Chapter 13

Production and Function of Serotonin in Cardiac Cells

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http://dx.doi.org/10.5772/intechopen.69111

Abstract

Serotonin [5-hydroxy-tryptamine (5-HT)] exerts a number of effects in the mammalian heart: increase in heart rate, increase in force of contraction, fibrosis of cardiac valves, coronary constriction, arrhythmias and thrombosis. These effects are, in part, mediated by 5-HT-receptors, in part, directly by 5-HT action on intracellular proteins. In the beginning, 5-HT was thought to be only produced in the gut and then transported into the heart via platelets, because platelets can take up 5-HT in the gut and enter the capillaries and thus the mammalian heart. 5-HT is to a large extent metabolized in the liver and excreted via the urine. Here, we will also overview data that argue for additional pathways, namely production and degradation of 5-HT in the cells of the heart itself.

Keywords: heart, human atrium, serotonin, 5-hydroxytryptophan, MAO

1. Introduction

Practically, all physiological systems of the mammalian body have been reported to be affected by 5-hydroxy-tryptamine (5-HT). Prominently affected systems are the central nerve system and the peripheral nerve system but 5-HT also plays a complex role in the gut, the liver and e.g. spleen. However, 5-HT also seems to have profound (patho)-physiological roles in the heart. Some drugs that are devised to treat non-cardiac diseases alter the level of 5-HT in the heart or act as agonists/antagonists on one or more of the 5-HT-receptors in the mammalian heart. Finally, there is evidence that in cardiovascular diseases 5-HT itself can affect the heart in a compensatory or detrimental way. Some newer aspects of the action and generation of 5-HT in the mammalian heart with special emphasis on the human heart will be addressed here. Finally, gaps in our knowledge, conflicting views, some challenging hypotheses and suggestions for further research will be put forward.

2. Historical aspects

The history of 5-HT goes back in time. Some write that the first hint of 5-HT's existence can be traced back to the work of Otto Weiss (1896, Göttingen, Germany) [1], who noted that serum in contrast to plasma exerted vasoconstrictory responses in dogs, a finding which one could now explained by high (serum) and low (plasma) levels of 5-HT in the samples of Weiss [2].

Enterochromaffin cells were first described in the lining of the gastrointestinal tract at the end of the nineteenth century (Charkow in ancient Imperial Russia) [3]. Using various staining reactions, these enterochromaffin cells were found in the gut of many species [4]. Early work described an increase in blood pressure in one rabbit with extracts from human carcinoid tumors (tumors derived from enterochromaffin cells [5]). Stimulated by these findings, Vittorio Erspamer in Italy (working in Pavia, Rome and later in Bari, Italy) studied acetone extracts of mucosal intestinal strips from animals (mainly rabbits) for decades. In an early paper, he presented an original recording for a positive inotropic effect (PIE) of "enteramine" (the putative active ingredient of his acetone extract) on the frog heart, conceivably the first inotropic effect reported for 5-HT [6]. Later he purified the extract further and reported the presence of a putative indolalkylamine that increased force in isolated hearts of various kinds of molluscs [7]. His efforts culminated in identifying his "enteramine" as 5-hydroxy-tryptamine [8]. 5-HT was, independently from Erspamer, studied by the group of Irvine H. Page in the USA (Cleveland, Ohio) and given its current name "serotonin" [9]. The American authors were investigating naturally occurring vasoconstrictory compounds (vasoconstriction being tested in rabbit ear arteries) in serum of humans in order to find a putative cause of peripheral arterial hypertension in humans. As a first step, they partially purified a vasoconstrictory compound from clotted serum of beef [10] and later this vasoconstrictor (their "serotonin") by chemical synthesis was identified as 5-hydroxy-tryptamine [11]. Synthetic 5-HT was shown in early work to act on blood pressure in animals (cats and rabbits [12]) and hypertensive patients [12]. These authors noted in patients an initial fall in blood pressure (measured in brachial arteries, absent in the presence of atropine) followed by a modest increase in blood pressure (up to 20 mm Hg increase). Patients injected with 5-HT complained of nausea, tightness of the breast, and dizziness, but the pulse rate was not reported [12]. A clear positive chronotropic effect (PCE) of 5-HT by venous injection in humans was published some years later [13, 14]. Initial attempts using biological tests failed [6] to detect 5-HT in the heart, but several decades later, the presence of 5-HT in the mammalian heart (hamster, human heart) has been proven (using more sensitive methods (fluorescence): e.g. [15]).

3. Sources of cardiac 5-HT

Ninety percent of 5-HT in the body is present in enterochromaffin cells in the gut, 5% in platelets, and about 2% in brain [16]. 5-HT in the blood is mainly assumed to be synthesized in enterochromaffin cells of the gastrointestinal tract [17, 18]. 5-HT is released from these enterochromaffin cells and is taken up rapidly by thrombocytes (review: [19, 20]). Alternatively,

5-HT enters the portal vein and passes into liver cells where it is rapidly degraded by monoamine oxidase-A (MAO-A) (see below) and its metabolites leave the body via the urine. Thus, platelets are commonly thought to be the main source of 5-HT that reaches the mammalian heart. Many cell types like mast cells also contain 5-HT (see below) and small numbers of mast cells are present in the mammalian heart [19]. Many immune cells contain 5-HT and are also found in small numbers in the heart. Newer data (using more sensitive analytical methods: HPLC, GC, MS) cast some doubt on this classical concept (see below). Thus, 5-HT was detected not only in hamster heart and human heart [15] but also in mouse heart [21], rat neonatal cardiomyocytes [22], and adult mouse cardiomyocytes [23]. The content of 5-HT in the hamster heart was reduced by the treatment of the living hamster with pargyline, an inhibitor of MAO-A [15] suggesting degradation of 5-HT in the heart via MAO-A. Moreover, the level of 5-HT in the hamster heart was not reduced by injecting in the living hamster a dose of 6-hydroxy-dopamine, sufficiently high to reduce cardiac norepinephrine levels, suggesting that cardiac 5-HT is not derived to a measurable extent from the neuronal cells in the hamster heart [15]. Compound 48/80, a substance that is known to release 5-HT from cells in other organ systems, increased force of contraction in isolated atrial preparation of 5-HT_4-receptor overexpressing mice, indicating that releasable 5-HT is present in these cardiac preparations, but leaving open the question of its cellular origin [24].

5-HT is formed from L-tryptophan by the enzyme tryptophan hydroxylase (TPH, see next paragraph). Peroral treatment of animals or humans with tryptophan (an essential amino acid) increases body concentrations of tryptophan. Uptake of tryptophan in the gut is brought about by the protein transporter enzymes SLC6A19 and SLC16A10 [25]. Protein-rich food is known to compete with these transporters and will lead to lower levels of tryptophan in the body [25]. Effects of 5-HT in the heart were usually thought to be due to 5-HT released from intact platelets. Indeed huge amounts of 5-HT can be released from activated thrombi in the heart. These thrombi are formed in atrial fibrillation and contain, of course, thrombocytes. 5-HT released from thrombi may then reach by diffusion endothelial cells. If these endothelial cells were lacking (for instance after local injury), 5-HT may act on 5-HT-receptors on the outer surface of smooth muscle cells or may reach cardiomyocytes. Conceivably, 5-HT in the plasma may reach the heart from the lungs (lung veins, left atrium, and left ventricle) and then enter the coronaries and thence affect the whole heart. In addition, 5-HT in the plasma may come from the periphery (via the right atrium and right ventricle) and exert right heart sided effects. Indeed, in tumors producing 5-HT (carcinoids, see below), such pathways are accepted to occur. Depending on the anatomic localization of the tumor, vasoconstriction would occur and should explain cases of left or right (or global) hypertrophy or contractile failure of the heart [26]. Furthermore, the 5-HT producing enzyme TPH1 (see below) was detected in pulmonary endothelial cells and could therefore generate 5-HT in the lung and it is conceivable that this 5-HT of pulmonary origin reaches the left heart via the pulmonary veins [27]:

There is precedence in the literature that a neurotransmitter like 5-HT can be formed in the heart. Here, we mention as an example noradrenaline which can act in an autocrine and paracrine fashion: there is evidence for the presence, synthesis (and degradation), and intracellular action of noradrenaline in heart muscle cells on β- [28] and α-adrenoceptors (most of the

latter being detected intracellularly in the nuclear membrane, for overview [29]). We speculate that the 5-HT-receptors (which are phylogenetically assumed to be much older than adrenoceptors) might also be detectable intracellularly in cardiomyocytes when more sensitive techniques will become available (**Figure 1**). It is notoriously difficult to detect endogenous G-protein-coupled receptors with specific, highly sensitive antibodies. Progress in this regard would be highly desired. Interestingly, 5-HT can exert intracellular effects via oxidation of 5-HT in mitochondria (e.g. in mouse heart) and formation of free radicals. In that way, 5-HT

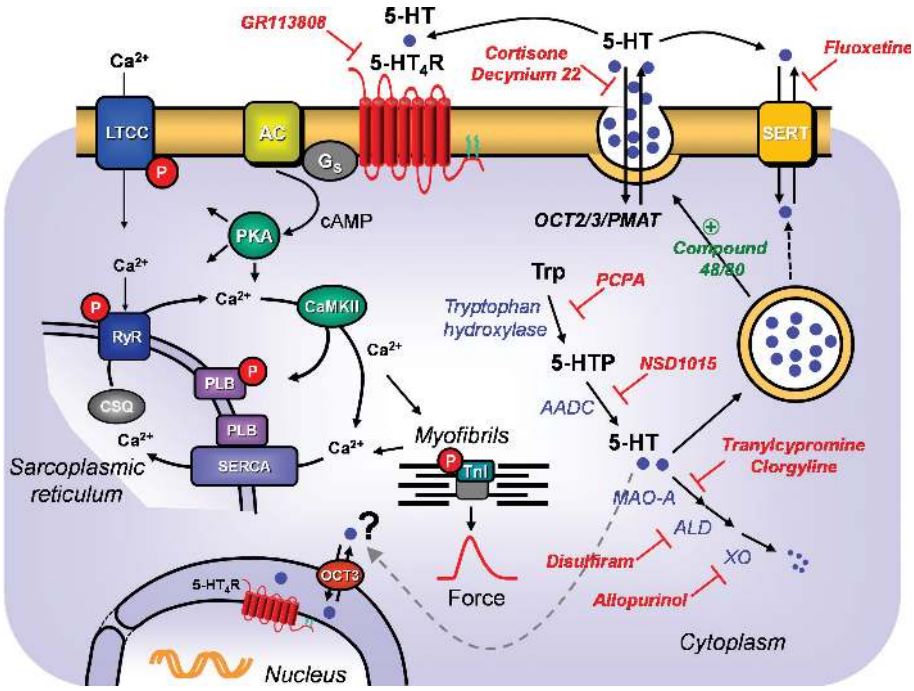

Figure 1. Hypothetical fates of 5-HT in the mammalian heart. Ca^{2+} enters the mammalian heart cell via the L-type Ca^{2+} channel (LTCC). This process can be enhanced by 5-HT via a cascade starting with the 5-HT_4 receptor (inhibitable by GR113808) occupation of which by 5-HT elevates activity of adenylyl cyclase (AC) in the sarcolemma via stimulatory G-proteins (Gs), elevates subsequent production of cAMP, and thereby activates cAMP-dependent protein kinase (PKA). PKA increases cardiac force generation and relaxation by increasing the phosphorylation state (P) of LTCC, phospholamban (PLB), and other regulatory proteins. Trigger Ca^{2+} initiates release of Ca^{2+} from the sarcoplasmic reticulum via ryanodine receptors (RYR) into the cytosol. There, Ca^{2+} activates myofilaments and this activation leads to increased inotropy. In diastole, Ca^{2+} is taken up into the sarcoplasmic reticulum via a sarcoplasmic reticulum Ca^{2+} ATPase (SERCA), the activity of which is enhanced due to an increased phosphorylation state of PLB. We tentatively propose that 5-HT is stored in cardiomyocytes in a hypothetical locus from which it can be released by compound 48/80 and extruded from the cardiomyocytes, possibly via OCT2 and/or OCT3 and/or PMAT (inhibitable by cortisone, decynium 22). From the outside of the cardiomyocytes, 5-HT might be pumped back into the cardiomyocyte via SERT (inhibitable by fluoxetine). 5-HT might be formed in cardiomyocytes from tryptophan (Trp) via the enzyme tryptophan hydroxylase to generate 5-hydroxytryptophan (5-HTP) and thereafter decarboxylated by AADC (inhibitable by NSD1015) to 5-HT that is degraded via MAO-A (inhibitable by tranylcypromine) and its metabolites are substrates for aldehyde dehydrogenases (ALD; disulfiram-sensitive) or xanthine oxidases (XO; allopurinol-sensitive). In addition, one can speculate that 5-HT can pass through the outer nuclear membrane via OCT and then activate the inner nuclear membrane located 5-HT_4 receptor which activates than AC via Gs leading to phosphorylation of substrates in the nucleus and to altered gene transcription.

can also act receptor independently, at least in high concentrations to lead to apoptosis and necrosis, at least in the mouse heart [17, 30].

Furthermore, 5-HT can form covalent links to intracellular proteins and thence altering their functional role: transglutaminases can initiate covalent binding of 5-HT to fibrinogen, to small G-proteins, and to several other proteins present in platelets (review: [31]).

On the surface of platelets, a 5-HT_{2A}-receptor is known to be expressed. Its activation will activate thrombosis. 5-HT is thought to enter platelets via serotonin transporter (SERT) (for review, see Refs. [32, 33]). Within the platelet, 5-HT is either degraded via oxidation or transported via Vesicular monoamine transporter (VMAT) into vesicles in platelets which will store (VMAT1 and VMAT2 are also present in other non-neuronal cells, saliva cells [34], and renal tubular cells [35]; it is worthwhile to try to detect VMAT in cardiomyocytes, which has apparently not yet been reported) 5-HT and protect 5-HT from degradation. Upon an appropriate stimulus, 5-HT containing vesicles can reach the outer membrane of the platelets, fuse, and release 5-HT out of the platelets into the plasma. It has been shown that high blood platelet levels of 5-HT can serotonylate the protein rab4, which then inhibits the shift of SERT from the sublemmal space into the plasmalemma and hence quantitatively reduces its own uptake via SERT into platelets (which has been suggested to be of pathological relevance). There, 5-HT can act via the above-mentioned receptors in an autocrine or paracrine way [31, 36, 37]. Moreover, it stands to reason that 5-HT produced within cardiomyocytes might also exit the cardiomyocyte wherein it was formed (speculatively using uptake 1 or 2 and/or SERT, see below) to act in an autocrine or paracrine fashion at least under pathophysiological conditions.

5-HT can be compartmentalized in relevant cells: in peritoneal mast cells from rats, 5-HT was not only present in storage vesicles but also in the nucleus [38]. It is possible that mast cells produce relevant amounts of 5-HT because they contain their own TPH1 [19]. Compound 48/80 can release 5-HT from mast cells and PCPA (an inhibitor of TPH activity) can reduce the levels of 5-HT in the cytosol of mast cells but not the nucleus of mast cells [38]. Likewise, clorgyline (a MAO-A inhibitor) and fluoxetine (a SERT-inhibitor) could decrease the cytosolic but surprisingly also the nuclear amounts of 5-HT in mast cells [38]. These data argue for the existence of functionally distinct subcellular pools of 5-HT. Similar studies in cardiomyocytes are apparently lacking and are keenly awaited.

5-HT is not only produced in the mammalian body but also in the plant kingdom and is found in foodstuff such as nuts, bananas, oranges, coffee, and peaches [39]. This might be an additional source of 5-HT reaching the heart. Finally, there are data that in the lumen of the gut, bacteria form 5-HT, which may be absorbed and may also reach the heart [40]. Uptake via the intestine could be achieved by SERT which present and active in epithelial cell of the gut (in crypts of intestine, rat [41]).

4. Enzymes for synthesis of 5-HT in the heart

The isoform TPH1 is mainly expressed in the gut (but also in the pineal gland [21]), whereas TPH2 is mainly found in the CNS (but also in enteric nerve cells [21, 36]). Knockout of TPH1 reduced cardiac (adult mouse) 5-HT levels to about 10% of wild-type levels, indicating a relevant

production of 5-HT in the heart [21]. Some TPH1-knockout mice exhibited signs of left ventricular systolic failure without histologically detectable fibrosis [21] suggesting beneficial effects of the presence of 5-HT for cardiac function. In RNA from HL-1 cells and neonatal rat heart cells in Northern blots, TPH1 was detectable and TPH2 was missing [22] (similarly in adult hamster heart [42]). In RNA prepared from whole adult mouse hearts, TPH1 but not TPH2 was detected by PCR [43, 44]. Western blotting revealed low levels of TPH1 in mouse and rat adult heart homogenates. Fittingly, with the same antibody under similar conditions, no signal for TPH1 was noted in TPH1-knockout mouse hearts [44]. However, the localization of TPH is uncertain: in rat hearts in immunohistology, TPH1 was located only in cardiac mast cells, but in mouse heart no signal was noted in cardiac mast cells [44]. This might be explained by the antibody used, as others detected in immunohistology TPH in mouse cardiomyocytes as well as human atrial cardiomyocytes [45]. Amino acid decarboxylase (AADC, which is identical to dopamine decarboxylase [46]) on mRNA level was detected in heart (by PCR in neonatal rat cardiomyocytes but not in non-cardiomyocytes from neonatal rat hearts [22]). Subsequently, the activity of AADC will result in the generation of 5-HT. In apparent contrast to neonatal cardiomyocytes, AADC was detected via Western blotting in endothelial cells but not in cardiomyocytes of adult rat hearts and adult mouse hearts [44]. Whether this is due to age differences or lack of translation of RNA or too low protein levels of AADC or the features of the antibody used is still an open question. Others, however, noted in immunohistology the presence of AADC also in cardiomyocytes using slices from adult mouse heart and human right atrium [45]. Moreover, addition of 5-hydroxytryptophan (5-HTP, the direct precursor of 5-HT) enhanced 5-HT levels in these isolated cardiac mouse myocytes [23]. Interestingly, 5-HTP can exert functional effects in the heart. More specifically, in electrically driven left atrial preparations of transgenic mice (which overexpress the human 5-HT_4-receptor in the heart, see below), 5-HTP exerted time- and concentration-dependent positive inotropic effects (PIE) or increased the beating rate [positive chronotropic effect (PCE)] of right atrial preparations [45, 47]. Injection of 5-HTP into intact mice led to an increase of 5-HTP but allows of 5-HT in the cardiac tissue of mice [44]. Injection of benzerazide in intact mice, in contrast, reduced the cardiac levels of 5-HT [44]. Likewise, 5-HTP exerted a PIE in atrium from 5-HT_4 overexpressing mice or human right atrial preparations [47] (**Figure 2**). These contractile effects were blocked by NSD-1015 (**Figure 2**), suggesting they result from the enzymatic formation of 5-HT in these mouse or more importantly human cardiac preparations. Similarly, injection of 5-HPT in living whole mice (and in isolated buffer perfused hearts) led to a measurable increase in the cardiac content of 5-HT [44], and the effect was blocked by injection of benzerazide (an AADC inhibitor, used in treatment of Parkinson's disease). The authors posited that 5-HTP derived from platelets led to 5-HT synthesis in the heart [44]. In earlier work in the kidney, infusion of 5-HTP led to vasoconstriction which was reversed (or block by pretreatment) with carbidopa (a dopa decarboxylase inhibitor [48]). Infusion of 5-HTP led to increased levels of 5-HT in the renal venous effluent and in urine and these elevations of 5-HT returned to baseline values if carbidopa was additionally applied. These data are consistent with renal formation of 5-HT from 5-HTP via dopa decarboxylase activity [48].

A drawback of these pharmacological experiments is always that their interpretation is highly dependent upon the specificity of the inhibitory drugs used. It would be useful to refute or confirm these pharmacological experiments by studying cardiomyocytes from mice with

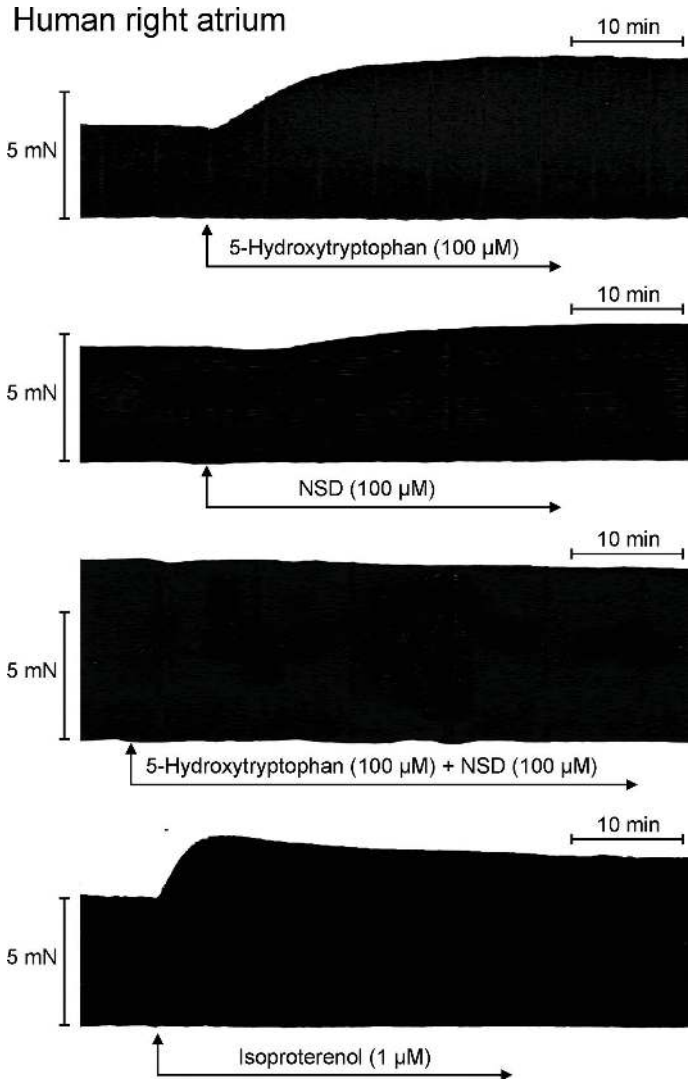

Figure 2. Typical original recording of isolated electrically stimulated trabeculae from a human atrium. The ordinate indicates force of contraction in milli Newton (mN), and the abscissae indicate time in minutes exemplified by scale bars. Of note, 5-hydroxytryptophan increases force of contraction (lane 1) and this effect was gone in the presence of NSD 1015, suggesting that 5-HT formation is necessary. NSD always exerted a small contractile effect of unknown origin. Isoproterenol, an unselective β-adrenoceptor agonist, was used as positive control.

cardiac-specific knockout of TPH1 and/or aromatic L-amino acid decarboxylase (AADC). Data for the local generation of 5-HT in peripheral arterial tissue (rat aorta, isolated human arterial coronary smooth muscle cells) are available and argue for local production and release independently of plasma or platelet levels of 5-HT [49, 50]. When one studied cardiac

tissue in adult human autopsies, in 72 or 80% of neurons within cardiac ganglia, tryptophan hydroxylase or dopa-decarboxylase immune reactivity was found, respectively, using commercial antibodies [51]. These levels were reduced in the presence of p-chlorophenylalanine (PCPA, an irreversible inhibitor of tryptophan hydroxylase activity) or 3-hydroxy-benzylhydrazine (NSD-1015), an inhibitor of aromatic L-amino acid decarboxylase (AADC [23]). Moreover, addition of 5-hydroxytryptophan (the direct precursor of 5-HT) enhanced 5-HT level in these isolated adult cardiac mouse myocytes [23].

5. Enzymes for degradation of 5-HT in the heart

As mentioned above in non-cardiac tissues, 5-HT is probably degraded by MAO-A. The same probably holds true for adult cardiac myocytes: levels of 5-HT were greatly elevated in the presence of tranylcypromine (clinically used as an antidepressant, inhibiting both MAO-A and MAO-B [23]) or in the presence of clorgylin (a MAO-A inhibitor [23]) but not by deprenyl (clinically used to treat Parkinson's disease, because it inhibits MAO-B [23]). MAO is especially active in gut, liver, and serotoninergic nerve cells. However, species differences exist. MAO-B is much less active in rat heart than MAO-A, and in human heart MAO-A and MAO-B are equally active [52]. The total activity of MAO is 100 times higher in the rat than in the wild-type mouse heart [53]. Likewise, MAO-B is mainly active in mouse heart, compared to MAO-A [54]. Hence, knockout of MAO-A in mice is probably not all that physiologically relevant for the human situation. At least in rat using ligand-binding experiments, even the regional cardiac distribution of MAO was found to be regionally different: there is a fivefold difference in MAO-A levels in parts of the ventricle of rat hearts [55]. The study of 5-HT levels in human cardiac tissue (preferably in cardiomyocytes, which is technically not highly reproducible, or stem cells, which have their own pitfalls) in the absence or presence of selective MAO inhibitors or genetic reduction of MAO levels in human cardiomyocytes are awaited with eagerness. Moreover, 5-HT can also be metabolized by the acrylalkylamine-N-acetyltransferase (present in the heart [56]). 5-HT can be degraded by MAO-A or MAO-B to 5-hydroxy-indole-acetaldehyde and by action of unspecific dehydrogenases and/or alcohol dehydrogenase 2 finally to 5-hydroxy-indole-acetic acid which leaves the body via the kidneys, and its concentration has been used in patients to monitor the presence of 5-HT-producing carcinoid tumors [26, 57]. Based on knockout experiments, 5-HT in the mouse is mainly degraded by MAO-A not MAO-B [58]. Inhibition of the activity of MAO by tranylcypromine potentiated the PIE of 5-HT in atrial preparations of 5-HT_4-receptor overexpressing mice [24]. 5-HT can also be metabolized by an indoleamine 2,3-dioxygenase (the rate limiting step in this pathway, with immunohistology detected in cardiomyocytes and active in mouse heart [59]) to kynurenine (present in mouse heart [60]). Indoleamine 2,3-dioxygenase (IDO) can be induced in infectious diseases like cardiac viral myocarditis [59]. Studying knockout mice for this enzyme supported an important role of IDO in acute viral myocarditis [59]. Furthermore, 5-HT can be metabolized even into melatonin (recent publication on levels of melatonin in rat heart: [61]) by hydroxyindole O-methyltransferase (enzyme present and active in mammalian heart: [56]) in the heart and this melatonin may play a role in protection against cardiac ischemia [62].

6. Uptake 1 of 5-HT in the heart

Classically, re-uptake of 5-HT (but also of neurotransmitters like histamine, noradrenaline, or dopamine) into nerve cells has been called uptake 1 and is assumed to be mediated for 5-HT by SERT (and by dopamine transporter (DAT) for dopamine, as well as by noradrenaline transporter (NAT = NET) for noradrenaline, however, their specificity of transport shows some overlap, which may explain compensations in knockout mouse models [63]). SERT is blocked by some antidepressant drugs like fluoxetine. Likewise, genetic deletion of SERT (total knockout) led to a decrease of 5-HT levels from 29 to 0.4 μM in whole blood, probably as a result of lack of reuptake via SERT into platelets, clearly indicating that SERT is not only active in the central nervous system but also in the periphery. Uptake 1 is energy dependent because it acts against a neurotransmitter gradient. Uptake 1 can also be blocked by cocaine (which is, however, unspecific because it blocks at least also NAT and DAT). Interestingly, the EC_{50} of 5-HT in the presence of cocaine for the PIE is much smaller in human isolated atrial preparations (39 nM) than in the absence of cocaine (230 nM: [64]): this could mean that cocaine inhibits the uptake 1 into nerve cells or that it inhibits reuptake of 5-HT into cardiomyocytes by inhibiting SERT in cardiomyocytes. At low concentrations of 5-HT (50 nM), about 70% of 5-HT is taken up via uptake 1 (the remainder via uptake 2 see below). SERT has been found in the lung (endothelial cells and smooth muscle cells: [65]; rat aorta: [49]) on cardiac valves (rat: [66], dog: [67], human valvular tissue: [43]), conduction system of the mouse, mouse cardiomyocytes, and mouse cardiac endothelial cells [68–70]. At least in fetal cardiomyocytes, SERT was seen in immunohistology [71]. Some detected SERT in the endocardium and endothelium of coronary arterial cells and capillaries, while they failed to detect SERT in cardiomyocytes from adult mice [43]. Others using different experimental conditions detected SERT in cardiomyocytes from adult mouse heart and human right atrium [45]. Functional evidence for the activity and therefore presence of SERT are also available: 5-HT, applied in cell culture of adult rat ventricular myocytes induced cellular hypertrophy and this hypertrophy was attenuated by imipramine [72, 73]. This is functional proof that cardiomyocytes can take up 5-HT and might argue for an involvement of SERT in this process. Knockout of SERT in mice was accompanied in whole blood by an about 10-fold reduction of 5-HT levels [43]. Interestingly, adult mice with global knockout of SERT showed left ventricular dilatation and systolic heart failure (decreased fractional shortening in echocardiography) which was accompanied and possibly caused, in part, by cardiac ventricular interstitial fibrosis as well as cardiac valve fibrosis effects present also on 5-HT_{1B}-receptor knockout mice and hence not 5-HT_{1B}-receptor mediated [43]. SERT is reversible in its transporter function: during ischemia, in the presence of tyramine of amphetamines, intracellular 5-HT can leave mouse cardiomyocytes [68]. The functional role of SERT in the heart is evident from the observation that fluoxetine can shift the concentration response curve for the positive inotropic effect of 5-HT to lower concentrations of 5-HT in the left atrium of mice overexpressing the 5-HT_4-receptor [24]. A prominent pathway is initiated by the enzyme indoleamine-2,3-dioxygenase (IDO, which opens and destroys the indole ring system of tryptophan), which feeds into the so-called kynurenine pathway (review: [19]).

7. Uptake 2 of 5-HT in the heart

Uptake of neurotransmitters (like 5-HT) into non-neuronal cells (such as smooth muscle cells, fibroblasts, endothelial cells, or cardiomyocytes—have been called "uptake 2") and is assumed to be mediated by proteins such as OCT1, OCT2, OCT3, and PMAT. Uptake 2 is not energy dependent because it follows a neurotransmitter gradient. Another difference between uptake 1 and 2 relies on the fact that uptake 2 is much less specific for 5-HT than uptake 1. Usually, proteins that comprise uptake 2 will also transport other neurotransmitters like dopamine and noradrenaline [63]. Uptake 2 is usually inhibited by cortisone (but also by synthetic dexamethasone, by aldosterone, and by budesonide) via unknown mechanisms and divergent specificity for OCT1-3 and PMAT [63, 74]) and more specifically by decynium 22 [57, 63]. At higher concentrations of 5-HT (10 μM), it is mainly transported via uptake 2 (in synaptosomes, regarding decynium 22 as uptake 2-specific [57]). In the CNS, proteins responsible for uptake 2 have been detected not only in nerve cells but also in non-nerve cells (glial cells [63]). Uptake 2 is functionally relevant in the heart because decynium 22 affects the concentration response curve of 5-HT on force of contraction in isolated atrium of 5-HT_4-receptor overexpressing mice [24]. OCT2, OCT3, and PMAT have been detected by immunohistology in mouse or human cardiomyocytes [45] and by immunofluorescence (OCT1, OCT3) in the human heart [75].

8. Inotropic effects of 5-HT in the heart, species differences

A positive inotropic effect (PIE) of 5-HT was described in the heart of many mammalian species. More specifically, a PIE was described in cardiac preparations from cats, guinea pigs, dogs, pigs, and rats [76–80]. The PIE in cats is indirectly mediated via release of endogenous noradrenaline [81]. The PIE in the same species can be region dependent: for instance, in rats, a PIE in left atrium but not in papillary muscle was reported [82]. Similarly, in human atrial but not ventricular preparations, 5-HT exerted a PIE [83, 84]. Later, it was noted that in ventricular preparations from patient in end-stage heart failure a noteworthy effect of 5-HT was detectable and this effect was more pronounced in the presence of the phosphodiesterase inhibitor 3-isobutyl-1methylxanthine (IBMX) [85]. Interestingly, similar findings were reported in pigs: only in the presence of IBMX in ventricular preparations of pigs, a PIE to 5-HT could be noticed [86] suggesting that the low number of 5-HT_4-receptors was unable to raise cyclic-3′,5′-adenosine monophosphate (cAMP) levels to inotropically relevant levels in the presence of substantial endogenous unopposed phosphodiesterase activity in ventricular preparations of humans and pigs. In isolated paced left atrial preparations of wild-type mice, no PIE in the absence [87] or presence (Käufler, Gergs, Neumann, unpublished observations, 2017) of 100 μM IBMX to 5-HT (1 nM–1 μM) was, however, observed, underscoring species differences. The EC_{50} value for the PIE of 5-HT in isolated preparations from human right atrium was between 309 and 230 nM [80]. In mouse adult cardiomyocytes, the 5-HT level was estimated to amount to 2.9 pmol/mg protein [23]. Concentrations of 5-HT in isolated samples from human hearts (freshly frozen, after autopsy, from the right atrium, from papillary muscles) were reported from 0.08 to 0.4 μg/g [15], recalculated as about 0.45 to 2.3 μM. Such

differences might be due to contamination with platelets (for very high values) or postmortal degradation (for low levels). Assuming a homogenous distribution of 5-HT in isolated mouse adult cardiomyocytes, intracellular concentrations of 200 nM for 5-HT have been calculated [23]. These concentrations are well in the range of EC_{50} values for the 5-HT-receptors like those responsible for inotropy in some mammalian species including humans [20, 88]. At high concentrations of 5-HT for prolonged times in the organ bath, a second negative inotropic effect of 5-HT was noted, which was alternatively explained as desensitization by activation of phosphodiesterases [89]. Homologous desensitization in the isolated atrium (also in left ventricle of the living animal) can be clearly shown for the PIE effect of 5-HT in 5-HT_4-receptor overexpressing mice [90, 91] like in isolated human cardiac preparations (review: [92]).

9. Chronotropic and proarrhythmic effects of 5-HT in the heart

Positive chronotropic effects of 5-HT were noted in isolated atrial preparations of rats [93], cats [94], pigs [95] as well as guinea pigs [96] and awake humans [14]. Even bradycardia can be elicited by 5-HT via the von Bezold-Jarisch reflex [97]. In whole pigs and isolated pig cardiac preparations, 5-HT increased the heart rate via 5-HT_4-receptors [86, 92, 98]. It is assumed that the effect is brought about by 5-HT_4-receptors initiating a cascade via Gs, AC, cAMP and then activating hyperpolarization-activated, cyclic nucleotide-gated cation channels (HCN) in the sinus node [86]. 5-HT increased the HCN-coded current called I_f in isolated human atrial cardiomyocytes and was mediated by 5-HT_4-receptors (using specific receptor antagonists [99–101]). In one of the first studies on humans, 5-HT induced cardiac arrhythmias *in vivo* (tachycardia and P wave inversions in two patients: [14]). Interestingly, 5-HT induced arrhythmias even in isolated electrically driven human atrial cardiomyocytes, proving that arrhythmia does not need indirect pathways but is sufficiently explained by direct activation of receptors (5-HT_4-receptors) [102]. Interestingly, the incidence of arrhythmias was enhanced in isolated atria from humans treated prior to surgery with β-adrenoceptor blockers [102, 103]. The arrhythmias could be explained on a single cell basis via late afterdepolarizations [104, 105]. In addition, arrhythmogenesis due to 5-HT might also involve stimulation L-type Ca^{2+}-channels and potassium channels [86, 106]. 5-HT may also be relevant to sustain an existing arrhythmia: during pre-existing atrial fibrillation, more 5-HT will be released from thrombocytes [107]. This can increase local concentrations of 5-HT, which can act on 5-HT_4-receptors to sustain fibrillation (for further hypothetical mechanisms: [92]). Mechanistically interesting is the observation that in some children autoantibodies against 5-HT_4-receptors exist which have been suggested to lead to AV blocks in neonates [108]. In 5-HT_4-receptor overexpressing mice, arrhythmias under basal conditions or after 5-HT stimulation have been observed [23, 87, 109]. The 5-HT_3-receptor might be antiarrhythmic: general deletion of the 5-HT_3-receptor in mice led to spontaneous ventricular tachycardia and increased sudden death in pregnant mice. It was speculated that 5-HT_3-receptor blockers should therefore be avoided in pregnant women [110]. Consistent with this, ondansetron, a blocker of 5-HT_3-receptors, has been reported to elicit arrhythmias in patients [111]. In addition, prolongation of P-waves and highly elevated T-waves (interpreted as a sign of repolarization abnormalities) were described in mice with knockout of 5-HT_{2B}-receptors [112].

10. Effects of 5-HT on cardiac vasculature, species differences

5-HT can induce vasoconstriction also in coronary arteries [20]. During reperfusion of coronary arteries, 5-HT can have detrimental effects like apoptosis and necrosis [72]. In man, a more subtle picture emerges: without endothelium or in defective endothelium (arteriosclerosis, coronaries injected *in vivo* with 5-HT in patients having received transplanted hearts), 5-HT induces vasoconstriction, but in the presence of functional endothelium, 5-HT induces vasodilation in human coronary arterial strips [113–115]. Others noted in human coronary vessel strips with intact endothelium (obtained from transplanted hearts) a 5-HT-mediated vasoconstriction that was in part ketanserin-sensitive [116]. In isolated strips from human pulmonary veins or arteries, 5-HT led to vasoconstriction (regardless of the presence or absence of endothelium) and was interpreted to be mediated by 5-HT_2- and 5-HT_1-receptors while ligand-binding studies presented evidence for the expression of 5-HT_4-, 5-HT_{2A}-, and 5-HT_{1D}-receptors in these tissues [117]. In summary, vasoconstriction can be mediated by 5-HT_{2A}- and 5-HT_{1D}-like receptors and the latter are more relevant for vasoconstriction [114, 118].

11. Use of genetically modified mice to study functional effects of 5-HT in the heart

Gain of function animal models like mice that overexpress in a cardiac specific way 5-HT_4-receptors [87], MAO-A [119], 5-HT_{2B}-receptors [120] or SERT [121] have been described and used to better understand the role(s) of 5-HT in the mammalian heart. However, animal models with loss of function are much more abundant (**Table 1**). The cardiac phenotypes of mice overexpressing SERT or 5-HT_4-receptors (in the heart) have been discussed in this text. 5-HT_{2B}-receptor overexpressing mice, however, had no defect in systolic function (unaltered ejection fraction). Interestingly, their heart weight to body weight ratio was increased (cardiac hypertrophy). This was explained by an increase in the number and size of cardiomyocytes. Further changes were an increase in the number and activity of mitochondria in hearts from transgenic mice but no cardiac fibrosis was noted. It is possible that the hypertrophy is due to constitutive activation of the PLC pathway by the overexpressed 5-HT_{2B}-receptor [120]. Interestingly, in 5-HT_{2B}-receptor knockout mice (made by the same group), a dilated cardiomyopathy (with decreased systolic function, small sized cardiomyocytes) was noted [112] (**Table 1**). Surprisingly, the knockout of the 5-HT_{2B}-receptor exhibited gender-specific differences in the phenotype. For instance, ECG alterations (prolongation of P-wave) were more pronounced in female than male 5-HT_{2B} knockout mice [112].

To the best of our knowledge, mice with cardiac-specific knockout of the genes listed in **Table 1** have not been described in the literature and might be meaningful new study systems. In addition to the mouse models listed in **Table 1**, there is also a SERT knockout rat in the literature [147]. This rat model should be useful in some regards, because historically most work on hypertension was done in rats. In this context, mice with cardiac-specific overexpression of 5-HT_{2B}-receptors could be generated by mating 5-HT_{2B} knockout mice and 5-HT_{2B}-receptor overexpressing mice, an interesting line of research for other 5-HT-receptors [148].

Protein	Function	References
5-HT1A	Serotonin-receptor	[122]
5-HT1B	Serotonin-receptor	[123]
5-HT1D	Serotonin-receptor	[124]
5-HT2A	Serotonin-receptor	[125]
5-HT2B	Serotonin-receptor	[126]
5-HT2C	Serotonin-receptor	[127]
5-HT3A	Serotonin-receptor	[110, 128]
5-HT4	Serotonin-receptor	[129]
5-HT5	Serotonin-receptor	[130]
5-HT6	Serotonin-receptor	[131]
5-HT6	Serotonin-receptor	[132]
5-HTT (SERT)	Serotonin-transporter	[133–135]
TPH1	Serotonin synthesis	[21, 37]
Dopa-decarboxylase	Serotonin synthesis	[136]
MAO-A	Serotonin degradation	[137]
MAO-B	Serotonin degradation	[138]
VMAT1	Serotonin uptake	[139]
VMAT2	Serotonin uptake	[140]
PMAT	Serotonin uptake	[141]
OCT1	Serotonin uptake	[142]
OCT2	Serotonin uptake	[143]
OCT3	Serotonin uptake	[144]
IDO	Serotonin degradation	[59]
Alcohol dehydrogenase	Serotonin degradation	[145]
Xanthine oxidase	Serotonin degradation	[146]

Table 1. Constitutive knockouts of genes relevant for serotonin handling.

12. 5-HT-receptors present in the heart: cell and species differences

The current thinking is that 5-HT can act via membrane bound receptors called 5-$HT_{1\text{-}7}$ ([20, 149], review: [150]). The 5-HT_3-receptor is a ligand-gated ion channel, whereas all other 5-HT-receptors are G-protein-coupled receptors. The 5-HT_1-receptors as well as 5-HT_7-receptors can inhibit the activity of adenylyl cyclase via Gi/q, whereas 5-HT_4-, 5-HT_5-, and 5-HT_6-receptors can increase the activity of adenylyl cyclase via Gs. 5-HT_2-receptors, via G_q/G_{11}, can activate PLC and thereby increase IP3 levels as well as generate diacylglycerol and

subsequently diacylglycerol can activate PKC. Moreover, 5-HT_{2A}- and 5-HT_{2C}-receptors can also activate phospholipase A_2. In the whole mouse heart, the following receptors have been described on mRNA level: 5-HT_{1A}-, 5-HT_{1B}-, 5-HT_{1D}-, 5-HT_{2A}-, 5-HT_{2B}-, 5-HT_{2C}-, 5-HT_3-, and 5-HT_4-receptors [43]. Surprisingly, others failed to detect the 5-HT_4-receptor in mouse heart and only reported on 5-HT_{2A}- and 5-HT_{2B}-receptors [151]. Others failed to detect 5-HT_{2C}-receptors in neonatal rat cardiomyocytes, which offers the possibility that the cardiac expression of 5-HT-receptors might be developmentally regulated or likewise be species dependent or in different cell types of the heart [22]. Apparently, the 5-HT_6-receptor was not found by PCR in adult mouse whole hearts [43]. Four isoforms of mouse 5-HT_4-receptors exist (on RNA level) in mouse atria [152]. On RNA level, 5-HT_{4a}- and 5-HT_{4b}-receptors are also present in human atrium [153, 154] and to a lesser extent in human cardiac ventricle [85, 155]. As mentioned before, 5-HT_{2A}-receptors mediate the effects of 5-HT in thrombocytes [156]. The PIE of 5-HT in rat atrium is probably mediated by 5-HT_{2A}-receptors [82]. 5-HT_{2A}- and 5-HT_4-receptors are, however, present on RNA in rats [82], but the 5-HT_4-receptors in rat hearts only become functional (mediating a PIE) in stress (myocardial infarction: overview in [157]). The 5-HT_2-receptors can activate phospholipase C and can elevate IP3 levels in the rat heart [82]. 5-HT_{2A}-receptors are found in human arterial smooth muscle cells and can lead to vasoconstriction [158, 159]. Initially, 5-HT_3-receptors seemed only to be present in nerve cells in the heart and might mediate the "von Bezold-Jarisch" reflex [97]. The 5-HT_3-receptors seem to be found in epicardial afferent sensory nerve ending of the vagus [160]. More recently, however, using a new knockout mouse, 5-HT_3-receptors were found at least in the ventricle of wild-type mice [110]. The 5-HT_4-receptor (but not, for instance, a 5-HT_2-receptor) mediates the PIE and PCE in the human heart [64, 92]. The study of the 5-HT_4-receptor structure is complicated because many splice variants are known which might have different physiological and/or pathophysiological roles [157]. No convincing antibodies to 5-HT_4-receptors let alone for splice variants have been published in the literature (and our own unpublished observations). Hence, protein levels of these receptors are difficult to assess. At least, some radioactive ligand-binding studies shed some light on the protein expression levels in the heart and found measurable but very low densities of 5-HT_4-receptors in the heart [161]. Really specific antibodies for 5-HT_4-receptors with high affinity are highly desirable. 5-HT_1-receptors are present in endothelial cells and smooth muscle cells in human coronary arteries and mediate vasoconstrictory effects of 5-HT [158] and can inhibit AC activity [162]. PIE of 5-HT in human atrium and ventricle are 5-HT_4-receptor mediated (trabeculae: [64]). 5-HT_{2B}-receptors are present in cardiac valves. Their simulation by 5-HT, fenfluramine (indirectly by inhibiting SERT or by releasing 5-HT from platelets), ergotamine derivatives, methysergide, and recreational drugs ("ecstacy") can lead to deadly valve ruptures [163–165]. Typically, these drugs are present in all parts of the blood circulation; hence, the valve dysfunction can take place in the right as well as in the left heart. An excellent review on 5-HT-receptors in the vascular system especially the heart of humans is to be found in the literature and will be helpful for in depth information [157].

13. Signal transduction mechanisms of 5-HT-receptors in the heart

Moreover, 5-HT in isolated atrial preparations from human hearts increased cAMP content, PKA activity [64, 80], and the phosphorylation state of phospholamban (PLB) and the

inhibitory subunit of troponin (TNI, [88]), and these effects were blocked by 5-HT_4-receptor antagonists [88]. Hence, these effects were probably 5-HT_4-receptor mediated [88]. In electrophysiological experiments, 5-HT elevated the L-type Ca^{2+}-current in human atrium [83, 166, 167] but not human ventricle [83, 168]. Mechanistically important, 5-HT increased the contractility in isolated atrial paced human cardiomyocytes [103]. Stimulation of 5-HT_{2A}-receptors led to increases of IP3 content [82]. Similarly, in transgenic mice that overexpress 5-HT_4-receptors in the mouse heart, 5-HT led to PIE and PCE in intact mice (using echocardiography), in isolated perfused hearts, in isolated left atria (electrically driven), or isolated spontaneously beating right atria. These effects were accompanied by cAMP increases, increased phosphorylation state of PLB (on amino acid serine 16 and threonine 17), increase in current through L-type Ca^{2+}-channels, and increase in the free Ca^{2+} content in the cytosol in mice ventricular preparations or whole hearts [87]. In addition, increased phosphorylation of PLB was also noted in atrial preparations from 5-HT_4-receptor overexpressing mice [169]. In these mice, the *in vivo* activity of agonists could be studied on contractility [90]. Here, one can recapitulate findings in cloned receptors, for instance, cisapride was less potent and effective to increase force of contraction than 5-HT. Moreover, cisapride induced concentration-dependent tachycardia (and arrhythmias) in spontaneously beating isolated right atrial preparations of 5-HT_4-receptor overexpressing mice [170], similar to tachycardias described in some patients treated with cisapride [171]. However, prucalopride was less potent but equieffective compared to 5-HT [109, 170, 172]. In addition, 5-HT is able to desensitize the 5-HT_4-receptor not only in 5-HT_4-receptor overexpressing mice in the atrium [90] but also in the ventricle [172, 173]. LSD and ergotamine *in vitro* displayed biased signaling for β-arrestin at 5-HT_{2B}- and 5-HT_{1B}-receptors [174].

14. Altered expression or function of cardiac 5-HT or its receptors under pathophysiological conditions

14.1. Carcinoid syndrome

In the carcinoid syndrome (typically due to tumors arising from enterochromaffin cells of the gut that in 10% of cases produce high levels of 5-HT: cf. [23] for a clinical example, large patient series: [26]), high circulating levels of 5-HT, which can stimulate 5-HT-receptors, and lesions of the *right* cardiac valves have been reported. Normally, the pulmonary circulation is assumed to remove free circulating 5-HT from the plasma and very little 5-HT in the plasma would reach the left ventricle (discussed in Ref. [43]). However, when a carcinoid tumor is located to the lung or an open foramen ovale is present or exceedingly high plasma 5-HT levels occur from a carcinoid in the gut or liver, which would spill over into the pulmonary veins, *left* cardiac lesions like valve failure have also been noted [43].

14.2. MAO-dependent oxidative stress

By altering cardiac levels of 5-HT, MAO might be of clinical relevance in patients. This can be tentatively concluded from the following animal studies. Cardiac-specific overexpression of MAO-A (in mice) led to decreased cardiac levels of 5-HT (and noradrenaline). This was

accompanied by increased levels of free radicals in the mouse heart, as well as oxidation of mitochondrial DNA, cardiac fibrosis, and ventricular heart failure [53]. Oppositely, a knockout of MAO-A in mice was functionally beneficial because it reduced left ventricular dilatation and left ventricular dysfunction after hypertension (via aortic banding). Accordingly, aortic banding (an experimental model to increase cardiac afterload) increased protein levels of MAO-A threefold [119]. High cardiac concentrations of 5-HT can lead to cardiac hypertrophy (and later on, possibly, to heart failure, see below) via receptor-independent mechanism(s) or 5-HT-receptor-dependent mechanisms. In more detail, high cardiac intracellular levels of 5-HT are oxidized in mitochondria via MAO activity: this leads to the generation of deleterious free radicals [119]. In aging rat hearts, MAO-A activity was increased, which may exacerbate deleterious effects of cardiac 5-HT [119]. In rat cardiac myocytes, high intracellular levels of 5-HT led to enhanced MAO-dependent oxidative stress followed by release of cytochrome c from cardiac mitochondria, upregulation of proapoptotic BAX protein, downregulation of antiapoptotic Bcl2 protein, and thus to detrimental apoptosis [72].

14.3. Hypertension

In peripheral arterial hypertension, more 5-HT can be found in the plasma, and via covalent modification of the protein rab4, the function of SERT in platelets is reduced and thus a circulus vitiosus might start [175]. Moreover, it has been suggested that 5-HT might act on small G-proteins (by inducing serotonylation of these proteins) in smooth muscle cells in pulmonary arteries, rendering the arteries more susceptible to 5-HT-induced vasoconstriction and thus leading to sustained pulmonary hypertension and death [36]. Serotonylation of several proteins in rat aorta has likewise been reported [176]. Pulmonary hypertension might be causally related to 5-HT: plasma levels of 5-HT are twofold to threefold higher in patients suffering from this disease and augmented 5-HT plasma levels may lead to constriction of pulmonary arteries and thus to pulmonary hypertension in humans [177]. This is in line with animal experiments: in TPH1 knockout mice, hypoxia (placing the animals into chambers with low partial pressure of oxygen) was less prone to rise right ventricular pressure compared to WT animals [178]. In a rat model of pulmonary hypertension (induced by monocrotaline), blocking 5-HT_{2B}-receptors was protective for right ventricular function [179].

14.4. Cardiac hypertrophy

Interestingly, a blocker of 5-HT_{2A}-receptors attenuated cardiac hypertrophy after aortic banding in mice, suggesting a role of this receptor in cardiac hypertrophy, and in this context, hypertrophy (transiently) increased the expression of the 5-HT_{2A}-receptors in mouse cardiomyocytes after aortic banding [180]. The classical isoproterenol-induced hypertrophy in a mouse model was reduced in mice treated with a 5-HT_{2B} blocker or in 5-HT_{2B}-receptor knockout mice, probably by inhibiting peroxide generation in mitochondria [2, 181]. Interestingly, a isoproterenol-induced cardiac hypertrophy (a classical animal model of hypertrophy) seemed to require 5-HT_{2B}-receptors on cardiac fibroblasts [148]. Fittingly, in patients with cardiac hypertrophy, the expression of 5-HT_{2B}-receptors was elevated (radioligand binding [148]). 5-HT_{2B}-receptors were detected with immunohistology in human cardiomyocytes and human

non-cardiomyocytes; however, it is an open question (and a mechanistically very important question) whether overexpression of these receptors in human heart failure occurs in cardiomyocytes and/or in non-cardiomyocytes [148].

14.5. Heart failure

In heart failure, 5-HT might be altered: increases in plasma 5-HT levels in patients with decompensated systolic heart failure [182] or diastolic heart failure [183] have been described. These studies concluded that 5-HT elevation may be a compensatory mechanism, trying to increase cardiac output by increasing heart rate and cardiac force [182]. In atrial samples from heart failure patients, the PIE of 5-HT was reduced. Moreover, biochemical correlates of receptor coupling like the extent to which 5-HT could increase AC activity [184] or increase L-type Ca^{2+}-currents, was attenuated in samples from heart failure patients [168]. Some of these effects were reversed after β-adrenergic blockade of patients prior to surgery [185]. In a rat model of heart failure (infarction), the mRNA of 5-HT_4-receptors increased and a robust PIE of 5-HT (which was lacking in normal rats without heart failure) became apparent [186]. Moreover, there are data that in human heart failure a PIE of 5-HT and upregulation of 5-HT_4-receptors become measurable [85, 155]. Interestingly, the PIE of 5-HT increased with NYHA class but the PIE of β-adrenergic stimulation decreased with NYHA class [85]. In a pilot study with heart failure patients, the EF increased after being treated with a 5-HT_4-receptor antagonist (piboserod [187]). This might mean that activation of 5-HT_4-receptors is deleterious in human heart failure. In apparent contrast to this conclusion, in lipopolysaccharide (LPS)-induced sepsis (another accepted model of heart failure), overexpression of 5-HT_4-receptors seemed to protect the heart by interference with the toll-like receptor 4 pathway [188].

14.6. Atrial fibrillation

In patients with chronic (more than 1 month persistent) atrial fibrillation, the expression of 5-HT_4-receptor mRNA levels was found to be decreased by about 36% (irrespective of β-adrenoceptor treatment) in comparison to controls in sinus rhythm and this change in receptors level was suggested to be a protective mechanism [189]. Others found the expression of 5-HT_{4b}-receptors to be downregulated (mRNA) in acute atrial fibrillation but upregulated with atrial fibrillation lasting more than 1 year [190]. Protein data for 5-HT_4-receptors in atrial fibrillation would clearly be desirable to resolve these somewhat contradictory findings. In aging, the uptake of 5-HT in platelets is augmented, concentrations of 5-HT in platelets are therefore higher, and thence 5-HT is more prone to induce aggregation of platelets and thus thrombosis (e.g. [191]).

14.7. Aging

At least in pigs, the PIE of 5-HT in atrium and ventricle *in vitro* is increased from neonates to adulthood [85, 86]. The opposite occurs in rats: fetal rat ventricles express highly the mRNA for 5-HT_4-receptors and are accompanied by (and probably causes) a large PIE to 5-HT in neonatal cardiac preparation. In contrast, in adult rats, as mentioned before, 5-HT is devoid of a

PIE in the rat ventricle [82, 192]. In human atria, 5-HT stimulates AC less in aging, which was explained by increased levels of Gi proteins [193]. Hence, age-dependent changes in cardiac response to 5-HT are known, but much more refined data are clearly needed from further work.

So sum up these findings, it is possible that 5-HT causes or at least contributes to cardiac hypertrophy, arterial or pulmonary hypertension, heart failure, cardiac aging, and cardiac arrhythmias.

15. Possible cardiac side effects of serotoninergic drugs

Drugs elevating 5-HT: SERT *inhibitors* (specific serotonin reuptake inhibitors, SSRIs), they are suggested to increase 5-HT not only in brain synapses but also in cardiac tissue and therefore they might be implicated in arrhythmias (citalopram: [194]). Warning notices have been sent out for citalopram in this regard by regulatory authorities (FDA: 2012). A recent study noted enhanced risks of valve disease in patients who take SSRI [195], presumably because high plasma membrane concentrations of 5-HT activate 5-HT_{2B}-receptors. *5-HTP* has been suggested to be used as add on to SSRI in order to treat depression, because it is metabolized to 5-HT. *5-HTP* is therefore predicted, indirectly, to lead to arrhythmias in patients.

5-HT_1-receptors: *Sumatriptan* and congeners are well known to have the ability to contract coronary arteries and can lead to myocardial infarctions [196]. Buspirone is a drug acting among others on 5-HT_{1A}-receptors and has been shown to lead to tachycardia.

5-HT_2-receptors: *Ergotamine* and *LSD* (but also *fenfluramine*) stimulate 5-HT_{1B}-receptors but also detrimental 5-HT_{2B}-receptors (leading to valve fibrosis) [174]. In addition, an important metabolite of fenfluramine called *norfenfluramine* could bind with high affinity to 5-HT_{2B}-receptors and could stimulate in the receptor-transfected HEK cells the IP3 levels, presumably initiating fibroplasia *in vivo* in humans [197]. In 2014, pimavanserin is an antagonist at 5-HT_{2A}-receptors entered the market in the USA as an antipsychotic drug and to treat Parkinson's disease [198]. Interestingly, the producing company lists as contraindications irregular heartbeat. In some countries, *ketanserin* (a classical 5-HT_{2A}-antagonist) has been used for many years to treat *hypertension*. However, the antihypertensive effect is probably due to an additional α_1-adrenoceptor antagonistic effect of ketanserin [2]. Moreover, its use has rapidly declined when it was suggested to lead to deadly arrhythmias (ketanserin can make QT prolongation and thereby lead to torsade de pointes). The reason for this is that the K^+ channel hERG (human ether-a-go-go-related gene) is blocked by ketanserin (reviewed in [2]).

5-HT_{2C}-receptors: A newer serotonergic drug is the 5-HT_{2C}-agonist *lorcaserin* that was approved by the FDA in June 2012 in order to bring about weight loss by action in the CNS [198]. Lorcaserin was developed because older drugs for weight loss were withdrawn, in the past, from the market (e.g. fenfluramine) because they led to fibrosis (reviewed in Ref. [70]). Clearly, one can speculate that lorcaserin might also have agonistic properties at 5-HT_{2B}-receptors and thus may have effects on valves. Initial studies did not detect an increased risk of lorcaserin for valvulopathies, however the incidence of headaches was increased versus placebo which may mean that lorcaserin can act agonistic on other 5-HT receptors [199] and

side effects should carefully monitored by physicians and communicated to the regulatory authorities.

5-HT_4-receptors: *Metoclopramide* acts on many receptors but in this context the activation of 5-HT_4-receptors is important [200]. One has speculated that 5-HT_4-receptor agonists might be useful to treat patients with sinus bradycardia, slowing of AV conduction, and autonomic dysfunction of the heart [201]. 5-HT_4-receptor agonists are used in some countries to treat irritable bowel disease (e.g. prucalopride [202]), bladder dysfunction [203], and Morbus Alzheimer (e.g. [204]). However, early on a clinical study detected arrhythmias in ECG of healthy volunteers [205], which used the 5-HT_4-receptor agonist *prucalopride*, and hence caution in its used is advised. The 5-HT_4-receptor agonist (RS 67333) *donecopride*, in addition, inhibits the activity of acetylcholine esterases [206] and might be useful for the treatment of Morbus Alzheimer. However, this compound is expected to lead to arrhythmias in sensitive patients via its agonist activity of cardiac 5-HT_4-receptors. 5-HT_4-receptor agonists have been developed to treat anxiety or chronic obstipation. *5-HT_4-receptor antagonists* have been suggested for the treatment of supraventricular arrhythmias [159, 189] but were not successful due to side effects [106].

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