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Targeting Cardiac Mast Cells: Pharmacological Modulation of the Local Renin-Angiotensin System

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Abstract

Enhanced production of angiotensin II and excessive release of norepinephrine in the ischemic heart are major causes of arrhythmias and sudden cardiac death. Mast cell-dependent mechanisms are pivotal in the local formation of angiotensin II and modulation of norepinephrine release in cardiac pathophysiology. Cardiac mast cells increase in number in myocardial ischemia and are located in close proximity to sympathetic neurons expressing angiotensin AT₁- and histamine H₃-receptors. Once activated, cardiac mast cells release a host of potent pro-inflammatory and pro-fibrotic cytokines, chemokines, preformed mediators (e.g., histamine) and proteases (e.g., renin). In myocardial ischemia, angiotensin II (formed locally from mast cell-derived renin) and histamine (also released from local mast cells) respectively activate AT₁- and H₃-receptors on sympathetic nerve endings. Stimulation of angiotensin AT₁-receptors is arrhythmogenic whereas H₃-receptor activation is cardioprotective. It is likely that in ischemia/reperfusion the balance may be tipped toward the deleterious effects of mast cell renin, as demonstrated in mast cell-deficient mice, lacking mast cell renin and histamine in the heart. In these mice, no ventricular fibrillation occurs at reperfusion following ischemia, as opposed to wild-type hearts which all fibrillate. Preventing mast cell degranulation in the heart and inhibiting the activation of a local reninangiotensin system, hence abolishing its detrimental effects on cardiac rhythmicity, appears to be more significant than the loss of histamine-induced cardioprotection. This suggests that therapeutic targets in the treatment of myocardial ischemia, and potentially congestive heart failure and hypertension, should include prevention of mast cell degranulation, mast cell renin inhibition, local ACE inhibition, ANG II antagonism and H₃-receptor activation.

Keywords

arrhythmias; cardiac renin-angiotensin system; histamine H₃-receptors; mast-cell renin; myocardial ischemia-reperfusion; norepinephrine; sensory and sympathetic nerve endings; sodium-proton exchanger

Introduction

Release of pathological amounts of norepinephrine (NE) from cardiac sympathetic nerve during myocardial ischemia can result in arrhythmias and sudden cardiac death [1–4]. We

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Conflicts of Interest None

propose the existence of two mast cell-dependent effectors which can modulate NE release by targeting sympathetic nerves. One, is represented by angiotensin II (ANG II), which is formed locally by a process initiated by mast cell-derived renin, and functions as a positive modulator [5–9]. The other, comprises histamine, which is directly released from mast cells, and functions as a negative modulator [3,10].

Cardiac mast cells are juxtaposed to nerves [11–13]; upon their degranulation by reactive oxygen species (ROS) and toxic aldehydes in myocardial ischemia [9,14–17], and by IgE cross-linking in immediate hypersensitivity reactions [18–20], mast cells release both renin and histamine. Renin initiates the activation of a local renin-angiotensin system (RAS) which culminates in the formation of ANG II [6–8]. ANG II then binds to AT₁-receptors (AT₁R), which are also expressed in sympathetic nerves [5], while histamine activates H₃-receptors (H₃R) on sympathetic [21,22] and sensory [11,13] nerve endings. Notably, mast cell number, ANG II formation and histamine release all increase in myocardial ischemia [7,23–25].

Inasmuch as AT₁R and H₃R have opposing effects on NE release, an imbalance between renin and histamine release from mast cells may determine the extent of arrhythmic dysfunction in myocardial ischemia. Several myocardial ischemia models in mouse and guinea pig have been used to test the function of AT₁R and/or H₃R [6,21,26–28]. Various *in vitro* models of nerve endings have also been employed to study the activation of AT₁R and H₃R by ANG II and histamine, respectively. These include cultured neuroblastoma and pheochromocytoma cells stably transfected with either AT₁R or H₃R, as well as guinea-pig, mouse and human heart synaptosomes expressing native AT₁R and H₃R [5,7,8,27,29–33]. Collectively, studies in these models indicate that a link exists between mast cell mediators and myocardial ischemia.

Depending on the extent of ischemia, NE is released by enhanced exocytosis (vesicular release) and/or by reversal of the NE transporter (NET) in an outward direction (non-vesicular or carrier-mediated release) [3,21,26,34]. In severe ischemia, intraneuronal metabolic acidosis and ATP depletion develop. As a result, the Na⁺_{in}/H⁺_{out} exchanger (NHE) is activated and this, coupled with a failure of the ATP-dependent Na⁺_{out}/K⁺_{in}-ATPase, leads to Na⁺ accumulation in sympathetic nerves. ATP depletion also contributes to malfunctioning of vesicular H⁺-ATPase and this impairs the storage of NE, thus increasing free cytosolic NE. The combination of high intraneuronal Na⁺ and high cytosolic NE causes the NE transporter to reverse its mode from reuptake to release, and this results in a non-vesicular, carrier-mediated release of pathological amounts of NE from the nerve terminal [3,35,36]. Exocytotic and carrier-mediated NE release from sympathetic nerves are each augmented or inhibited by activation of AT₁R and H₃R, respectively [3,5,30]. Most important, the severity of reperfusion arrhythmias directly correlates with the magnitude of NE release in myocardial ischemia [3]. Thus, based on these studies, ANG II is arrhythmogenic whereas histamine is cardioprotective. Since cardiac dysfunction worsens with increasing NE release [37–42], the elucidation of the two mast cell-dependent mechanisms (i.e., ANG II and histamine) will foster the development of specific therapies targeting mast-cell renin and H₃R in myocardial ischemia [3,6] and potentially in congestive heart failure and hypertension.

Cardiac Mast Cells

The presence of mast cells has been documented in the heart of amphibians [43], rodents [44], canines [45], and humans [7,46–48]. Mast cells generally reside in the interstitial space between myocytes, and are often juxtaposed to nerves [7,12,13]. In the heart, the close

proximity of mast cells to nerves may be particularly relevant to the generation and progression of arrhythmias.

Activated cardiac mast cells release a host of potent pro-inflammatory and pro-fibrotic cytokines, chemokines, preformed mediators (e.g., histamine) [49], in addition to proteases (e.g., renin) [6,7,9,12,13]. The strategic peri-neuronal location of cardiac mast cells in addition to their accumulation in pathological conditions may promote the development of myocardial dysfunction [45]. In fact, mast cell density is markedly increased in heart failure, with significant numbers found in patients with idiopathic and ischemic cardiomyopathy [7,23,25]. It is clear that cardiac mast cells play a role in a variety of cardiac disorders, but due to the complex composition of their secretory granules and the plasticity of their phenotype, their precise contribution must still be elucidated.

Mast Cell-Derived Renin and Activation of AT₁R on Sympathetic Nerve Endings

Discovery of Mast Cell Renin and a Local Cardiac RAS

Traditionally, the RAS has been viewed as a circulating axis whereby renin, the rate-limiting enzyme of the RAS, once released by renal juxtaglomerular cells into the circulation, cleaves liver-derived angiotensinogen to form ANG I, an inactive decapeptide. ANG I is converted to the biologically active product ANG II by angiotensin-converting enzyme (ACE), located on the luminal side of the vascular endothelium. Circulating ANG II regulates blood pressure, plasma volume, sympathetic neural activity, and thirst responses [50,51].

The notion of a local tissue-specific RAS, in addition to the classic circulating RAS [50,51], has now gained general recognition [52–55]. Yet, whether renin is synthesized locally in various organs or exclusively released into the circulation by renal juxtaglomerular cells, and then taken up by local tissues, remains controversial [53,55,56]. All RAS components have been identified in cardiac tissue [12,52,57–59] most ANG II found in the heart is synthesized *in situ* from locally produced, rather than blood-derived ANG I [60–62]. Angiotensinogen, ANG I, ACE, and ANG II are also found in cardiac interstitial fluid [63,64]. In fact, local ANG II concentrations may exceed plasma levels and play important roles in the control of cardiac function [65], in cardiac pathophysiology, such as hypertrophy and infarction [66,67], and in the transition from atherosclerosis to aortic aneurysm [68]. Local ANG II production increases in the ischemic myocardium [24], possibly also via non-ACE enzymes, including chymase [69–71]. Some investigators contend that the kidney is the major source of cardiac renin, because circulating plasma renin is capable of crossing from coronary capillaries into the cardiac interstitium [72]. While some groups demonstrated that cardiac renin disappears within two days of bilateral nephrectomy [73,74], others detected ANG II in the plasma 5 days after bilateral nephrectomy [75].

The finding that mast cells are a novel source of active renin is based on immunohistochemical evidence in intact rodent heart [12,13] and further strengthened by the demonstration that mast cells synthesize renin protein [7,8,12]. Using both polyclonal and monoclonal anti-renin antibodies, cardiac mast cells in rodents were found to be immunopositive for renin. These observations were further extended to the human mastocytoma cell line, HMC-1 [12] and human heart mast cells [8]. Additionally, using a combination of immuno-magnetic separation and FACS sorting, we have isolated human lung mast cells from patients undergoing lobectomy [8][20]. These native mast cells, express renin both at the message and protein level. Notably, we were able to elicit the release ANG I-forming activity from these human mast cells, and 60% of this activity was sensitive to direct renin inhibition [20]. Similarly, we found that mast cells isolated from the rat kidney express renin

protein, the activity of which is pharmacologically inhibitable by direct renin inhibition [76]. Thus, although HMC-1 cells may not be representative of all mast cells [77], we found that renin is indeed present in native mast cells from various organs, and its release in the lung, heart and kidney is associated with ANG II-induced bronchoconstriction, cardiac arrhythmias and renal fibrosis, respectively [6,20,76].

At variance with these findings, Krop et al. reported that fresh mast cells obtained from bone marrow of systemic mastocytosis patients did not contain or release ANG I-generating activity [77]. However, these isolated cells may not be true representative of all mast cells. Indeed, systemic mastocytosis is a heterogeneous disorder characterized by the abnormal growth and accumulation of morphologically and immunophenotypically abnormal mast cells in one or more organs [78].

Recently, Krop et al. found no evidence of ANG I-forming activity in the coronary perfusate of electrically paced *ex vivo* rat hearts following the administration of compound 48/80, either in control conditions or two weeks after the induction of a myocardial infarction. Based on these negative findings, they suggested that mast cells are an unlikely source of renin in the heart [77]. In contrast, Bispo-da-Silva et al. found that 48/80-induced mast cell degranulation in the isolated rat heart did elicit the release of ANG I-forming activity in the coronary effluent, thus indicating that cardiac mast cells are indeed a source of ANG I-forming activity [79]. Yet, this ANG I-forming activity was not affected by the renin inhibitor aliskiren, a finding interpreted to suggest the release from cardiac mast cells of a still unidentified proteolytic activity responsible for the release of ANG I from renin substrate [79]. Nonetheless, it has to be taken into account that, as a renin inhibitor, aliskiren is not as effective in the rat as in other species [80]. Thus, the lack of aliskiren blockade in the Bispo-da-Silva's experiments should be taken with caution.

Notwithstanding the documented presence of renin in cardiac, pulmonary and renal mast cells of the rat [12,20,76], it appears that degranulation by the secretagogue 48/80 is a controversial means to release mast cell renin in the rat heart [77,79]. This is unlike the guinea pig and mouse heart, in which not only 48/80, but also ischemia/reperfusion, immediate hypersensitivity reactions, toxic aldehydes and reactive oxygen species, as well as mast cell-degranulating neuropeptides, elicit the release of renin activity in the coronary effluent, in association with norepinephrine release and reperfusion arrhythmias [6,9,13,19]. These arrhythmias, which do not occur in the mast cell-deficient mouse heart, are the result of local RAS activation; indeed, they are sensitive to mast cell stabilization, direct renin inhibition and ANG II type 1 receptor blockade [6,33]. Hence, it appears that species differences play a role in these discrepancies in the release of renin from cardiac mast cells. Aside from species differences, there are other possible explanations. For instance, we demonstrated a marked increase in renin release during reperfusion following 20-minute global ischemia, whereas Krop et al. did not observe renin release. Since renin is released at reperfusion by toxic aldehydes and reactive oxygen species which degranulate cardiac mast cells [9], no such effect may have been measurable two weeks after coronary ligation without reperfusion in Krop's experiments [77].

Cathepsin-D and chymase: Other mast cell proteases involved in ANG II formation

The notion that mast cells contain renin and are involved in the local formation of ANG II may not be all too surprising. Mast cells are known to store and release cathepsin-D and chymase, two proteases also involved in the formation of ANG II [25,70,81]. Cathepsin-D is similar to renin in that it also cleaves angiotensinogen to ANG I, although at a rate of 10^5 times slower than renin [82]. BLAST analysis reveals that cathepsin-D is 60% homologous to renin at the amino acid level [12]. Chymase, acting independently of ACE, cleaves the phenylalanine-histidine peptide bond in ANG I to generate ANG II [83]. Mast cell-derived

chymase has been recognized as an important factor in the formation of ANG II in the heart [69,70,84–88]. Thus, the potential use of chymase inhibitors to delay the evolution of heart failure has been advocated [82,89]. Indeed, chymase inhibition prevents cardiac fibrosis and improves diastolic dysfunction in the progression of heart failure [90]. Interestingly, chymase is found in high levels in the ischemic heart [91], and the majority of cardiac ANG I is apparently converted by chymase [91]. The expression of renin, cathepsin-D and chymase makes mast cells a unique local target in dealing with disorders in which ANG II production in the heart is increased.

Relevance of the (Pro)renin Receptor

The possibility that mast cell renin originates from the circulation and is taken up from the interstitial fluid must be considered. (Pro)renin receptor (ATP6AP2)[(P)RR][61,92–94] mRNA has been reported to be expressed in activated mast cells from pancreatic lymph nodes of the DR^{+/+} BioBreeding rat [95]. Yet, to date, there has been no evidence indicating that mast cells express either the mannose 6-phosphate receptor (M6PR)[96–98] or the (P)RR at the protein level. In fact, immunofluorescence staining of the rat kidney with the anti-(pro)renin receptor antibody (kindly supplied by Dr. G. Nguyen) showed staining of the distal tubules as previously reported [93], but no (pro)renin receptor staining in kidney mast cells in the peritubular region [76]. It is conceivable, however, that renin could be retained by mast cells by a surface receptor yet to be identified.

Both M6PR and (P)RR bind prorenin and renin with high affinity and are of great interest in the RAS field. Indeed, the identification of mechanisms of receptor expression, binding and activation, as well as prorenin internalization, can lead to potentially innovative therapeutics. The M6PR is a clearance receptor which binds and internalizes human prorenin and renin [96,99]. Prorenin and renin bind with high affinity ($K_d \sim 1$ nM) to the M6PR, which is found on smooth muscle cells, cardiomyocytes, fibroblasts, endothelial cells [96–98], and several types of hematopoietic cells, including monocytes and dendritic cells [100,101]. It is known that binding of prorenin to the M6PR results in degradation of renin preventing further ANG I generation [102].

In contrast, binding of prorenin to the recently-identified (P)RR, which is localized to the mesangium of the glomeruli and to the subendothelium of the coronary and renal arteries, induces a four-fold increase in renin's catalytic activity [93]. Pioneering work by Nguyen and colleagues has revealed that the (P)RR has a single transmembrane domain and the receptor has no homology with any known membrane protein [93].

Release of Mast Cell-Derived Renin, Local ANG II Formation and NE Release

Once it was demonstrated that mast cells synthesize, store and release renin upon activation [7,12], further studies addressed the role of mast cell-derived renin in myocardial ischemia/reperfusion [6], a condition in which both mast cells and ANG II are known to be involved [69,103]. Experiments in Langendorff-perfused guinea pig and mouse hearts subjected to ischemia/reperfusion revealed the pivotal role played by renin released from mast cells and subsequent local ANG II formation in the development of cardiac arrhythmias [6,7]. In isolated hearts subjected to myocardial ischemia/reperfusion, toxic aldehydes [e.g., acetaldehyde and 4-hydroxynonenal (4-HNE)] are formed. They cause mast cell degranulation and the release of renin, which cleaves interstitial angiotensinogen to form ANG I; this is followed by the generation of ANG II via local ACE and/or chymase. ANG II then activates AT₁R located on the membrane of sympathetic nerves, promoting exocytotic and/or carrier-mediated release of NE via NET [6,9]. Once released, NE largely contributes to reperfusion arrhythmias (such as ventricular tachycardia and ventricular fibrillation), which are abrogated by mast cell stabilization, renin inhibition or AT₁R blockade [6,7].

Interestingly, ANG II may also exert cardioprotective effects by activating AT₂R [104], and/or by its ACE2-mediated conversion to ANG-(1–7) which activates the MAS receptor [105]. In both cases, the beneficial effects result from an increased production of vasodilating prostanoids and nitric oxide [106,107]. These effects come clearly into play when AT₁R are blocked [70,108].

Furthermore, an important link exists in the heart between sensory nerves and renin-containing mast cells, in that in ischemia/reperfusion cardiac sensory nerves release neuropeptides such as Substance P and CGRP which, by degranulating mast cells, promote renin release, thus activating a local RAS [13]. Notably, these arrhythmias do not occur in hearts isolated from mast-cell deficient animals [6]. Aside from facilitating NE release and its arrhythmogenic effects, ANG II can also directly elicit cardiac arrhythmias without sympathetic intervention [109,110].

The mechanism responsible for the induction of carrier-mediated NE release by ANG II was investigated in human neuroblastoma SH-SY5Y-AT_{1A} cells [5], an optimal model of sympathetic nerve endings [29]. AT₁R activation in these cells was found to increase the activity of membrane-bound NHE [5]. Enhanced NHE activity resulted in an accumulation of intracellular Na⁺ which triggered the reversal of the Na⁺-dependent NET, leading to excessive NE release. In addition to this cultured-cell model, experiments conducted in guinea-pig heart sympathetic nerve endings (expressing native AT₁R) also demonstrated that ANG II elicits carrier-mediated NE release via NHE activation [5]. Targeting mast cell renin and local AT₁R may offer a novel approach in the prevention and treatment of myocardial ischemia and ANG II-associated disorders.

Mast Cell-Derived Histamine and Activation of H₃R on Sympathetic Nerve Endings

Activation of Histamine Receptors in Myocardial Ischemia

Myocardial ischemia leads to the generation of ROS and toxic aldehydes, in both mast cells and cardiac myocytes, serving as intracrine and paracrine signals, respectively [9,14–17,111–117]. These cause degranulation of cardiac mast cells [9] and consequent release of histamine into the myocardial interstitium and along the lining of the coronary vessels [14–17]. The anoxic human heart has been shown to release endogenous histamine [34]; further, histamine spillover into the coronary effluent of *ex vivo* canine and murine hearts is markedly increased during reperfusion following a period of global ischemia [21,27], indicating that in ischemia/reperfusion cardiac noradrenergic terminals are exposed to higher than normal histamine levels.

Although histamine can directly activate arrhythmogenic H₁R and H₂R [118], a cardioprotective relationship exists between the release of histamine from cardiac mast cells and the attenuation of NE release from sympathetic nerves during myocardial ischemia. This beneficial interaction between mast cells and sympathetic nerves in the heart involves activation of G_{i/o}-linked H₃R present on sympathetic nerves. Indeed, the activation threshold of H₁R and H₂R is much higher than that of H₃R (micromolar for H₁R and H₂R, and nanomolar for H₃R) [119], suggesting that H₃R become activated at a lower concentration of free histamine than H₁R and H₂R. H₃R are inhibitory heteroreceptors that negatively modulate transmitter release and were originally identified in central histaminergic pathways [120]. Pharmacological identification of H₃R has been made in mouse [27], guinea-pig [121], canine [122] and human heart [22], clearly suggestive of a functional role for their activation by endogenous histamine in this organ. These findings imply that H₃R are normally quiescent, yet available for activation by histamine released during myocardial ischemia [21,27].

NE release in Myocardial Ischemia

Excessive release of NE from sympathetic nerves is a key contributor to the generation of cardiac arrhythmias [1–4]. Two major mechanisms regulate NE release from sympathetic nerves, exocytosis and non-vesicular (carrier-mediated) release. Under physiological conditions, and relatively short-lasting myocardial ischemia, NE release is exocytotic and is linked to a rise in intraneuronal Ca^{2+} entering via voltage-operated calcium channels (VOCC) or Ca^{2+} released from intracellular stores [3]. In contrast, during protracted myocardial ischemia NE is transported out of the cell by the NET in an outward direction. This results in a much greater efflux of NE from sympathetic nerves and the induction of severe arrhythmias [1,3]. This release process is known as non-vesicular or carrier-mediated [3]. Carrier-mediated release develops due to ATP depletion and metabolic acidosis in sympathetic nerves [3,123]. This activates neuronal NHE which increases intracellular Na^+ favoring NE efflux by NET in an outward mode [124]. Accordingly, whereas an increase in intracellular Ca^{2+} is pivotal for the exocytosis of NE [3], an increase in NHE activity is the most relevant factor for the carrier-mediated efflux of NE [3,5].

Cardioprotective Effect of H_3R Activation

Selective activation of H_3R reduces NE exocytosis evoked by neuronal depolarization or short-lasting myocardial ischemia [21,22]. This action results from an attenuation of Ca^{2+} influx into sympathetic nerves [125]. The H_3R -mediated decrease in intraneuronal Ca^{2+} involves an inhibition of adenylyl cyclase and decreased cAMP formation. Thus, diminished Protein Kinase A (PKA) activity leads to decreased phosphorylation of VOCC diminishing their opening probability [126]. A direct action of the $\text{G}\beta\gamma$ subunit liberated from $\text{G}\alpha\beta\gamma$ trimers following H_3R activation has also been shown to attenuate neuronal intracellular Ca^{2+} and thus attenuate NE exocytosis [33]. Moreover, an H_3R -dependent $\text{G}\beta\gamma$ -mediated stimulation of the MAPK- PLA_2 cascade also contributes to PGE_2 -induced anti-exocytotic effects [127].

As mentioned above, in protracted myocardial ischemia, activation of neuronal NHE is pivotal for the development of carrier-mediated NE release and associated arrhythmias [3]. ANG II, formed locally by mast cell-derived renin in myocardial ischemia [6,7], is a major NHE activator via AT_1R [5] and only a minor, indirect inhibitor via AT_2R [128]. ANG II elicits reperfusion arrhythmias by facilitating NE release [1–3,129] as well as by a direct action on cardiac myocytes and cells of the specialized conduction tissue of the heart [110,130–133]. Both of these actions are AT_1R -mediated [134].

Conversely, histamine, also locally released from mast cells by ROS and toxic aldehydes in myocardial ischemia [9,115,135,136], inhibits NHE activity via H_3R activation [30], thus attenuating NE release and alleviating arrhythmias [3,26]. Accordingly, we hypothesize that the activation of H_3R in myocardial ischemia serves a protective function in opposing the NE-releasing pro-arrhythmogenic actions of ANG II.

Conclusions

Collectively, this manuscript describes novel mast cell-dependent mechanisms promoting excessive NE release and ANG II formation in cardiac pathophysiology. These mechanisms represent new likely targets in the treatment of arrhythmias, congestive heart failure, and hypertension, conditions in which NE and ANG II play a major causal role. Mast cells are normally found in the heart in close proximity to AT_1R - and H_3R -expressing neurons. The number of mast cells increases in myocardial ischemia. Mast cell-derived renin (followed by local ANG II formation) and histamine can respectively activate AT_1R and H_3R on sympathetic nerves in myocardial ischemia as shown in Figure 1. The findings described in

this review demonstrate that stimulation of AT₁R is arrhythmogenic, while activation of H₃R is cardioprotective. It is likely that in ischemia/reperfusion the balance leans toward the deleterious effects of mast cell renin, as demonstrated in mast cell-deficient mice, lacking both renin and histamine in their hearts. In these mice, no ventricular fibrillation occurs at reperfusion following ischemia, as opposed to wild-type hearts which all fibrillate [27,28]. Thus, prevention of local cardiac RAS activation and its noxious arrhythmogenic effects appears to be more significant than the loss of histamine-induced cardioprotection.

Pharmacological targeting of cardiac mast cells offers several possible therapeutic opportunities to prevent and/or modulate the activation of a local renin-angiotensin system in the heart and to alleviate its dysfunctional consequences at various sequential steps of the RAS cascade (see Table 1). First, as illustrated in Fig. 1 and Table 1, prevention of mast cell degranulation can be attained by inhibiting the release of mast cell-degranulating peptides (e.g., Substance P and CGRP) from sensory nerve endings (e.g., with selective histamine H₃R agonists)[11,13]. Second, mast cell degranulation can be prevented by blocking the effect of mast cell-degranulating peptides at their receptors on the mast cell membrane (e.g., with Substance P and CGRP receptor antagonists)[13]. Third, mast cell degranulation can be prevented with mast cell stabilizers (e.g., disodium cromoglycate and related agents)[6,19]. Fourth, mast cell-degranulating ROS and toxic aldehydes which are produced in ischemia-reperfusion can be eliminated by agents that directly and selectively activate aldehyde dehydrogenase type-2 (ALDH2) in mast cell mitochondria [9]. Fifth, cardiac RAS activation can be prevented by direct renin inhibitors which block ANG I formation by renin released from local mast cells [6–8]. Sixth, ANG II formation can be prevented with ACE and chymase inhibitors [70]. Seventh, the ANG II-induced stimulation of NHE and its consequent induction of carrier-mediated NE release can be directly antagonized with AT₁R blockers [5,70] and, eighth, by inhibiting NHE activity with H₃R agonists [26,30,34]. Ninth, the direct arrhythmogenic effects of ANG II can be inhibited by antagonizing AT₁R in cardiac myocytes and in specialized conduction tissue cells [110,130–133]. Finally, it is conceivable that combining two or more of the pharmacological agents listed in Table 1 may offer a better prospect for the treatment of acute cardiac ischemic events and long-term remodeling changes associated with the activation of a local RAS, the elicitation of arrhythmias and the development of cardiac failure and hypertensive disease.

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List of Abbreviations

ACE	angiotensin-converting enzyme
ALDH2	aldehyde dehydrogenase type-2
ANG I	angiotensin I
ANG II	angiotensin II
Aogen	angiotensinogen
AT₁R	angiotensin type-1 receptor(s)
AT₂R	angiotensin type-2 receptor(s)
CGRP	calcitonin gene-related peptide
CHF	congestive heart failure

H₃R	histamine H ₃ -receptors
MC	mast cells
M6PR	mannose 6-phosphate receptor
NE	norepinephrine
NET	norepinephrine transporter
NHE	Na ⁺ _{in} /H ⁺ _{out} exchanger
NK1R	neurokinin1 receptor
(P)RR	(Pro)renin receptor (i.e., ATP6AP2)
RAS	renin-angiotensin system
ROS	reactive-oxygen species
SCD	sudden cardiac death
SP	Substance P
VOCC	voltage-operated calcium channels

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Figure 1. Proposed points of therapeutic intervention in the activation of a mast cell-derived cardiac RAS and its interaction with mast cell-released histamine in myocardial ischemia
 Numbers 1–9 in the figure correspond to the respective therapeutic targets listed in Table 1. CGRP(R), calcitonin gene-related peptide(receptor); SP, Substance P; NK1R, neurokinin 1 receptor; Aogen, angiotensinogen; ACE, angiotensin-converting enzyme; AT₁R, angiotensin AT₁-receptor; H₃R, histamine H₃-receptor; NET, norepinephrine transporter; NHE, Na⁺/H⁺ exchanger; CHF, congestive heart failure; SCD, sudden cardiac death.

Table 1

Proposed therapeutic targets to prevent the activation of mast cell-derived RAS in the heart.

See Fig.1	Target	Pharmacological Agents	Protective Effect	References
1	Sensory nerve endings	H ₃ R agonists	Prevention of release of MC-degranulating neuropeptides	[11,13]
2	MC membrane	SP and CGRP receptor blockers	Prevention of neuropeptide-induced MC-degranulation	[13]
3	MC membrane	MC stabilizers	Prevention of MC degranulation and renin release	[6,19]
4	ALDH2 in MC mitochondria	Selective ALDH2 activators	Prevention of MC degranulation by toxic aldehydes	[9]
5	Renin	Direct renin inhibitors	Prevention of RAS activation	[6]
6	ACE, chymase	ACE inhibitors, chymase inhibitors	Prevention of ANG II formation	[70]
7	NHE in sympathetic neurons	AT ₁ R blockers	Prevention of ANG II-induced NHE stimulation and carrier-mediated NE release	[5,70]
8	NHE in sympathetic neurons	H ₃ R agonists	Attenuation of ANG II-induced NHE stimulation and carrier-mediated NE release	[26,30,34]
9	AT ₁ R in cardiac myocytes and specialized conduction tissue cells	AT ₁ R blockers	Inhibition of the direct arrhythmogenic effects of ANG II	[110,130–133]