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The Function of Seven Transmembrane Receptors in the Cardiovascular System and Their Role in the Development of Cardiomyopathy

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Abstract

The G-protein-coupled receptors (GPCRs, also called seven-transmembrane receptor, 7TMRs, or heptahelical receptor) are a conserved family of seven transmembrane receptors which are essential not only in the healthy heart and blood vessels but also in for treatment and therapy of cardiovascular disease and failure. Heart failure is a global leading cause of morbidity and death and as such understanding 7TMRs, their functions, structures and potential for therapy is essential. This review will investigate the roles of the receptors in the healthy functioning cardiovascular system, and in cardiac disorders with an emphasis in cardiomyopathy. It will also explore the role of autoimmunity and autoantibodies against the G-protein-coupled receptors in cardiomyopathy.

Keywords: angiotensin, adrenoreceptors, cardiomyopathy, heart disease, endothelin-1, muscarinic receptors, vascular

1. Introduction

The 7 transmembrane receptors (7TMRs) also known as G-protein coupled receptors (GPCRs) constitute the largest family of plasma membrane receptors. The superfamily of 7TMRs includes receptors for hormones, neurotransmitters and ion channels, and is critical to mediate physiological and cellular processes [1, 2].

Composed of seven transmembrane hydrophobic alpha (α) helices joined by three intracellular and three extracellular loop structures, a cytoplasmic carboxyl terminus and an extracellular amino terminus (**Figure 1**), 7TMRs signal by stimulating heterotrimeric G proteins following the presentation of an agonist to the receptor [3]. Agonist binding at the 7TMR extracellular region initiates the formation of a G protein. Guanosine diphosphate (GDP) is released from the G protein in exchange for guanosine triphosphate (GTP). The GTP bound α subunit dissociates from the $\beta\gamma$ dimer, both of which activate several effectors such as adenylyl cyclase, phospholipases and ion channels [3]. The $G\alpha$ subunit can be categorised in

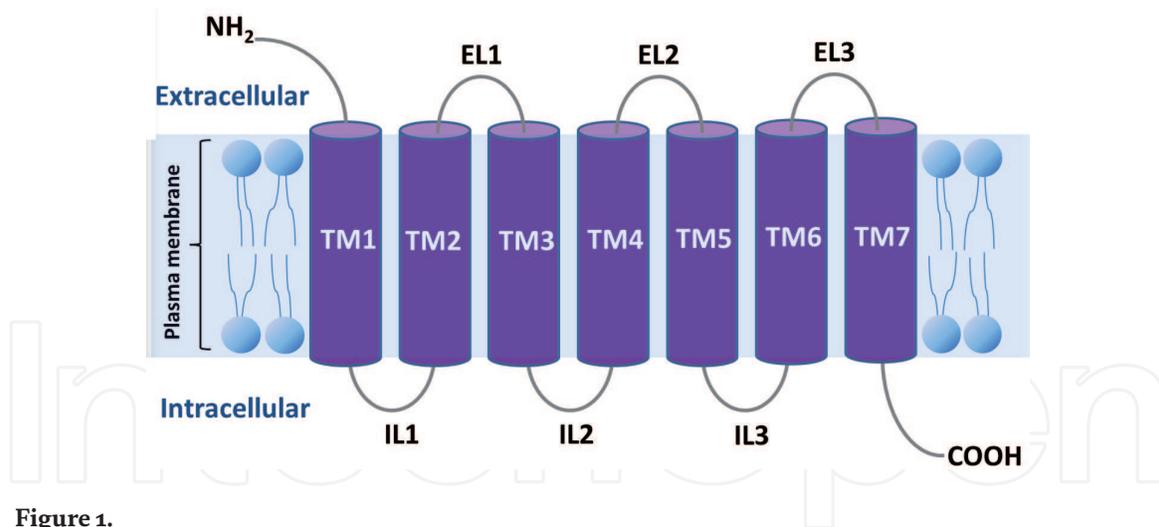


Figure 1.

General structure of a seven transmembrane receptor (7TMR)/G protein coupled receptor (GPCR). Extracellular loops 1–3 (EL1–3) and intracellular loops (IL1–3) connecting the 7 transmembrane helices (TM1–7). NH₂–N-terminal chain and COOH–C-terminal chain.

to sub groups $G\alpha_s$, $G\alpha_i$, $G\alpha_{q/11}$ and $G\alpha_{12/13}$ [3]. The $G\alpha$ subunits and the $G\beta\gamma$ dimer deriving from the heterotrimeric G protein can combine with downstream effector molecules such as adenylyl cyclase or phospholipase C to control cellular signalling pathways involving secondary messengers [3]. Examples of secondary messengers include cyclic adenosine monophosphate (cAMP), inositol-1,4,5-trisphosphate (IP₃) and diacylglycerol (DAG) which elicit cellular and physiological responses [4].

2. Cardiovascular effects of 7TMRs and therapeutic drug targets

7TMRs are the target for a large proportion of therapeutic drugs, currently encompassing more than 30% of prescription medications [5] which directly or indirectly alter cellular signalling mechanisms.

2.1 Adrenoreceptors (β -adrenergic receptors)

Adrenergic receptors (ARs; also known as adrenoreceptors) are a class of 7TMRs located in the heart and vasculature and are responsible for relaying sympathetic nervous system (SNS) messages into cardiovascular reactions [1]. The neurotransmitters norepinephrine (NE) and epinephrine (Epi), which originate from the SNS, exert their effects on cardiac cells and tissues by binding to adrenoreceptors [6]. A number of adrenoreceptor subgroups are present in the mammalian heart, including three α_1 -ARs, three α_2 -ARs and three β -ARs (β_1 , β_2 and β_3) [6].

β -Adrenergic receptors (β -ARs) are the most important and one of the most frequently studied receptors belonging to the family of G-protein coupled receptors [7]. There are three subtypes of β -ARs: β_1 , β_2 and β_3 , activation of which regulates important cardiovascular functions [7, 8]. The β_1 -ARs are characterised mainly for the heart, β_2 -ARs for blood vessels and β_3 -ARs for adipose tissue [9]. Within the vasculature the predominant subtype is β_2 -AR, which is 65–70% homologous to β_1 - and β_3 -ARs [8]. The agonists that bind with all three subtypes of β -ARs are the hormones adrenaline and noradrenaline, which help regulate cardiovascular and pulmonary function [10, 11].

Human genes encoding the β_2 -ARs are without introns and have been mapped to chromosome 5q31–32 [12]. The β -ARs consist of 413 amino acid residues, approximately 46.5 kDa [8]. There are three domains of β_2 -ARs: The extracellular domain,

the transmembrane domain responsible for the ligands binding and the intracellular domain, which interacts with G protein and kinases such as β -ARK [13]. β_2 -ARs occur mainly in the lungs, where their presence has been shown in airway smooth muscle (30,000–40,000 per cell), epithelial and endothelial cells, type II cells and mast cells [8]. Moreover β_2 -ARs are in heart, kidney and blood vessels—mainly arterioles [8, 14].

As in the other G-receptors the signalling pathway of β_2 -ARs, which bind with a hormone ligand includes three basic steps: Receptor binding, G protein activation and effector system activation. β_2 -ARs may occur in two forms, activated and inactivated [6]. The binding of β -ARs agonist with β_2 -receptor activates the pathway in which Gs coupled proteins are involved. The stimulation of G proteins causes guanosine triphosphate (GTP) to bind to the α -subunit ($G_s\alpha$) that activates it. The G-subunits dissociate, and α -subunits stimulate adenylate cyclase (AC) to formation of cyclic adenosine 3',5'-monophosphate (cAMP). It is stated that cAMP acts as a catalyst for the process of activation of protein kinase A (PKA) and due to that it is involved in control of muscle tone. On the other hand cAMP inhibits the release of cytosolic calcium ion (Ca^{2+}) in the smooth muscle cells, which leads to vascular relaxation (vasodilation) [8, 15].

Although the β_2 -ARs activated by β_2 -ARs agonists mostly influence the blood vessels (mainly arterioles and coronary arteries), they can also act in the heart and kidney. In the atrial and ventricular myocardium, stimulation of β_2 -ARs leads to increase in cardiac muscle contractility or relaxation, whilst in the kidneys it stimulates the release of renin, what it turn influences activation of the renin-angiotensin-aldosterone system [1, 8].

The primary role of the β -ARs in the heart is to coordinate the heart rate and contractility in response to the SNS neurotransmitters [6]. β_1 -AR is the most abundant subtype accounting for 75–80% in a healthy myocardium [6]. Around 15–18% of cardiomyocyte β -ARs are β_2 -AR whilst the remaining 2–3% of β -AR density is composed of β_3 -ARs [6]. Activation of β_1 -ARs and to a smaller degree β_2 -ARs, leads to an increase in cardiac contractility and an accelerated cardiac rate. Stimulation of the two predominate β -ARs also increases impulse transmission via the atrioventricular node [6]. The activation of cardiomyocyte β_1 - and β_2 -ARs also leads to a significant increase in free intracellular Ca^{2+} concentration [6]. Calcium is a secondary messenger in many biological systems. In cardiomyocytes, calcium affects ion channels which regulate ionic currents, impacting upon action potentials and muscle contractility [16]. β_3 -AR appears to illicit an opposite effect on cardiac function to that induced by β_1 - and β_2 -ARs in that it acts to prevent cardiac hyperstimulation from NE and Epi (**Table 1**) [6].

Constant elevation of catecholamines leading to β -AR signalling changes results in overstimulation of cardiac function [1]. Reducing the β -AR activity is vital to alleviate the risk of long-term cardiac tissue damage such as cardiomyopathy. Propranolol was discovered to be a β -AR antagonist in 1964, a so called β -blocker. Alprenolol and Practolol β -blockers have also been used for the management of heart failure [1]. β -Blockers function to overcome the harmful effects of norepinephrine which overstimulate the β_1 -AR, leading to a reduction in cardiac workload [1]. The most recently used β -blockers bisoprolol and carvedilol target both β_1 - and β_2 -ARs produce a survival benefit for heart failure patients [1]. In rats β_2 -AR agonists (fenoterol and zinterol) were shown to reduce progression of left ventricular modelling in dilated cardiomyopathy in addition to decreasing myocardial cell death [17]. In a later study the same group determined that in a rat model of dilated ischemic cardiomyopathy, Metoprolol, a β_1 -AR blocker, action is enhanced when given in combination with the β_2 -AR agonist fenoterol [18].

Action	β_1 -AR	β_2 -AR	β_3 -AR
Heart muscle contraction		Yes	Yes
Increases cardiac output	Yes	Yes	
Increases heart rate in SA node	Yes	Yes	
Increases atrial contractility	Yes	Yes	
Increases contractility and automaticity of ventricular muscle	Yes	Yes	
Dilates muscular blood vessels		Yes	Yes
Increases perfusion in blood vessels		Yes	
Metabolism/lipolysis/thermogenesis			Yes
Prevent cardiac hyperstimulation			Yes

Table 1.
Actions of β -adrenergic receptors.

The β_2 -ARs have also been directed implicated in patients with ischaemic cardiomyopathy. A Gln27Glu polymorphism of β_2 -AR was discovered in a study investigating 155 people with heart failure of ischaemic aetiology with impaired Left Ventricular Ejection Fraction $\leq 35\%$ [19]. Three allele categories were discovered, the most common genotype in heart failure was Gln27Gln, and the least common was Glu27Glu, whilst Gln27Glu was not significantly different between heart failure and control subjects. The study concluded that the Glu allele was associated with lower myocardial infarction rate and highlighted that patient response to β -blockade therapy may be altered [19]. Likewise β_1 -AR (Ser49Gly, Arg389Gly) and β_2 -AR (Arg16Gly, Gln27Glu, Thr164Ile) polymorphisms did not alter in a Polish cohort study of patients with idiopathic dilated cardiomyopathy [20]. It is of interest that in patients with Takotsubo cardiomyopathy, β -AR polymorphisms (β_1 -AR (Gly389Arg) and β_2 -AR (Arg16Gly and Gln27Glu)) were significantly different to controls but similar to patients with ST-elevation myocardial infarction [21]. Work combining beta-blockers with ACE-inhibitors/angiotensin receptor blockers over the years using meta-analysis data has shown reduced recurrence of the disorder [22].

A murine model depleting levels of β_2 -ARs also resulted in diabetic cardiomyopathy in vivo and reduced β_2 -ARs in cardiomyocytes grown under in hyperglycemic conditions [23]. Conversely, overexpression of β_2 -ARs (by 300 fold) in mice showed that over time severe cardiomyopathy was observed, resulting in interstitial fibrosis, loss of myocytes and myocyte hypertrophy. In the majority of the 81% of mice that died within 15 months, heart failure was observed [24]. These results were similar to other transgenic overexpression mouse lines. The authors hypothesised that a number of mechanisms from activation of growth or transcriptional factors, cross-talk with other pathways, necrosis or apoptosis of cardiac myocytes and/or high heart rates limiting energy supply.

The human heart also possesses α_1 adrenoreceptors (α_1 -AR) although in a smaller quantity to the β -ARs [25]. The α_1 -ARs are expressed in the heart, both the α_{1A} - and α_{1B} -AR subtypes are expressed in human myocytes, and have been shown to regulate contractility [26, 27]. The α_1 -ARs combine with the $G_{q/11}$ family of G proteins, in turn activating phospholipase C. The secondary messenger IP_3 binds to receptors on the membrane of the sarcoplasmic reticulum, triggering the release of intracellular Ca^{2+} [6]. The raised Ca^{2+} level leads an increase in vasoconstriction [6]. The coupling of α_1 -ARs to the $G_{q/11}$ family of G proteins also produces DAG and subsequent protein kinase C [6].

In heart failure the α_1 -ARs may offer a protective benefit to maintain cardiac inotropy, preventing cardiomyocyte apoptosis and maladaptive cardiac remodelling [6]. Although a small study, loss of β_1 -AR and no change in β_2 -AR levels in end-stage dilated cardiomyopathy patients was observed alongside a loss of α_{1A} -ARs [28]. Although the role of β_1 -AR in heart failure has long been described, this interaction between the α -ARs was novel as the few previous studies had shown no change or increases in α -ARs binding but these were different types of heart failure. In addition a total of 26 proteins of interest were also identified in the cardiomyopathy patients, some of which have been linked to G-protein coupled receptor signalling and desensitisation [28]. Prostatic binding protein levels decreased whereas increases in ANP32A and clathrin were noted. Also of interest are Takotsubo cardiomyopathy (also known as stress cardiomyopathy) patients. This condition is often reversible, and two studies have shown that several β_1 -AR and α_{2c} -AR polymorphisms were not implicated in Takotsubo cardiomyopathy [29, 30].

2.2 Angiotensin II type 1 and 2 receptors

Angiotensin II (AngII) is an important protein in the renin-angiotensin system (RAS). In the bloodstream renin converts angiotensinogen (derived from liver) into angiotensin I, which in turn is transformed into AngII by angiotensin converting enzyme (ACE) [14, 31, 32]. AngII can be also secreted in some local tissues including within the brain, heart, arteries and kidney [32].

The Angiotensin II type 1 and 2 receptors (AT_1 and AT_2 receptors) belong to the wide family of G-protein coupled receptors (GPCRs), members of which have seven transmembrane spanning domains and is the biggest member of the human genome [31, 33]. The distinction and classification of AT_1 and AT_2 receptors is based on their varied affinity for different non-peptide antagonists [34]. Moreover the AT_1 and AT_2 receptors differ between each other in their number of amino acids, tissue-specific expression and mechanisms of signal transferring [13]. Both of these receptors occur in all mammals and bind a peptide hormone angiotensin II (AngII), which is the most important effector in the RAS [32].

The main role of angiotensin becomes apparent in the cardiovascular and endocrine systems where it regulates blood pressure and hydro-electrolytic homeostasis [32, 33]. It is stated that the main physiological functions of AngII (vasoconstriction, aldosterone secretion, renal regulations cellular dedifferentiation and proliferation) are mediated mostly by the AT_1 subtype of angiotensin receptor [14, 31, 33–36]. In humans, the genes encoding AT_1 receptors are mapped on chromosome 3q21–3q25 [37]. The AT_1 receptors consist of 359 amino acids, with a molecular weight of 41 kDa, and their amino sequence reveals 20–35% homology with other GPCRs [31].

In adult mammals, AT_1 receptors are mainly expressed in kidney (glomeruli, proximal tubules, vasculature, medullary interstitial cells), adrenal glands (cortex, medulla), heart (myocardium, ganglia, conduction system), brain (circumventricular organs, thalamus, basal ganglia, cerebellar cortex, medulla oblongata) and vasculature (smooth muscles, adventitia) [32, 38]. Rats and mice can have two isoforms of the Angiotensin II 1 receptor: AT_{1A} and AT_{1B} with amino acid sequence convergence seen at 94% [14, 31, 33, 34]. AT_{1A} receptors are present predominantly in vascular smooth muscle, liver, lung and kidney whilst AT_{1B} receptors occur mainly in the adrenal gland and anterior pituitary [31, 34, 38]. The rodent AT_{1A} and AT_{1B} receptor genes are situated on chromosomes 17 and 2 respectively [38].

The activity of angiotensin II through AT_1 receptors should be considered in physiological and pathophysiological conditions. The physiological signalling pathway involves the renin-angiotensin-aldosterone system and leads to changes in blood

pressure primarily through vasoconstriction of arteries and arterioles, secretion of aldosterone from adrenal gland and sodium reabsorption by via the kidney tubules [32]. Ang II mediates vasoconstriction through the IP₃/DAG pathway, which uses Gq/11 protein-coupled receptors. Gq/11 activates phospholipase C (PLC), which hydrolyses phosphatidylinositol 4,5-bisphosphate (PIP₂) and produces diacyl glycerol (DAG) and inositol trisphosphate (IP₃). IP₃ causes an increase in intracellular calcium whilst DAG activates protein kinases C [31]. The increased concentration of calcium (Ca²⁺ ions) within vascular smooth muscle cells leads to vasoconstriction which results in an increase in blood pressure or may causing a localised reduction in blood flow in some specific tissues [32, 36]. AngII acting through the AT₁ receptors located in the zona glomerulosa of the adrenal gland stimulates the release of aldosterone [32]. Aldosterone then acts on the distal convoluted tubules and the cortical collecting ducts in kidney, firstly causing sodium (Na⁺) retention, leading to increased peripheral resistance and secondly causing resorption of water from urine which also increases extracellular fluid volume. Both of these mechanisms lead to an elevation in arterial pressure [32].

Considering the pathological conditions, the activity of AngII through AT₁ receptors may induce the proliferation of vascular smooth muscle cells which in turn promotes myocyte hypertrophy and causes vascular fibrosis. Proliferation of smooth muscle cells is also involved in the initial stages of atherosclerotic plaques formation in arteries [32]. AngII binding to AT₁ receptors also activate the multiple intracellular signalling pathway that promotes atherosclerosis. The pathway includes oxidative stress, inflammation, endothelial dysfunction, tissue remodelling, proliferation fibrosis, thrombosis and autostimulation. Moreover AngII may participate in the process of atherosclerosis lesion formation as it stimulates the release of endothelin-1 (ET-1) from the endothelial cells [32]. In addition to inducing proliferation and atherosclerotic plaques formation, AngII may have an effect on the developing/developed plaques. Atherosclerotic plaque stability and disruption is in turn associated with matrix metalloproteinase (MMP) enzymes, the production of which can be stimulated by AngII [32]. The MMPs are inhibited by tissue inhibitors of metalloproteinases (TIMPs) and disruption of the balance between MMPs and TIMPs may lead to cardiovascular diseases [37, 39]. Moreover, in pathological states, the activation of AT₁ receptor by AngII may cause vascular remodelling and growth by expression of autocrine growth factors (including fibroblast growth factor and platelet-derived growth factor) in vascular smooth muscle cells [32, 40].

The activation of AT₂ receptors by AngII has an opposite effect to AT₁ receptors. It means that the functions of AngII mediated by AT₂ receptors are vasodilation, natriuresis and inhibition of cellular growth and proliferation [14]. Genes encoding AT₂ receptors are localised on chromosome Xq22-q2 [13, 31]. The molecular weight of AT₂ receptors is approximately 41 kDa and they consist of 363 amino acids [13, 41].

AT₂ receptor expression has been localised in both foetal and adult tissues. In foetuses, expression of AT₂ receptors is intense, especially in a cardiovascular system [13]. In adult mammals the expression of AT₂ receptor is still observed in heart (mainly in myocardium) and renal blood vessels but is significantly lower than before birth [13, 38]. Expression of AT₂ receptors has been also noted in the adrenal gland (cortex and medulla), brain (thalamus, cerebellar cortex), mesenteric and uterine arteries [38, 42].

It is stated that the AT₂ receptor acts to stabilise blood pressure by controlling vascular tone by vasodilation [13]. In this action the AT₂ receptor together with other GPCR family B2 receptors for bradykinin form a stable functional

heterodimer, which causes the increase of nitric oxide (NO) and stimulating cyclic guanosine monophosphate (cGMP) synthesis. The cGMP contributes to relaxation of smooth muscles, which in large veins, large arteries, and smaller arterioles leads to vasodilation and causes decreased blood pressure. It has also been suggested that activation of AT₂ receptors by AngII may inhibit arterial and myocardial hypertrophy and fibrosis in the ageing heart and vasculature.

Therefore AngII exerts its influence via the activation of the Angiotensin II type I receptor (AT₁R), a 7TMR located in vascular smooth muscle as well as in the kidneys, brain and adrenal glands in an effort to maintain sodium/water homeostasis and moderate vasoconstriction [1]. AT₁R acts to control arterial pressure, blood volume and to encourage growth and proliferation through the activation of cellular signalling mechanisms [15]. The AT₁R is a G_{q/11} coupled receptor [25]. Stimulation by AngII leads to the activation of phospholipase C-β and the release of DAG and IP₃, followed by the activation of protein kinase C and movement of intracellular calcium [3]. AT₁Rs are upregulated in cardiac tissue in response to hypertrophic triggers, encouraging unfavourable cardiac remodelling in heart failure [9]. These complex roles have resulted in a number of angiotensin receptor blockers (ARBs) and angiotensin converting enzyme (ACE) inhibitors to be developed and used as cardiovascular treatments. ARBs and ACE inhibitors have demonstrated a reduction in deleterious left ventricular remodelling, such as hypertrophy and myocardial stiffness which is associated with heart failure [6]. ACE inhibitors alongside antagonists of the AT₁R, the -sartans, have become one of the main pharmaceutical treatments for hypertension and cardiovascular disease [1]. Commonly used ARBs include Losartan, Valsartan and Candesartan [43]. ARBs function to interfere with the renin-angiotensin system by preventing the binding of AngII to AT₁R. This inhibition of AngII results in vascular smooth muscle relaxation, a reduction in cellular hypertrophy, and a decrease in plasma volume resulting from an increase in salt and water excretion [43].

A number of advances in terms of cardiomyopathy and ANGII and its receptors have been made in the last few years. In terms of cardiomyopathy, the AngII receptor inhibitor LCZ696 has been shown to inhibit extracellular signal-regulated kinase (ERK), resulting in increased survival in pregnancy-associated cardiomyopathy mice. The authors indicated that by reducing cardiac hypertrophy, fibrosis and apoptosis it could act as a potential treatment for this cardiomyopathy [44]. Another study showed that this angiotensin receptor-neprilysin inhibitor reduced inflammation, oxidative stress and apoptosis *in vitro* and *in vivo* [45]. It has also been stated that in end-stage hypertrophic cardiomyopathy, the modern Angiotensin receptor neprilysin inhibitor treatments are both safe and effective [46]. Angiotensin-converting enzyme 2 (ACE2) has also showed therapeutic potential when looking at doxorubicin-induced cardiomyopathy rat models [47]. The enzyme reduced apoptosis, inflammatory responses, and oxidative stress and reduced mortality and myocardial fibrosis whilst improving ventricular remodelling and cardiac function. They also showed activation of the AMPK and PI3K-AKT pathways, inhibition of the ERK pathway, and decreased TGF-β1 [47]. Sulforaphane, which activates nuclear factor erythroid 2-related factor 2 (Nrf2), has also been shown to present angiotensin II-induced cardiomyopathy via Akt/GSK-3β/Fyn-mediated Nrf2 activation [48].

Aldehyde dehydrogenase 2 (ALDH2) has also been shown to protect against alcoholic cardiomyopathy [49]. By decreasing angiotensinogen and AngII this cardioprotective enzyme inhibited local RAS in mice by inhibiting the p38 MAPK/CREB pathway. In another form of cardiomyopathy, hypertrophic, ACE inhibitors angiotensin-receptor blockers have been used to try and regulate the

renin-angiotensin-aldosterone system [50]. This has resulted in patients having a lower risk of developing atrial fibrillation which is associated with hypertrophic cardiomyopathy.

Much work has looked into polymorphisms in the angiotensin-converting enzyme gene itself in relation to hypertrophic cardiomyopathy risk; however, the studies have sometimes shown conflicting results. A systematic review and meta-analysis indicated that the ACE insertion/deletion (I/D of 287 base pairs in intron 16) polymorphism was probably a risk for hypertrophic cardiomyopathy [51]. People with the DD genotype have increased levels of ACE and angiotensin II and therefore more hypertrophy and fibrosis, as seen in other situations where their levels increase. Although many of the 1 in 500 people affected by hypertrophic cardiomyopathy have mutations in the genes coding for sarcomeric proteins, polymorphisms in the components of the RAS are implicated. ACE DD has also been associated with dilated cardiomyopathy patients, angiotensin receptor type 11166CC genotypes with both hypertrophic and dilated cardiomyopathy and the 235TT genotype of angiotensinogen (M235T) is associated with hypertrophic, dilated and restrictive cardiomyopathy [52].

Overstimulation of AngII has also been reported in dilated cardiomyopathy [53] and AT1R overexpression resulted in female mice being more affected (especially in terms of heart failure and increased mortality) than males [53]. In particular, ventricular hypertrophy and dilation and changes in Ca^{2+} activity and homeostasis were observed, and these reflect that clinical observations that dilated cardiomyopathy can be exacerbated in women in comparison to men. This can also be linked to oestrogen which increases angiotensinogen and decreased renin, ACE and AT1R expression but of course following menopause these effects are lost [54].

Much has been investigated in relation to the use of ACE inhibitors in patients with ischemic cardiomyopathy. Much work has been carried out in patients with an ejection fraction of less than 40% with these enzymes working well. More recently attention has turned to those with an ejection fraction of more than 40% who were studied less. In patients with 40–50% ejection fraction, the ACE inhibitors were seen to reduce the risk of mortality, nonfatal myocardial infarction and stroke by 21% [55].

2.3 Endothelin-1 (ET-1) receptor

There are three different forms of 21-amino acid peptides, which belong to the endothelin peptide family: ET-1, ET-2, and ET-3 [56]. They vary in biological function and may affect blood vessels as well as other tissues both within and outside of the cardiovascular system [56]. The predominant form of endothelin peptide is an isopeptide ET-1 with potent vasoconstrictor and proliferative properties [57]. ET-1 is synthesized by endothelial cells, airway smooth muscles cells, cardiomyocytes, macrophages, leukocytes and mesangial cells [57].

There are two subtypes of receptors which are mediated by endothelin, known as Endothelin Type A receptor (ET_A) and type B (ET_B) [57]. Although mediated by the same peptide agonist, activity of these two subtypes is usually opposite, as the ET_A receptor promotes vasoconstriction, growth, and inflammation whilst ET_B receptors may cause both vasoconstriction and vasodilation and also increases in sodium excretion and inhibition of growth and inflammation [57–59].

The potential to bind with ET_A receptors is the same for ET-1 and ET-2 endothelin but lower for ET-3 endothelin, whilst the potential binding rate with ET_B receptors is equal for every form of endothelin [57, 58]. In people the genes responsible for expression of the ET_A receptors are situated on chromosome 4q31.22-q31.23, whilst genes encoding ET_B receptors are mapped onto

chromosome 13q22.3 [60]. The molecular weight of the ET_A and ET_B receptors are 48 and 50 kDa respectively [61, 62]. The human 427 amino acid long ET_A receptors and 442 amino acid long ET_B receptors are approximately 64% homologous [58]. The homology of ET_A and ET_B receptors in humans and other mammalian species is between 88% and 97% [58].

ET_A receptors are expressed predominantly in the heart (coronary vasculature and cardiomyocytes), lungs (pulmonary artery), kidney (renal artery, afferent and efferent arteriole, cortical vasculature, mesangial cells), brain (cerebral vasculature) and adrenal gland. ET_B receptors also occur in the heart (coronary vasculature and cardiomyocytes), lungs (pulmonary artery), kidney (renal artery, afferent and efferent arteriole, medullar vasculature), brain (cerebral vasculature) and adrenal gland [63].

The ET_A receptors mediated by ET-1 endothelin in vascular smooth muscle cells promoting vasoconstriction, hypertension, hypertrophy, fibrosis and inflammatory changes, including atherosclerosis and due to that has activity similar to the AT₁ receptors mediated by AngII [63]. The vasoconstrictive pathway of ET_A receptors includes: Coupling to phospholipase C (PLC) via GTP-binding protein, phospholipase C activation, phosphatidyl inositol hydrolysis, inositol 1,4,5 triphosphate (IP3) generation and 1,2-diacylglycerol (DCG) accumulation. Inositol triphosphate is a signalling molecule that leads to mobilisation of Ca²⁺ from intra- and extra-cellular sources resulting in long-lasting vasoconstriction [56, 64].

The ET_B receptors mediated by ET-1 endothelin in the vascular endothelium are involved in the clearance of ET-1 and stimulate vasodilation due to the nitric oxide and cyclooxygenase metabolites production, which also exert vasorelaxant effects on the underlying smooth muscle. Moreover, the ET_B receptors have a natriuretic action causing sodium and water resorption from the distal tubules and collecting ducts in the kidney. The ET_B receptors, which occur in smooth muscle cells, additionally act as vasoconstrictors [57, 63, 64].

In the last few years research into endothelin has progressed the information known about links to cardiomyopathies. Some of the early published studies showed that ET-1 and its receptor either played a causative role in hypertrophic cardiomyopathy, idiopathic dilated cardiomyopathy and uremic cardiomyopathy or could be a marker [65–68]. Indeed work in cats has even reflected the increased ET-1 levels in cases of hypertrophic, dilated, restrictive and unclassified cardiomyopathy [69]. More work has now been carried out into other cardiomyopathies and the potential mechanisms of action. Much like ACE2, the endothelin receptor blocker bosentan has been shown to inhibit doxorubicin-induced cardiomyopathy in a rodent model [70]. This study looked at the receptor blocker as elevated levels of ET-1 were discovered in doxorubicin treated patients. The in vitro studies indicated that activation of the epidermal growth factor (EGF) receptor and the MEK1/2-ERK1/2 cascade were possible mechanisms of action [70]. A good review looking at endothelin-1 and atrial cardiomyopathy, published in 2019 brings together the information in this area. The work over the years has indicated that endothelin-1 plays an active role affecting Ca²⁺ levels, via the ET-1-superoxide-MMP9 cascade and via apoptosis, resulting in both electrical and anatomical remodelling [71].

Not only is endothelin-1 a potential therapeutic route but it also shows promise in predicting patient outcomes. A recent study investigating new-onset atrial fibrillation in patients with obstructive hypertrophic cardiomyopathy has shown that elevated pre-operative levels may indicate increased likelihood of atrial fibrillation [72]. Big endothelin-1, the precursor of endothelin-1 has also been shown to be useful when predicting prognosis for hypertrophic cardiomyopathy patients and the authors have suggested that it should be added to marker panels [73, 74]. Endothelin

1 has also been implicated as a modifier in dilated cardiomyopathy. With variations including the rare G > A and a C > T at c.90 seen in dilated cardiomyopathy patients and *EDN1* polymorphisms linked to increased risk of the disorder, likely by altered the stability of the protein [75]. A model of diabetic cardiomyopathy in rats also showed that plasma endothelin-2 levels were higher than controls and that overexpression of the protein results in a more severe phenotype [76].

2.4 Muscarinic receptors

Cardiac function is controlled by the SNS and parasympathetic nervous system (PNS). Parasympathetic vagal nerves are distributed throughout all areas of the heart, particularly in the ventricles [77]. Cardiac muscarinic receptors are activated by acetylcholine, having been stimulated by vagal nerve activation. The muscarinic acetylcholine receptors (M-ChR) are glycoproteins belonging to the 7TMR superfamily [77]. The M₂ subtype of M-ChR are the most prevalent group within the mammalian heart and their function is opposed to the β -ARs in that they cause a reduction in myocardium contractility and a lower cardiac rate [10]. M-ChR exert their influence on the myocardium via the G α_1 -coupled receptors which inhibit adenylyl cyclase whilst the G $\beta\gamma$ dimer impedes the activity of potassium channels in the sinoatrial node [1]. M-ChR can also exert an effect over Ca²⁺ channels [77] affecting cardiac contractility.

Heart failure patients demonstrate an increase in M₂ muscarinic receptor density, with activated M₂ receptors encouraging an inotropic response [9]. One study using serum from a patient showed that when autoantibodies to the muscarinic receptors and β -ARs were activated it resulted in cardiomyopathy and atrial tachyarrhythmias [78]. Along a similar line, autoantibodies against β_1 -ARs have been shown to cause sudden death in idiopathic dilated cardiomyopathy patients [79]. Antibodies to β -ARs have been discovered in people with idiopathic dilated cardiomyopathy, even leading to the suggestion of a form of 'adrenergic cardiomyopathy' [80]. In addition autoantibodies against muscarinic receptors have also been noted in cases of peripartum cardiomyopathy [81], dilated cardiomyopathy [82–85], and M₂-muscarinic acetylcholine receptor autoantibodies have been implicated in playing a role in atrial fibrillation in dilated cardiomyopathy patients [86]. Similar increases were not observed in patients with Takotsubo cardiomyopathy [87] or in rats with cirrhotic cardiomyopathy [88]. Autoantibodies against cardiomyocytes, β_1 - or β_2 -ARs or M₂ muscarinic receptors were not noted in 20 people with Takotsubo cardiomyopathy in comparison to healthy controls, or in rats with cirrhotic cardiomyopathy.

3. Conclusions

The superfamily of 7TMRs includes receptors for hormones, neurotransmitters and ion channels, and are critical to mediate physiological and cellular processes [1, 2]. This chapter has investigated adrenoreceptors (both α - and β -adrenergic receptors) and the components of the renin-angiotensin system (RAS) especially AngII, ACE and the AT1 and AT2 receptors. The chapter has also looked at endothelin-1 (ET-1) and its receptor, and precursor Big endothelin-1 and finally the muscarinic receptors. By looking at their numerous effects in both healthy and diseased vasculature and cardiac disorders, especially cardiomyopathies, it can be seen that there are wide ranging effects. Developing these 7TMRs as markers of disease, for prognosis, diagnosis and therapeutic treatments is becoming more important as their many roles as being uncovered in the cardiovascular system.

Acknowledgements

The authors would like to thank their institutions for funding them. Ewelina Prozorowska, Kristýna Glocová, and Lucy Slater were undertaking research internships with Catrin Sian Rutland at The University of Nottingham, UK. Kristýna Glocová had her internship funded by The European Association of Veterinary Anatomists (EAVA), Young Research Career Development Award; therefore, Kristýna and Catrin would like to thank the EAVA. The ORCID ID of Catrin Rutland is <https://orcid.org/0000-0002-2009-4898>.

Conflicts of interest

The authors declare no conflicts of interest.

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