promoter containing transgene also leads to specific defects. Transgenic (TG) mice overexpressing the Gq-coupled 5-HT_{2B}R exhibit hypertrophy that is due to increased number and growth of cardiomyocytes. The overexpression of 5-HT_{2B}R raises the expression of hypertrophic genes such as ANF and β-MHC as an evidence of hypertrophic response in the TG heart. This hypertrophic response is a direct effect of overexpression of 5-HT_{2B}R in the myocardium, since hypertrophy was observed without evidence of hemodynamic overload. Cardiac fibrosis was not observed in TG hearts, indicating that cardiomyocyte-specific overexpression of 5-HT_{2B}R does not alter remodeling in non-myocyte cells through paracrine mechanisms [20].

Several factors might be responsible for the development of compensated hypertrophy after overexpression of 5-HT_{2B}R. A first possibility to explain the

development of hypertrophy is the change in signaling pathways and Gq protein repertoire coupling. Overexpression of Gq-downstream signaling molecules has been associated with the induction of a cardiomyopathy characterized by a ventricular hypertrophy: cardiac-specific overexpression of constitutively active δ-PKC and ε-PKC isoforms caused identical, non-pathological hypertrophic phenotypes [21,22]; TG expressing an activated MEK1 cDNA in the heart also demonstrated concentric hypertrophy without signs of cardiomyopathy [23].

Another possible cause of hypertrophy after overexpression of 5-HT_{2B}R could be secondary to compensation for the early apoptosis and increased proliferation of cardiomyocytes. 5-HT_{2B}R KO newborn mice exhibit ventricular hypoplasia due to impaired cardiomyocyte proliferation [13]. It is possible that overexpression of 5-HT_{2B}R in the heart activates mitogenic pathway(s) before birth and then inhibits apoptosis in terminally differentiated and non-proliferative cardiomyocytes after the birth.

The involvement of Gq-coupled receptors in regulating cardiomyocyte growth has not yet been fully understood despite the use of both loss-of-function and gain-of-function experiments to a given receptor *in vivo*. For example, TG mice overexpressing the angiotensin AT1 receptor in the myocardium develop cardiac hypertrophy [24], but pressure overload and stretch-induced hypertrophy still occur in AT1 KO mice [25]; cardiac specific overexpression of constitutively active alpha-1B adrenergic receptor in TG results in mild cardiac hypertrophy [26] but no hypertrophy developed in TG mice overexpressing the wild type alpha-1B adrenergic receptor [27]. Mice with selective Gq and G11 ablation in cardiomyocytes showed no detectable ventricular hypertrophy in response to pressure-overload induced by aortic constriction [28].

Mitochondrial defects are observed in the 5-HT_{2B}R KO and transgenic hearts.
Mitochondrial dysfunction has been reported in human cardiac diseases including ischemic and non-ischemic heart failure, myocardial infarction, arrhythmia, myocarditis and dilated cardiomyopathy [29,30]. Although damage in mitochondria is a key step leading to programmed cell death, no typical apoptotic bodies were observed in the heart of 5-HT_{2B}R KO [15]. Altered mitochondrial membrane integrity was observed, however, in the cardiomyocytes of 5-HT_{2B}R KO mice that presented dilated cardiomyopathy (figure 2). Furthermore, reduced succinate dehydrogenase (SHD) and cytochrome C (cytoC) oxidase (COX) indicated altered functions of electron transport complexes II and IV, respectively [31]. Increased lactate plasma levels in KO mice confirmed these observations [31]. Decreased oxidative phosphorylation and respiration that lead to lactate production have also been observed in human mitochondrial myopathies and animal models for dilated cardiomyopathy [32]. 5-HT_{2B}R KO cardiomyocytes may be in the pre-apoptotic stage long before nuclear events became morphologically manifested *in vivo*. Accordingly, evidence of cytoC redistribution from mitochondria to cytoplasm and caspase activation without nuclear morphology of apoptosis has also been observed in idiopathic dilated cardiomyopathic in human heart [33]. These data raise the issue how cardiomyocytes seemingly tolerate some cytosolic

cytoC. The balance between nuclear fragmentation and protein cleavage is variable in cardiomyocytes [34]. Other factors might explain the presence of processed caspase-3 in cells that are not undergoing apoptosis.

Overexpression of 5-HT_{2B}R in the mouse heart leads to abnormally high mitochondrial numbers as observed by transmission electron microscopic analysis and red ragged fibers staining. Moreover, mitochondrial enzyme activities such as COX and SDH are increased in TG mice heart. This increase in oxidative phosphorylation activity is also suggestive of an accumulation of mitochondria in the TG heart [20].

Mitochondria are targets in 5-HT_{2B}R survival signals in isolated cardiomyocytes. Mitochondria represent an essential component of many apoptotic pathways by controlling the release of cytoC into the cytosol [33,35]. Released cytoC from mitochondria forms an activation complex with apoptotic protein-activating factor (APAF)-1 and caspase-9, which activates downstream caspases to execute final morphological and biochemical alterations [36]. This pathway is tightly regulated by a group of antiapoptotic proteins, such as Bcl-2, and proapoptotic proteins, such as Bax [37]. Further downstream regulation occurs through various inhibitors of caspases [38]. Cardiomyocytes also use a mitochondria-dependent apoptotic pathway [39]. In isolated cardiomyocytes, serum withdrawal is a classical inducer of apoptosis. Our work has shown that 5-HT *via* the 5-HT_{2B}R acts as a survival factor, by inhibiting serum withdrawal-induced apoptosis as manifested by DNA fragmentation, nuclear chromatin condensation and TUNEL labeling [31]. 5-HT prevents cytoC release and caspase-9 and -3 activation following serum deprivation *via* cross talks between phosphatidylinositol-3 kinase (PI3K) / Akt and ERK1/2 signaling pathways. Upon activation of Akt by 5-HT, phosphorylation of IKappaB-alpha triggers its degradation to release NF-KappaB. This activation of NF-KB inhibits serum deprivation-induced the adenine nucleotide translocator (ANT) expression to maintain mitochondrial permeability [31]. Parallel to this pathway, ERK activation by 5-HT inhibits elevation of Bax expression induced by serum deprivation. Defects in survival pathway in the 5-HT_{2B}R KO heart are not secondary to the cardiomyopathy, since defective cardiomyocyte survival can be reverse by transfection of 5-HT_{2B}R cDNA and LIF survival signaling is intact. In addition, 5-HT did not induce hypertrophy of cultured cardiomyocytes (unpublished observation).

5-HT via 5-HT_{2B}R regulates the expression of ANT-1 in the heart.
Although alternative mechanisms of mitochondrial membrane permeabilization may exist, ANT-1 emerges as a major player in the regulation of cell death [40]. The ANT-1 combines mitochondrial energy-producing and cytosolic energy-consuming processes. Impaired ANT-1 functions have been observed in heart tissue from patients with dilated cardiomyopathy [41]. A shift in the ANT isoform transcription profile was found in heart tissue from patients with dilated cardiomyopathy, but not in that from such patients with ischemic or valvular cardiomyopathy. The shift is characterized by an increase in ANT-1, a decrease in ANT-2 and an unchanged ANT-3 proportion. This

alteration in the ANT isoform pattern is not a general phenomenon of end-stage heart failure, and clearly occurs already before the heart is terminally damaged. Therefore, an altered ANT isoform expression appears to be a feature of a dilated cardiomyopathy-specific gene program [42]. ANT-1 KO mice exhibited severe cardiomyopathy [43] and point mutations in the ANT-1 gene have been reported in cases of human mitochondrial diseases [44]. ANT-1 overexpression leads to phenotypic alterations typical of apoptosis, *i.e.* collapsed mitochondrial membrane potential, cytoC release, caspase activation and DNA degradation [45]. In the 5-HT_{2B}R KO hearts, elevated expression level of ANT-1 was detected. In cardiomyocytes, ANT-1 is a main target of PI3K / Akt signaling that control mitochondrial permeability [31]. Moreover, ANT-1 downregulation was observed in 5-HT_{2B}R overexpressing TG hearts [20] (figure 3). Interestingly, histological and ultrastructural examination of muscle from ANT-1 null KO mice revealed red ragged fibers, COX and SDH activation, cardiac hypertrophy with mitochondrial proliferation similar to 5-HT_{2B}R TG mice [43].

5-HT via 5-HT2B R regulates Bax expression in the heart.

The proto-oncogenes Bcl-2 -an inhibitor of apoptosis and Bax -an inducer of apoptosis play critical roles in the molecular circuit controlling apoptosis in cardiac muscle. The ratio of Bax to Bcl-2 determines survival or death after an apoptotic stimulus. Patients with mild heart failure show significantly higher Bax/Bcl-2 ratios than patients with advanced heart failure. The susceptibility of myocytes to apoptosis is significantly increased in the early phase of heart failure, but decreases with worsening of the disease due to depressed expression of the Bax onco-protein. This increased susceptibility to apoptosis may have a role in the transition from mild to severe heart failure in patients with idiopathic dilated cardiomyopathy [46].

In cardiomyocyte culture, the effect of 5-HT *via* 5-HT_{2B}R was to downregulate Bax expression that was completely inhibited by the ERK1/2 inhibitor PD-09858. In neonatal cardiomyocytes, Bax is necessary, but not sufficient, to control cytoC release; cytoC diffusion is controlled by both ERK1/2 and PI3K/Akt. While the Bcl-2 family of proteins, at least in part, controls the mitochondrial apoptosis, only ERK1/2 inhibition can overturn 5-HT-induced down regulation of Bax in cardiomyocytes [31]. Bax forms membrane pores that control mitochondrial permeability and release cytoC. Bcl-2 and Bcl-XL inhibit formation of these pores, however, no alteration in the expression of these genes could be detected in 5-HT_{2B}R KO heart mRNA. *In vivo*, analysis in KO mice heart showed that the Bax expression level was increased. Our data indicate that 5-HT/5-HT_{2B}R cytoprotective signaling targets mitochondria by regulating Bax and ANT-1 expression in heart.

A proposed model for transition from hypertrophic to dilated cardiomyopathy.

Hypertrophy is viewed as compensatory and the transition to heart failure occurs *via* the constitutive activation of proapoptotic signals due to extensive hypertrophic stimulus. In cardiac tissue, apoptosis is a form of programmed cell death distinct from

necrotic cell death. It has been proposed that ventricular dilatation and neurohormonal activation during heart failure lead to up-regulation of transcriptional factors induced during cardiomyocyte hypertrophy that prepared the cells for entry in the cell cycle [47]. However, terminally differentiated cardiomyocytes cannot divide and, instead, they undergo apoptosis. Initiation of apoptosis is associated with activation of upstream cascades, including the release of cytoC from mitochondria to cytoplasm and processing of proteolytic caspases [48]. Persistent aerobic conditioning induces a compensated hypertrophy that is thought to be beneficial to the heart. These functional changes may increase the mitochondria proliferation rate. Failing mitochondrial functions may lead to decompensation due to induction of apoptotic signaling. Intrinsic determinants of mitochondrial apoptosis have recently been elucidated that modify or abort decompensation: Cardiac hypertrophy induced by the Gq pathway upregulates Nix expression whereas, a generalized increase in apoptotic mediators did not occur [49]. Recent data on 5-HT_{2B}R signaling pathway indicate that 5-HT can control expression of the nuclear genes Bax and ANT-1, which regulate mitochondrial function. It is becoming clear that 5-HT signaling *via* 5-HT_{2B}R converges onto mitochondria, major cellular compartments, which can modify cardiac hypertrophy or decompensation (figure 4). These findings promise to have important implications for the understanding of congenital heart disease and the development of potential therapeutic interventions for cardiovascular disease.

Acknowledgements

The excellent drawings of Dr. Laurent Désaubry are greatly appreciated. We thank Dr P. Dollé for critical reading of the manuscript and for helpful discussions. This work has been supported by funds from the Centre National de la Recherche Scientifique, the Institut National de la Santé et de la Recherche Médicale, the Hôpital Universitaire de Strasbourg, the Université Louis Pasteur and by grants from the Fondation de France, the Fondation pour la Recherche Médicale, the Association pour la Recherche contre le Cancer. CGN is supported by a fellowship from the Lefoulon-Delalande Fondation.

Figure Legends

Nebigil Figure 1

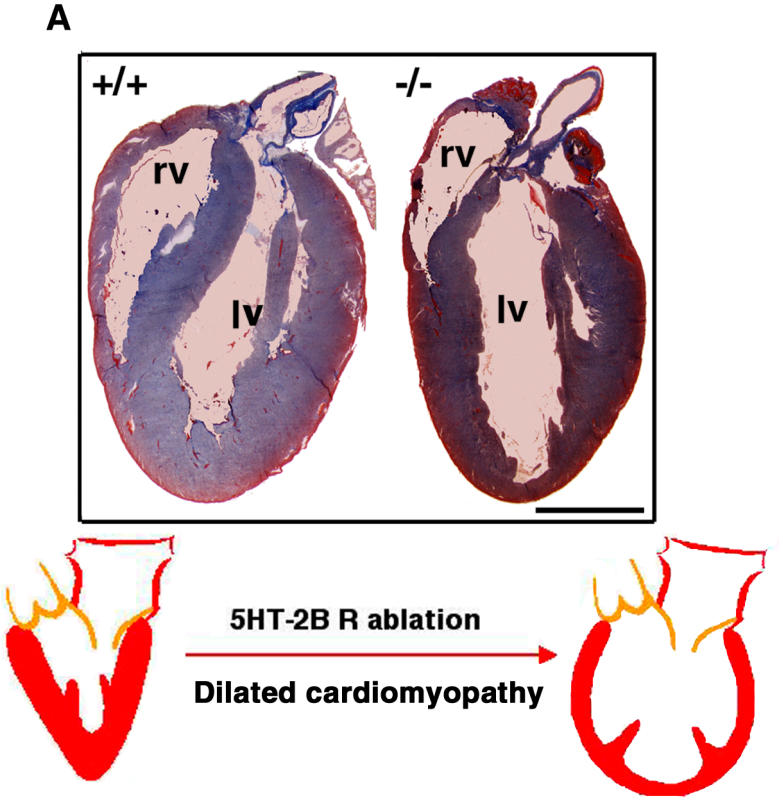

Figure 1. Ablation of 5-HT_{2B}R in mice leads dilated cardiomyopathy without compensatory hypertrophic response. A representative sagittal section from adult hearts (12 weeks old) show thinning of the left venticle (lv) for in 5-HT_{2B}R KO (-/-) mice compared to wild type (+/+) . rv: right ventricle; Bar: 200 μm. Adapted from [15].

Nebigil figure 2

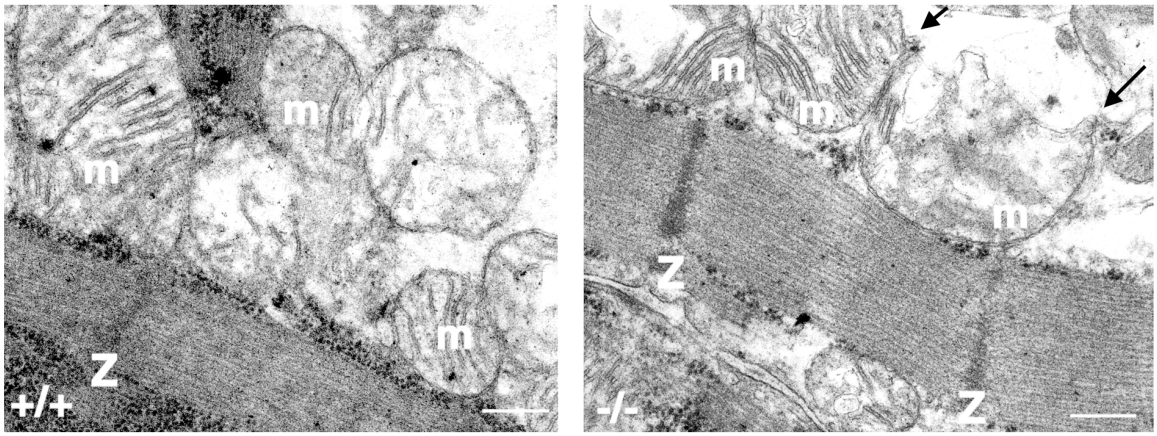

Figure 2. 5-HT_{2B}R mutant mice display alterations of cardiomyocyte cytoarchitecture. Transmission electronic microscopy on ultra-thin sections of the compact layer from left ventricles of 5-HT_{2B}R wild type (+/+) and KO (-/-) newborn mice shows mitochondrial defects (m, arrow). Z-bands (Z). Bars: 1 μm.

Nebigil figure 3

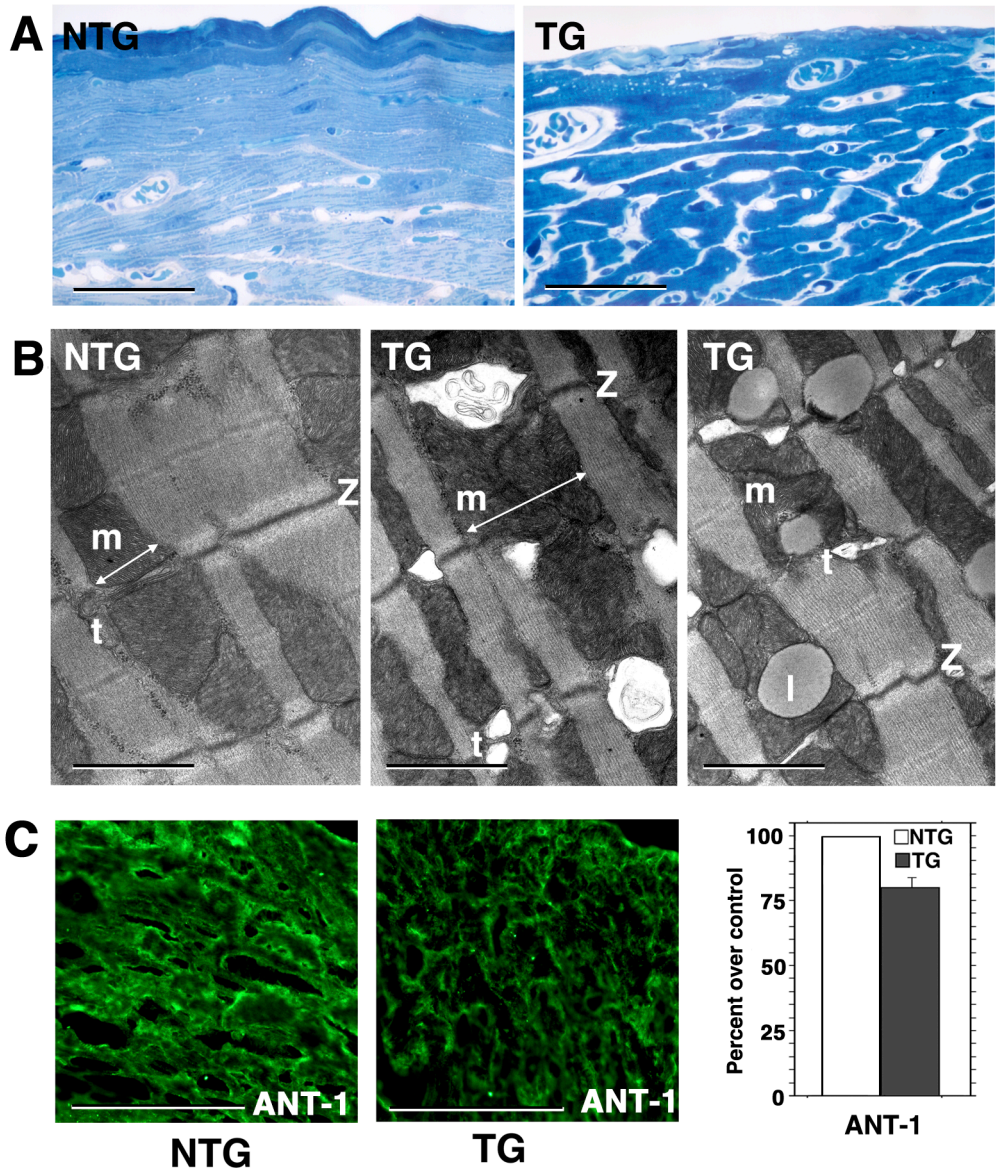

Figure 3. Histological analysis of 5-HT_{2B} TG mouse heart. The analysis of the compact layer of adult mice heart was performed on semi-thin sections (A) and by transmission electronic microscopy on ultra-thin sections (B) of wild type (NTG) and transgenic (TG) mice. Lipid (l), mitochondria (m, arrow), and T-tubules (t) alterations. Z-bands (Z). Bars: A 40 μm, and B 1 μm. As a mitochondrial marker, the ANT-1 protein expression (C) was evaluated by immuno-histochemical staining. ANT-1 protein expression levels evaluated by densitometric analysis of western blot are expressed as percent of NTG. Bars=120 μm. Adapted from [20].

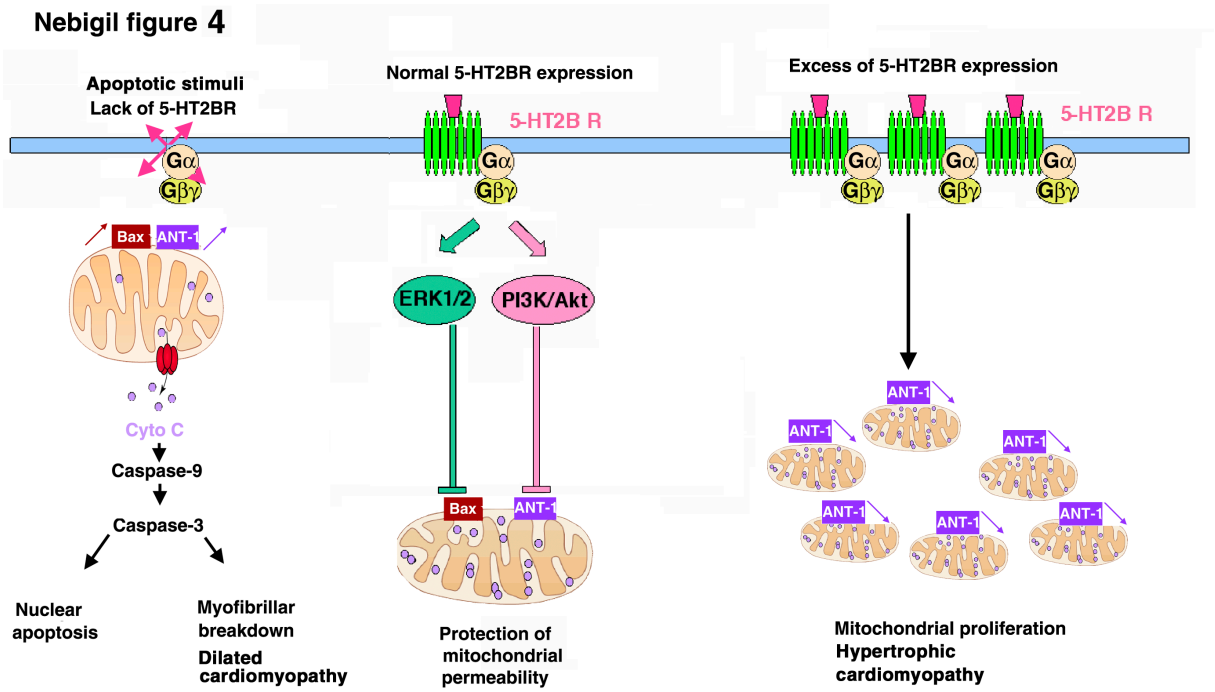

Figure 4. The role of mitochondria for the transition between hypertrophy and dilated cardiomyopathy**.** Schematic presentation of 5-HT cytoprotective signaling pathways in cardiomyocytes. 5-HT binding to 5-HT_{2B}R activates both PI3K/Akt and ERK kinases that inhibits ANT-1 and Bax expression, respectively to control mitochondrial membrane permeability (middle). In the 5-HT_{2B}R knockout mice as a model of dilated cardiomyopathy, the Gq-coupled 5-HT_{2B}R signaling regulates mitochondrial structure and function thereby controlling myofibrillar organization in the heart (left). In the 5-HT_{2B}R overexpressing mice, the Gq-coupled 5-HT_{2B}R signaling regulates ANT-1 expression and mitochondria number thereby giving rise to hypertrophic heart (right).

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