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Review

Endothelin and cardiac arrhythmias: do endothelin antagonists have a therapeutic potential as antiarrhythmic drugs?

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Abstract

Endothelin-1 (ET-1), the predominant isoform of the ET peptide family and a potent vasoconstrictor, has been shown to aggravate ischemia-induced ventricular arrhythmias. However, there is also evidence that ET-1 may have a direct arrhythmogenic action that is not solely attributable to myocardial ischemia. Proposed mechanisms for the arrhythmogenic effects of ET-1 are prolongation or increased dispersion of monophasic action potential duration, QT prolongation, development of early afterdepolarizations, acidosis, and augmentation of cellular injury. As for an ionic basis for the observed electrophysiologic effects, ET-induced Ca^{2+} release from intracellular stores, generation of inositol triphosphate, inhibition of delayed rectifier K^+ current, and stimulation of the Na^+/H^+ exchanger may be involved. Recently, some studies have shown that ET receptor antagonists, which promise to be powerful tools in cardiovascular medicine, may also demonstrate antiarrhythmic properties. This review describes the current state of knowledge on the interactions between the ET system and cardiac arrhythmias, and discusses the therapeutic potential of ET antagonists as antiarrhythmic drugs.

Keywords: Antiarrhythmic agents; Arrhythmia (mechanisms); Endothelins

1. Introduction

There is an accumulating body of evidence suggesting that endothelin-1 (ET-1), the predominant isoform of the 21-amino acid ET peptide family and a potent vasoconstrictor, also has arrhythmogenic effects [1–11]. Recently, a small number of animal studies have shown that ET antagonists, which compete for binding sites for ET-1, may demonstrate antiarrhythmic properties [12–14]. This article aims to provide a review of the current state of knowledge on the proarrhythmic effects of ET-1 as well as the therapeutic potential of ET antagonists as antiarrhythmic drugs.

2. Endothelin: an endogenous peptide

The vascular endothelium regulates vascular tone and cell proliferation through release of vasoactive factors, growth factors, and controls blood coagulation and platelet aggregation [15]. Soon after the discovery of endothelium-derived relaxing factor [16], it became clear that the endothelium is also a source of vasoconstrictor substances. Originally described as an endothelium-derived vasoconstricting factor released upon stimulation with vasoactive agonists [17], it was named endothelin thereafter [18]. The discovery of this peptide initiated a new field of biomedical research leading to better understanding of the pathogenesis of numerous disease states and to the development of novel therapeutics. In the cardiovascular system, ET-1 is an extremely potent vasoconstrictor and stimulates cell proliferation in an autocrine fashion in various cell types including endothelial, vascular smooth

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muscle and mesangial cells, and cardiac myocytes [19,20]. ET-1 has recently been identified to play an important role for vascular remodeling and function in hypertension and atherosclerosis [21,22]. Interactions between ET-1, vasoactive mediators, blood cells, and the arterial vessel wall are shown in Fig. 1.

2.1. Regulation of endothelin synthesis

Transcription of the preproET-1 gene leads to production of prepro-ET-1, a 203-amino-acid peptide, which is cleaved by specific peptidases to the inactive 38-amino acid precursor big ET-1 [18]. Big ET-1 is further processed to ET-1 by several endothelin converting enzymes (ECE) [23,24]. ET-1 gene transcription is regulated by growth factors, such as TNFα, TGFβ-1 and bFGF-2, in an autocrine manner [19]. Although plasma levels of ET-1 are rather low and may only reflect a fraction of actual production in the tissue, in numerous cardiovascular disorders associated with arrhythmias including atherosclerosis, acute myocardial infarction, and congestive heart failure, circulating levels of ET-1 are increased suggesting activation of the ET system [25,26].

2.2. Endothelin isoforms and receptors

ET-1 is the predominant isoform of a group of three 21 amino-acid peptides including ET-2 and ET-3 which show different profiles of activity in various tissues [27,28]. Both ET-1 and ET-3 (which differs from ET-1 by six amino acids) are vasoactive peptides, although ET-1 is more than 100-fold more potent than ET-3 as a vasoconstrictor. ET receptors consist of ET_A and ET_B subtypes in mammals [28]. The ET_A subtype accounts for more than 90% of ET receptors in isolated myocytes [29]. In addition, ET_A receptors predominate in the tunica media of intramyocardial vessels [30,31]. ET_B receptors are localized to other cell types, such as endothelial cells, and neuronal tissue and fibroblasts [32,33]. Although ET_A receptors are the predominant subtype in the vasculature, in other human tissues such as the kidney receptors are more abundant [34]. In the vasculature, the ET_A subtype is being exclusively expressed on vascular smooth muscle cells, whereas ET_B receptors are localized on both endothelial cells and — to a lesser extent — on certain vascular smooth muscle cells [35]. The ET_A receptor shows greater selectivity for ET-1 and ET-2 than for ET-3, while the three isopeptides are equipotent at the ET_B receptor. Stimulation of ET_A receptors causes contraction, proliferation and migration, whereas stimulation of ET_B receptors increases NO release and relaxation. Recent studies have shown that in the failing and non-failing human heart, ET_A and ET_B receptors coexist; however, ET_A receptors appear to be functionally relevant [36—38].

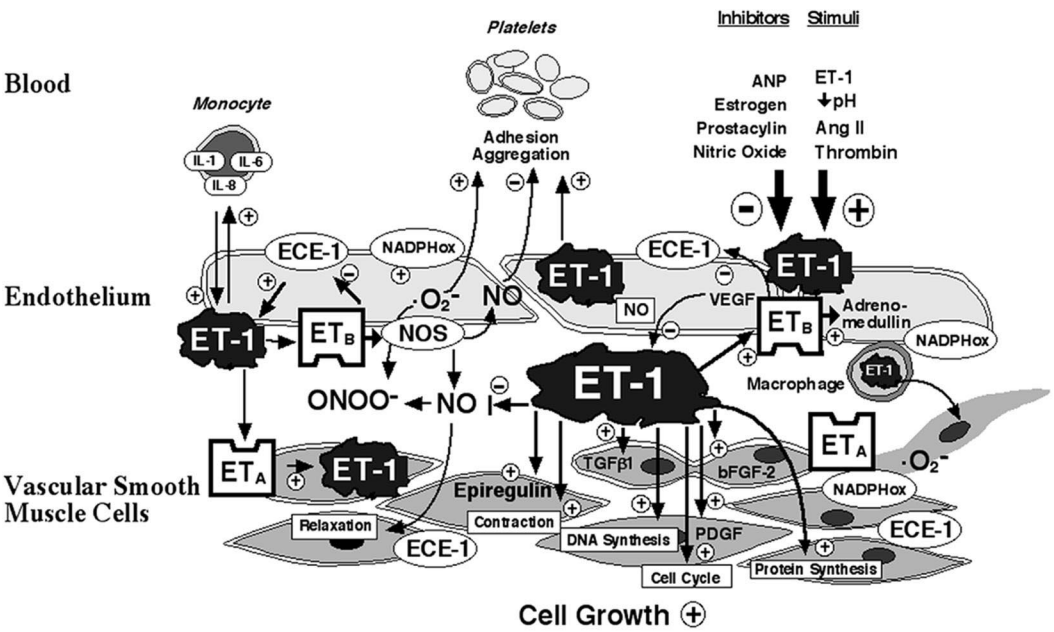

Fig. 1. Interactions between endothelin-1, vasoactive mediators, blood cells, and the arterial vessel wall: ET-1 is generated within endothelial and vascular smooth muscle cells in response to stimuli, such as angiotensin II, thrombin, decreased pH, and also by autocrine stimulation through ET-1. Stimulation of endothelial ET_B receptors stimulates release of NO and adrenomedullin as well as vasorelaxation, whereas ET_A receptors activate contraction, cell proliferation, and migration. ET-1 stimulates interleukin expression in monocytes, and increases platelet aggregation. In addition, ET-1 stimulates the production and potentiates the action of several growth factors, increases DNA and protein synthesis, and promotes cell cycle progression. (Ang II, angiotensin II; ANP, atrial natriuretic peptide; $ONOO^-$, peroxynitrite; ECE, endothelin converting enzyme; ET-1, endothelin-1; ET_A, endothelin subtype A receptor, ET_B, endothelin subtype B receptor; NO, nitric oxide; NOS, nitric oxide synthase; $^{\cdot}O_2^-$, superoxide anion; IL-1, interleukin 1; IL-6, interleukin 2, IL-8, interleukin 8; TGF-β1, transforming growth factor β1; bFGF-2, basic fibroblast growth factor-2; NADPHox, NADPH oxidase; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor; +, stimulation, −, inhibition.) (Reproduced from Ref. [28] Barton M, Lüscher TF. Endothelin antagonists for hypertension and renal disease. Curr Opin Nephrol Hypertens 1999;8:549–555, with permission).

2.3. Endothelin antagonists

Discovery of the ET receptors has enabled the development of specific receptor antagonists. These agents can be divided into receptor-selective (ET_A or ET_B) or unselective (blockade of both receptors) compounds. Several peptides or non-peptide compounds are now available and some are in clinical development (Table 1). Some of these compounds are peptides prohibiting oral application but orally active compounds have recently become available, some of which are already evaluated in clinical studies (e.g. bosentan tracleer®, a non-selective receptor antagonist) [39]. The cyclic pentapeptide ET antagonist, BQ-123, has been utilized in numerous studies investigating its non-cardiovascular [40,41] and cardiovascular effects [42–46]. Studies using ligand binding techniques to determine the affinity and selectivity of ET receptor agonists and antagonists in human left ventricle which expresses both ET_A and ET_B receptors showed that the ET antagonists BQ-123 and FR139317 are highly selective for the ET_A subtype with similar sub-nanomolar affinities as the endogenous agonist ligand ET-1 [46]. No species differences were detected in the binding profile of ET_A receptors. In contrast, the ET_B receptor antagonist, BQ-788, has a low, micromolar affinity and shows no significant binding in human left ventricular tissue. Cardiovascular ET_B receptors from human tissue may differ from those in other vascular beds from other species since the binding profile for ET_B selective ligands differed markedly for human tissue and rat and porcine heart tissue. These results suggest that extrapolating from data derived from animal studies to human studies appears to be more reliable for ET_A receptors as compared to ET_B receptors, yielding important implications for pharmacological inhibition of the receptors.

3. Arrhythmogenic effects of endothelin

3.1. Ischemia-induced effects of exogenous endothelin

Because of its vasoconstrictor potency, exogenously administered ET-1 may induce arrhythmias associated with myocardial ischemia. Lethal ventricular arrhythmias were reported in studies of perfused pig hearts, caused by a

Table 1
Some of the endothelin receptor antagonists currently under evaluation in preclinical studies and clinical trials[a]

Compound	Target	Company	Indication/comments[b]
A-127772	ET_A	Abbott	
A-182086	ET_A/ET_B	Abbott	
ABT-627	ET_A	Abbott	CHF, prostate cancer
BMS-182874	ET_A	Bristol Myers Squibb	CHF
BQ-123	ET_A	Banyu	I.v. use only
BQ-485	ET_A	Banyu	I.v. use only
CGS-27830	ET_A/ET_B	Novartis	
FR-139317	ET_A	Fujisawa Pharm.	
L-749329	ET_A	Merck	
L-753037	ET_A/ET_B	Merck	
LU135252 (darusentan)	ET_A	Knoll	CHF, hypertension
LU208075	ET_A	Knoll	CHF, hypertension
LU302146	ET_A	Knoll	Occlusive vascular disease
LU224332	ET_A/ET_B	Knoll	
PD-142893	ET_A/ET_B	Parke-Davis	Cardiovascular diseases
PD-147953	ET_A	Parke-Davis	Cardiovascular diseases
PD-151242	ET_A	Parke-Davis	Cardiovascular diseases
PD-155080	ET_A	Parke-Davis	Cardiovascular diseases
RO 47-0203 (3 basentan)	ET_A/ET_B	Hoffmann-La Roche	Heart failure, hypertension
RO 48-5695	ET_A/ET_B	Hoffmann-La Roche	
RO 61-1790	ET_A	Hoffmann-La Roche	SAH; i.v. use only
SB-209670	ET_A/ET_B	SmithKline Beecham	Cardiovascular indications, radiocontrast nephropathy
SB-247083	ET_A	SmithKline Beecham	
TAK-044	ET_A/ET_AET_B	Parke-Davis	CAD, SAH, renal transplant rejection; i.v. use only
TBC11251		Texas Biotechnology	CHF, primary pulmonary hypertension
ZD 1611	ET_A	Zeneca	Obstructive lung disease, primary pulmonary hypertension

[a] Compounds listed are either selective for the ET_A receptor or combined ET_A/ET_B receptor antagonists. Clinical information is noted if information was available. Some of the drugs are only suited for intravenous use due to their peptide structure.

[b] CHF, chronic heart failure; CAD, coronary artery disease; SAH, subarachnoidal hemorrhage.

(Modified from Ref. [28]; Barton M, Lüscher TF. Endothelin antagonists for hypertension and renal disease. Curr Opin Nephrol Hypertens 1999;8:549–555.)

progressive decline in coronary flow [47]. Salvati et al. demonstrated that the occurrence of arrhythmias always paralleled ECG changes typical of myocardial ischemia and a decrease in coronary blood flow in open-chest anesthetized dogs [4]. When infused into the left circumflex artery, ET-1 caused ventricular tachycardia degenerating into ventricular fibrillation at 80 pmol/kg, but fatal arrhythmias occurred already at lower doses (20 pmol/kg) during infusion into the left anterior descending artery. Garjani et al. assessed the effects of intravenous infusions of exogenous ET-1 on incidence and severity of ventricular arrhythmias during acute myocardial ischemia in anesthetized rats [12]. Exogenous ET-1 (at doses of 0.05 and 0.1 nmol/kg/min) increased the severity and incidence of ischemic arrhythmias dose-dependently. Both doses increased the total incidence of ventricular ectopic beats, whereas the higher dose also increased the total duration of ventricular tachycardia. Other investigators observed ventricular arrhythmias accompanying a moderate reduction in coronary blood flow [5] [8]. Intrapericardial infusion of ET-1 in dogs was shown to cause ischemic changes and induce monomorphic and polymorphic ventricular tachycardia which spontaneously disappeared or degenerated into ventricular fibrillation [7].

The cellular mechanisms of reperfusion-induced arrhythmias are likely to differ from those responsible for ischemic arrhythmias [48]. The results of published reports investigating the role of ET-1 on reperfusion arrhythmias are controversial. Some investigators demonstrated that ET-1 exacerbated reperfusion injury and reperfusion arrhythmias in rat hearts by a mechanism likely involving activation of the Na^+/H^+ exchanger [49–51]. In contrast, Jacobsen et al. demonstrated that reperfusion of ischemic rat hearts caused arrhythmias in the presence of norepinephrine or thrombin, but not ET-1 [52]. In parallel studies from the same group, ET-1 suppressed the development of reperfusion arrhythmias initiated by either agent [53]. It was proposed that inhibition of inositol triphosphate (IP_3) generation was responsible as a possible mechanism. However, the concept of antiarrhythmic potential of ET-1 in these in vitro studies with global ischemia should be evaluated with caution. The effects of ET-1 in vivo are multifactorial, including the action of cathecholamines, which may be absent or present only locally. Therefore, the discrepancies in the observed effects of ET-1, being proarrhythmic or antiarrhythmic, are related to the different conditions studied, and points out the importance of analyzing data in comparable models.

3.2. Direct arrhythmogenic effects of exogenous endothelin

Early after the discovery of the peptide, a direct role for ET-1 in arrhythmogenesis has been investigated. Yorikane et al. demonstrated, for the first time, that exogenous ET-1 may exhibit an arrhythmogenic action that is not solely attributable to myocardial ischemia [1–3]. When ET-1 was administered into the coronary ostia in anesthetized rats, ventricular arrhythmias developed at doses above 0.5 μg/kg and were precipitated into ventricular fibrillation at 1 μg/kg. At the time when the arrhythmias developed, the ischemic changes had already subsided, supporting the hypothesis that ET-1 might exert primary proarrhythmic effects. Recently, Szabo et al. compared the effects of total occlusion of left anterior descending artery (group A) to intracoronary administration of ET-1 (at a rate of 30 pmol/min, group B; and 60 pmol/min, group C) in open-chest mongrel dogs [54]. Blood samples for lactate measurements were collected from the coronary sinus (CS) and infrared imaging was applied to follow epimyocardial heat emission images. The investigators demonstrated that ET-1-induced arrhythmias occurred without any ischemic thermographic changes or elevations in CS lactate levels in group B and without CS lactate elevations in group C, whereas both parameters were significantly changed in group A. In a similar comparison study, Becker et al. analyzed three-dimensional activation patterns of ventricular arrhythmias induced by intracoronary administration of ET-1 in comparison with arrhythmias induced by ligation of the left anterior descending artery in foxhounds [55]. The investigators demonstrated marked differences in electrophysiological properties and the mechanisms for the maintenance of arrhythmias. ET-1 had no significant effect on local refractory periods, left ventricular conduction pattern and the overall activation pattern, whereas acute ischemia caused by ligation induced local conduction delay and prolonged refractoriness homogenously in all myocardial levels. Furthermore, ET-1-induced arrhythmias were exclusively based on focal mechanisms, whereas during ligation, macroreentrant mechanisms were involved in the maintenance of tachycardias. These differences support the hypothesis that ET-1 may exert an intrinsic arrhythmogenic effect. However, the investigators in both of the above-mentioned studies could not exclude the possibility that ET-1 infusion at the doses used could cause some degree of accompanying regional, if not generalized, ischemia. In any case, a direct role for ET-1 in the development of arrhythmias awaits more conclusive data, and this will be a difficult task in view of the agent's marked vasoconstrictive potency and its increased secretion in a complex substrate.

Although exogenous ET-1 infusion is known to cause arrhythmias under ischemic conditions and may also have a direct role in arrhythmogenesis, some studies suggest that ET-1 may, under certain conditions, be antiarrhythmic. Sharif et al. showed that a very low dose of ET-1, given as a bolus injection prior to ischemia, may protect against ischemic arrhythmias by mechanisms mimicking ischemic preconditioning [56]. In this study, ET receptor antagonists caused a further reduction in the number of ventricular ectopic beats, and the incidence of ventricular fibrillation and mortality. Downregulation of epsilon-subtype protein kinase C was suggested to play a role in preconditioning of

the coronary artery against vasoconstriction by ET-1 [57]. However, the hypothesis that suggests a possible beneficial role for ET-1 in ischemic preconditioning is not universally accepted [58].

3.3. Endogenous endothelin: are physiological levels arrhythmogenic?

Endogenous release of ET-1 occurs under basal and hypoxic or ischemic conditions. Under normoxic conditions, basal NO release results in tonic inhibition of ET-1 production [59]. Under ischemic conditions, ET-1 formation is still subject to modulation by NO, but this remains insufficient as compared to the increased net release and action of ET-1. The enhanced ET-1 formation contributes to the extension of ischemia-induced myocardial injury by resulting in myocardial and endothelial cell death with concomitant outflow of LDH, an established marker of cell viability, and L-arginine, the NO precursor.

Elevated plasma levels of ET-1 have been reported in animal experimental models of ischemia [60] as well as in patients with ischemic heart disease [25,61,62]. The clinical relevance of ET-1 in certain clinical situations, such as in the maintenance of basal vascular tone and blood pressure in humans, has been demonstrated by local and systemic vasodilatation in response to ET receptor antagonists [63,64]. However, most studies on ET arrhythmogenesis studied the effects of pharmacological quantities of exogenously administered ET-1. For example, despite the fact that very high concentrations of ET-1 were shown to be present in pericardial fluid of humans [65] and dogs [7], the level of exogenous ET-1 infused into the pericardial space that induced ventricular arrhythmias was 10-fold higher as compared to endogenous pericardial fluid ET-1 levels under physiological conditions [66]. It remains to be determined whether ET-1 levels in pericardial fluid or other body fluids can ever reach sufficiently high levels to induce arrhythmias in different pathophysiological conditions. On the other hand, circulating levels of ET-1, which represent only an overflow of endogenous tissue-bound ET-1, also do not reflect a true estimate of ET-1 activity. Although plasma levels may not be high enough to directly stimulate cardiac muscle, it is possible that locally synthesized and abluminally released ET-1 may stimulate cardiac muscle [67].

The available data showing the physiological importance of suppressing endogenous ET-1 using ET receptor blockers are very scarce. Raschack et al. demonstrated antiarrhythmic and antifibrillatory effects of an ET_A antagonist (LU 135252, darusentan) on ischemic ventricular arrhythmias in pigs, which have large non-self defibrillating hearts lacking relevant collateral circulation [14]. Intravenous injection of the drug at a dose of 3 mg/kg prior to occlusion of the left anterior descending artery significantly prolonged the time of regular sinus rhythm within the first 20 min of ischemia, reduced the number of ventricular ectopics and the total incidence of ventricular fibrillation. In humans, however, the clinical relevance of ET-1 activity under pathophysiological conditions of ischemia or other disease states is yet to be determined.

4. Mechanisms of endothelin-induced arrhythmias

Three basic concepts account for the majority of arrhythmias: reentry, increased automaticity and triggered activity. Reentry, which gives rise to arrhythmias in most cases, may occur over a large circuit (macroreentry) or may involve a small circuit (microreentry). Arrhythmias caused by microreentrant circuits, increased automaticity and triggered activity are determined to be focal in origin in electrophysiological testing.

The pathophysiological basis of ET-induced arrhythmias is not known. However, several mechanisms have been proposed (Table 2). Three-dimensional mapping revealed that all tachyarrhythmias caused by exogenous administration of ET-1 were exclusively based on mono or multifocal activity and there was no evidence of macroreentry. Transmembrane potential recordings using conventional microelectrode techniques showed that the dose-dependent positive inotropic response to ET-1 [68] was accompanied by prolongation of the cardiac action potential duration (APD) [3]. It has been suggested that early afterdepolarizations (EAD), oscillatory potentials that occur during the action potential plateau or during late repolarization, are involved in the genesis of ET-1-induced arrhythmias [3]. Similarly, a significant increase in endocardial and epicardial monophasic APD90 and QT interval were reported in several experiments [7–9]. Focal origin of arrhythmias, APD prolongation and generation of EADs favor triggered activity as a likely mechanism. Permanent bradycardia induced by radiofrequency ablation of the AV node augmented the direct proarrhythmic effect of ET-1 in dogs

Table 2
Mechanisms of action by which ET-1 may promote the development of arrhythmias[a]

	Arrhythmogenic mechanism	Molecular changes
Triggered activity	Early afterdepolarizations	Ca^{2+} mobilization (generation of IP_3)
	APD prolongation	$\downarrow K^+$ currents (inhibition of I_K)
Microreentry (?)	Increased dispersion of APD	
	Regional heterogeneity	

[a] APD, action potential duration; IP_3, inositol triphosphate. I_K, delayed rectifier K^+ current.

[10], supporting the hypothesis that triggered activity may be operative. Also compatible with this hypothesis, induction rates with programmed ventricular stimulation were low [8]. On the other hand, regional heterogeneity in the electrophysiological effects of ET-1 and increased AP dispersion [9] may favor microreentry, a mechanism which could not be ruled out in three-dimensional mapping [55].

4.1. Ion channels

ET-1 has been shown to regulate cardiac function through the modulation of ion channels. The role of Ca^{2+} channels in ET-1 arrhythmogenesis was investigated by Solti et al. [11] ET-1 was administered into the left anterior descending artery of 24 open-chest dogs. Twelve dogs received the Ca^{2+}-channel blocker verapamil before ET-1 administration and twelve animals served as controls. Electrophysiological studies were performed by programmed electrical stimulation of the heart. In the control group, sustained ventricular tachycardia and ventricular fibrillation developed in nine dogs, whereas in the verapamil-pretreated group, arrhythmias occurred only in two animals. This study may suggest that Ca^{2+} ion channels may be involved in the arrhythmogenic action of ET-1. It may be argued, however, that elimination of ventricular arrhythmias by Ca^{2+}-channel blockade could result from the antagonizing vasoconstrictive effects of ET-1 [69,70].

ET-1-induced vascular contraction is accompanied by an increase in intracellular Ca^{2+}, which consists of two phases: (a) an initial transient rapid Ca^{2+} release is the result of mobilization of Ca^{2+} from intracellular stores and (b) a sustained phase, which is dependent on external Ca^{2+} and is the result of transmembrane Ca^{2+} influx [71]. It has been proposed that ET-1 mobilizes Ca^{2+} from the sarcoplasmic reticulum store via IP_3, because generation of IP_3 accompanies ET-1 stimulation of smooth muscle cells [72]. Previous studies have implicated this water-soluble cytoplasmic second messenger in the genesis of arrhythmias under ischemic and reperfusion conditions [73–75]. However, molecules other than IP_3 may also mediate the ET-induced Ca^{2+} release from intracellular stores [71]. Concerning the nature of the ion channel through which transmembrane Ca^{2+} influx occurs, it was originally postulated that ET-1 was an endogenous ligand at voltage-dependent L-type Ca^{2+} channels [18]. The EADs induced by ET-1 were abolished by nicardipine, supporting the hypothesis that L-type currents ($I_{Ca,L}$) were involved in the genesis of EADs [3]. However, several studies reported contradictory observations showing no or only marginal effect of the same Ca^{2+} antagonists on ET-1-induced vasoconstriction [71].

In addition to Ca^{2+} influx, K^+ currents may also be involved for the observed electrophysiologic effects. The delayed rectifier K^+ current is important in the repolarization of the cardiac action potential. It has been shown that ET-1-induced inhibition of delayed rectifier K^+ current may be responsible for the APD prolongation, especially in the presence of β-adrenergic stimulation [76]. The dispersion of APD, which has been observed in some animal studies, may be caused by an altered balance between the inward and outward ion channels that are modulated by ET-1. In addition, as early pioneering work by Coraboeuf showed, acidosis that occurs during ischemia induces a decrease in K^+ conductance that can be responsible for ectopic foci causing arrhythmias by the mechanism of EADs [77]. ET-1 is also a mediator of the activation of the cardiac sarcolemmal Na^+/H^+ exchanger, which is causally linked with acidosis, while inhibition of the exchanger is known to be associated with a decreased susceptibility to severe ventricular arrhythmias [78,79]. In guinea pig papillary muscles in vitro, ET antagonism prevented hypoxia-induced impairment of intercellular coupling [14]. Therefore, it was speculated that the antiarrhythmic effects may be secondary to a direct cellular antihypoxic action. Apart from the above-mentioned possible mechanisms, ET receptor blockade may reduce cellular injury, an effect that may be antiarrhythmic independent of any effect on ion channels and repolarization.

5. Therapeutic potential of endothelin-antagonists

ET receptor blockade has been shown to have a therapeutic potential in experimental and early clinical studies in hypertension, atherosclerosis, heart failure, pulmonary disease, and renal end-organ damage [28,80]. The recent observation of the potential arrhythmogenic effects of ET-1 in animal studies has resulted in growing interest to investigate the antiarrhythmic potential of ET antagonists.

5.1. Which receptors are involved in endothelin arrhythmogenesis?

Ventricular arrhythmias induced by ET-1 are most likely to be suppressed by ET_A receptor antagonists. Garjani et al. showed that the ET_A receptor antagonist BQ-123 completely abolished the ventricular proarrhythmic effects of exogenous ET-1 during acute myocardial ischemia in anesthetized rats [12]. The antiarrhythmic potential of another ET_A receptor antagonist, BQ-485, was investigated in a study by Ercan et al. which showed complete blockade of the arrhythmogenic effects of ET-1 [13]. In BQ-485 pretreated rat hearts, ET-1 caused a fall in coronary perfusion pressure and a slight positive inotropic response. BQ-485 at the same concentration also caused a significant reduction in the duration of ventricular arrhythmias in the guinea pig isolated perfused heart. ET_A antagonists BQ-123 and A-127722 significantly reduced the arrhythmogenic effects of pulmonary big ET-1, which is converted into ET-1 during coronary passage, in a model of serial lung–heart perfusion in both control and atherosclerotic

rabbits [81]. Similarly, another ET_A antagonist LU 135252 reduced arrhythmic events in ischemic pigs [14].

Nonselective ET-1 receptor antagonists also may inhibit the arrhythmogenic actions of ET-1. Bosentan has been shown to effectively suppress intrapericardial ET-induced ventricular arrhythmias in dogs [82]. Likewise, intracoronary administration of SB 209670 inhibited the arrhythmogenic actions of ET-1 [83]. Another non-selective agent, TAK-044, significantly reduced reperfusion arrhythmias in rat hearts [84]. However, the role of ET_B receptors contributing to arrhythmias remains controversial. In a study by Alexiou et al., ET_A antagonists (BQ-123 and A-127722) partly suppressed the arrhythmias induced by ET-1, whereas ET_B antagonists (IRL-1038 and IRL-1025) had no effect [81]. In contrast, Sharif et al., demonstrated that the ET_B antagonist PD 161721 suppressed the number of ventricular ectopic beats, decreased the incidence of ventricular arrhythmias and mortality in rats after coronary artery occlusion [56].

6. Differential effects of endothelin in atria and ventricles

The arrhythmogenic effects of ET-1 are not confined to the ventricles but are also seen in the atria; however, other receptors may be operative. Burrell et al. demonstrated the occurrence of ET-1-induced arrhythmic contractions in human right atrial tissues obtained from patients undergoing cardiac surgery [85]. Interestingly, arrhythmogenic effects in human atria were prevented by an ET_A/ET_B receptor antagonist, but not BQ-123, precluding ET_A receptors. There may also be differences in electrophysiological properties. In isolated canine myocardium, ET-1 prolonged APD in His bundle and ventricular myocardium but shortened APD in atria, possibly related to a difference in ET-1 receptor expression between the ventricles and the atria [3]. Such a discrepancy is also seen in the differential atrial and ventricular positive inotropic effects of ET-1 in cardiac tissues from many species, including humans [86,87]. Whether this is also operative in vivo and has pathophysiological relevance for arrhythmogenesis remains to be elucidated. On the other hand, it is known that plasma levels of ET-1 are increased as a result of open heart surgery and remain high for at least 1 day postoperatively [88,89]. Therefore, ET-1 may have a possible role in the genesis of atrial tachyarrhythmias, such as transient postcardiac surgical atrial fibrillation.

7. Clinical relevance and conclusions

ET antagonists, which promise to be powerful tools in cardiovascular medicine, may also have a therapeutic potential as antiarrhythmic drugs. This hypothesis stems from multiple studies demonstrating that the potent vasoconstrictor ET-1 exerts arrhythmogenic effects, and several recent animal studies suggesting that ET antagonists may have antiarrhythmic properties. Development of myocardial ischemia is a likely mechanism for the arrhythmogenic effects of ET-1. A direct arrhythmogenic action that is not related to myocardial ischemia has also been proposed, but this topic remains to be elucidated. Whilst the available data is preclinical and cannot be easily extrapolated to human disease states, this is an interesting area of research. Clinical conditions such as ischemic syndromes and congestive heart failure are associated with a high risk of sudden death, believed in most cases secondary to ventricular tachyarrhythmias. Under such pathophysiological conditions, endogenous ET-1 might play an important role in the complex and multifactorial milieu of arrhythmogenesis. In this respect, the role of ET antagonists as potential antiarrhythmic agents, besides their other beneficial effects, may be of great clinical relevance. Controlled clinical studies are needed to investigate the effects of physiologically relevant concentrations of ET-1 on arrhythmogenesis and to determine whether ET antagonists have potential antiarrhythmic effects in humans.

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