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Endothelin B-receptors and sympathetic activation: Impact on ventricular arrhythmogenesis during acute myocardial infarction

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ABSTRACT

Aims: We investigated the role of endothelin-B receptors on sympathetic activation originating from the adrenal gland or from the myocardium and its impact on arrhythmogenesis during acute myocardial infarction.
Main methods: We studied two groups of rats ($n = 120$, 284 ± 2 g), namely wild-type and ETB-deficient. Myocardial infarction was induced by permanent ligation of the left coronary artery and ventricular tachyarrhythmias were evaluated from continuous electrocardiographic recordings. Sympathetic activation, measured by indices of heart rate variability, was evaluated after adrenalectomy or catecholamine depletion induced by reserpine. Acute left ventricular failure was assessed by total animal activity.
Key findings: Adrenalectomy decreased the total duration of tachyarrhythmias in ETB-deficient rats, but their incidence remained higher, compared to wild-type rats. After reserpine, heart rate variability indices and tachyarrhythmias were similar in the two groups during the initial, ischaemic phase. During evolving infarction, tachyarrhythmia duration was longer in ETB-deficient rats, despite lower sympathetic activation. Heart rate was lower in ETB-deficient rats throughout the 24-hour observation period, whereas activity was comparable in the two groups.
Significance: Endothelin-B receptors modulate sympathetic activation during acute myocardial infarction not only in the ventricular myocardium, but also in the adrenal gland. Sympathetic activation markedly increases early-phase ventricular tachyarrhythmias, but other mechanisms involving the endothelin system underlie delayed arrhythmogenesis.
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Introduction

Arrhythmogenesis during acute myocardial infarction (MI) accounts for most cases of sudden cardiac death (Rubart and Zipes, 2005), a major health-related problem worldwide. Two temporally distinct arrhythmia peaks have been described in acute MI-animal models that correspond to the pre- and in-hospital stages in the clinical setting (Di Diego and Antzelevitch, 2011). Polymorphic ventricular tachycardia (VT), degenerating into ventricular fibrillation (VF), during the early post-MI phase carries a particularly ominous prognosis, but VT and VF during the in-hospital phase are also associated with increased morbidity and mortality (Kolettis, 2013). Despite considerable research efforts during the past decades, several aspects of the pathophysiology of the MI-related VT/VF remain incompletely understood.

Acute coronary occlusion causes an immediate rise in plasma endothelin-1 (ET-1) (Miyauchi et al., 1989), aggravating myocardial ischaemia. Moreover, recent evidence indicates an emerging role of ET-1 in arrhythmogenesis during acute MI (Kolettis et al., 2013a). In addition to its direct arrhythmogenic actions mediated by enhanced spontaneous calcium transients (Proven et al., 2006), ET-1 modulates sympathetic activation, a well described participant in the genesis and maintenance of VT/VF (Schomig et al., 1991). This interaction is exerted

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in the ventricular myocardium (Tawa et al., 2012), in which the presence of both (ETA and ETB) ET-receptors has been demonstrated in sympathetic nerve varicosities (Isaka et al., 2007). In the isolated beating heart model (Backs et al., 2005), ET-1 increased the net norepinephrine release by ETA receptor-mediated inhibition of re-uptake; this effect was partly counteracted by attenuated exocytotic norepinephrine release, mediated by ETB receptors (Backs et al., 2005). By means of pharmacological blockade (Isaka et al., 2007; Yamamoto et al., 2005) or with the use of an animal model with genetic deficiency of ETB receptors (Yamamoto et al., 2005), these actions of ET-receptors were demonstrated also during myocardial ischaemia in the same model; increased norepinephrine release was found after ETA receptor activation immediately after ischaemia, whereas ETB receptors exerted protecting effects (Isaka et al., 2007; Yamamoto et al., 2005).

The opposing actions of ET-receptors were recently confirmed in the in vivo rat model, in which genetic deficiency of ETB receptors was associated with enhanced sympathetic activation and arrhythmogenesis during the early post-MI phase (Oikonomidis et al., 2010). However, this pattern differed during the delayed phase, indicating varying effects of ETB receptors along the course of acute MI (Oikonomidis et al., 2010). We hypothesized that the markedly different contributions of ETB receptors during acute ischaemia and evolving MI can be attributed to catecholamine depletion, produced by excessive norepinephrine release during the early post-MI phase.

A pattern of opposing actions of ET-receptors, similar to that described in the myocardium, has been also demonstrated in the isolated, perfused rat adrenal gland (Nagayama et al., 2000). Based on these findings, the adrenal gland constitutes an additional site of interaction between ET-1 and the sympathetic system, but the potential impact of this effect on ventricular arrhythmogenesis during acute MI is unknown. Thus, the second aim of the present work was to further explore the pathophysiologic role of ETB receptors in the adrenal gland, focusing on the genesis of ischaemia-related VT/VF.

Materials and methods

Animal study population and ethics

The study was conducted on 120 male rats, 17–22 weeks of age, weighing 255–340 g. To maintain this animal study population, the animals were replaced, in case of death due to excessive bleeding resulting from surgical manipulations.

The present work adheres to the guiding principles of the Declaration of Helsinki regarding ethical conduct of animal research, held by the World Medical Association. In addition, all experiments conform to European legislation (*European Union directive for the protection of animals used for scientific purposes 609/1986*, revised in *2010/63/EU*). The experimental protocols were approved by the responsible regulatory state authorities. The animals were given humane care and were housed in Plexiglas-chambers in groups of two; ad libitum access to standard rodent pellet-diet and water was provided at all times. The laboratory conditions were kept optimal, in terms of temperature, humidity and light-to-dark cycles.

To examine the pathophysiologic role of ETB-receptors on ventricular arrhythmogenesis during acute MI, two animal strains were included, namely wild-type and a previously well characterized homozygous rat strain, deficient in ETB receptors (Gariepy et al., 1998, 2000). This strain carries a naturally occurring deletion of the ETB-receptor gene that abrogates the expression of functional ETB-receptors; these transgenic rats exhibit a partially rescued phenotype and live into adulthood, providing a valuable tool in the study of the pathophysiologic role of ETB-receptors (Gariepy et al., 1998, 2000). A colony of this strain has been bred in our animal facilities, kindly provided by Professor M. Yanagisawa (Southwestern Medical Center, Dallas, USA and University of Tsukuba, Tsukuba, Japan).

Study protocols

The present work consisted of two protocols:

(i) In the *first* protocol, the effects of ETB-receptors in the adrenal gland were examined by comparing arrhythmogenesis in four animal groups, namely wild-type or ETB-deficient rats, with or without prior adrenalectomy. This comparison aids in the characterization of the contribution of the adrenal gland to arrhythmogenesis and permits the identification of the role of ETB-receptors in the adrenal gland versus that in the ventricular myocardium. As the relative importance of sympathetic activation on arrhythmogenesis decreases markedly past the early MI-stage (Clements-Jewery et al., 2002), we opted to examine the incidence of VT/VF for the first hour post-MI (defined as phase I).

(ii) In the *second* protocol, we investigated the effects of pharmacological catecholamine depletion (from sympathetic nerve terminals and chromaffin cells) on the incidence of VT/VF during acute and evolving MI in wild-type and ETB-deficient rats. This protocol eliminates the effects of sympathetic activation, thereby facilitating the study on the role of ETB-receptors on arrhythmogenesis via alternative mechanisms.

Arrhythmia time-intervals

As previously (Kolettis et al., 2013b), the incidence of VT/VF is reported separately for phase I (corresponding to ischaemia and onset of necrosis), for the 2nd until the 11th hour post-ligation (phase IIA, corresponding to evolving MI) and for the 12th until the 24th hour post-ligation (phase IIB, corresponding to established myocardial necrosis). This distinction is useful for its translational value in the clinical setting, but also from a pathophysiologic point of view, as it may aid in the identification of the varying underlying mechanisms (Di Diego and Antzelevitch, 2011; Kolettis, 2013; Kolettis et al., 2013b).

Adrenalectomy

Bilateral adrenalectomy was performed 3 days prior to MI induction. After tracheal intubation with a 14G-catheter, the rats were mechanically ventilated with a rodent apparatus (model 7025, Ugo Basile, Comerio, Italy) and anaesthesia was maintained with a mixture of oxygen and 2% sevoflurane. The adrenal glands were removed through bilateral dorsal mid-flank incisions, followed by hydrocortisone treatment (5 mg/kg/day subcutaneously), as previously outlined (Rafiq et al., 2011).

ECG-telemetry transmitters

Continuous electrocardiographic (ECG) monitoring was performed with the use of miniature telemetry transmitters (TCA-F40, Dataquest, Data Sciences International, *DSI*, Transoma Medical, Arden Hills, MN, USA); implantation of these devices enables long-term recording in conscious, unrestricted animals (Agelaki et al., 2007; Baltogiannis et al., 2005).

The animals were mechanically ventilated and anaesthetized, as above. As in previous experiments (Kolettis et al., 2008), the transmitters were implanted in the abdominal cavity, with two leads secured under the right axilla and at the left hind-limb area, respectively. During recording, the rats were placed on a receiver (RCA-1020, *DSI*) that continuously captured the signal; ECG was displayed with the use of a software programme (A.R.T. 2.2, *DSI*) and saved for subsequent analysis.

Reserpine administration

Pharmacological catecholamine depletion was induced with reserpine, administered at a dosage of 0.15 mg/kg (as an intraperitoneal

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