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Cardiac disease and arrhythmogenesis: Mechanistic insights from mouse models

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ABSTRACT

The mouse is the second mammalian species, after the human, in which substantial amount of the genomic information has been analyzed. With advances in transgenic technology, mutagenesis is now much easier to carry out in mice. Consequently, an increasing number of transgenic mouse systems have been generated for the study of cardiac arrhythmias in ion channelopathies and cardiomyopathies. Mouse hearts are also amenable to physical manipulation such as coronary artery ligation and transverse aortic constriction to induce heart failure, radiofrequency ablation of the AV node to model complete AV block and even implantation of a miniature pacemaker to induce cardiac dyssynchrony. Last but not least, pharmacological models, despite being simplistic, have enabled us to understand the physiological mechanisms of arrhythmias and evaluate the anti-arrhythmic properties of experimental agents, such as gap junction modulators, that may be exert therapeutic effects in other cardiac diseases. In this article, we examine these in turn, demonstrating that primary inherited arrhythmic syndromes are now recognized to be more complex than abnormality in a particular ion channel, involving alterations in gene expression and structural remodelling. Conversely, in cardiomyopathies and heart failure, mutations in ion channels and proteins have been identified as underlying causes, and electrophysiological remodelling are recognized pathological features. Transgenic techniques causing mutagenesis in mice are extremely powerful in dissecting the relative contributions of different genes play in producing disease phenotypes. Mouse models can serve as useful systems in which to explore how protein defects contribute to arrhythmias and direct future therapy.

1. Introduction

The mouse is the second mammalian species, after the humans [12], in which substantial amount of the genomic information has been analyzed [13]. With advances in transgenic technology [14], mutagenesis is now much easier to carry out in mice [15]. Consequently, an increasing number of transgenic mouse systems have been generated for the study of cardiac arrhythmias [16,17]. These models can be loosely divided into ion channelopathies with minimal structural abnormalities, and those of structural heart disease. The former group includes catecholaminergic polymorphic ventricular tachycardia (CPVT) [18], the long [19] and short QT syndromes (LQTS and SQTS), and Brugada syndrome (BrS) [20]. The latter group includes several types of cardiomyopathies, such as arrhythmogenic right ventricular dysplasia (ARVD) [21], dilated cardiomyopathy (DCM) [22] and hypertrophic cardiomyopathy (HCM) [23]. However, now it is much clearer that structural alterations are found in ion channelopathies; for example, myocardial fibrosis is observed in BrS [24–26], DCM and non-compaction cardiomyopathy features are found in cardiac ryanodine receptor 2 mutation that is classically observed in CPVT [27]. Conversely, cardiomyopathy has been associated with ion channel mutations, as exemplified by sodium channel mutation in DCM [28]. Thus, these categories inevitably contain some overlap. As previously suggested, a better classification of cardiomyopathy includes additional subtypes affecting the cytoskeleton, desmosome, sarcomere and ion channels [29]. Some authors have asserted that this classification is too complex for clinical use, proposing instead a "MOGES" classification based on "morphofunctional phenotype (M), organ(s) involvement (O), genetic inheritance pattern (G), etiological annotation (E) including genetic defect or underlying disease/substrate, and the functional status (S) of the disease" [30]. Atrial fibrillation is a particularly complex disease, involving an interplay between electrical and structural remodelling, autonomic imbalance, alterations in calcium handling and genetic factors [31]. Mouse studies have illustrated the importance of abnormal metabolism in the initiation of paroxysmal atrial fibrillation and its progression to persistent and permanent forms [32], and shed light on the electrophysiological abnormalities predisposing to arrhythmias [33], but will not be discussed further in this review.

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Non-genetic mouse models have also been used for the study of human cardiovascular conditions and associated arrhythmic properties [34]. Physical models include myocardial infarction produced by coronary artery ligation [35], hypertrophy and heart failure by transverse aortic constriction [36], complete AV block model by radiofrequency ablation of the AV node [37] and cardiac dyssynchrony model by implantation of a miniature pacemaker tailored to mouse hearts [38]. In contrast, pharmacological models include the use of cardiac glycosides [39], hypoxia [40], myocardial sensitizers [41] such as chloroform [42,43] and alterations in electrolyte concentrations, for example, potassium [44]. Cardiac toxins such as ethanol [45] and doxorubicin [46] have been used for modelling heart failure [47]. The different types of models are summarized in Fig. 1. In the next section, the advantages and disadvantages of mouse models, and comparisons between human cardiac physiology and mouse cardiac physiology will be discussed. The current understanding of each pathology, focusing on how mouse models have aided understanding, will then be reviewed in turn.

2. Advantages and disadvantages of mouse models

Several reasons justify the use of mice to study of human arrhythmia conditions. Firstly, 99% of mouse genes have a homologue in the human genome [13]. Secondly, both species have a similar set of ion channel genes [48]. Thirdly, the vast majority of these ion channel genes have nearly identical sequence homology in both species [49]. Fourthly, these genes have similar expression patterns, and their protein products show similar structural, electrophysiological [50] and pharmacological properties [48]. Finally, the same mutation in ion channel genes can often produce similar phenotypes in both species. For example, genetically engineered mice with altered potassium channel expression show prolonged ventricular action potential durations (APDs), prolonged electrocardiographic QT intervals and increased arrhythmogenicity, closely recapitulating the findings in the corresponding human conditions [51]. There are also advantages of using mice. The first relates to their vulnerability to arrhythmias. The mouse heart is electrically more stable than the human heart because of its small size, and spontaneous ventricular arrhythmias are therefore less likely to occur [49]. This means a smaller number of mice are lost due to unwanted lethal arrhythmias, potentially saving costs. The second relates to the relative ease of defibrillation. Arrhythmias are easier to reverse in mice than in larger species, making them invaluable for the evaluation of the effectiveness of antiarrhythmic drugs. However, caution must be taken because efficacy could be overestimated.

3. Comparisons between human and mouse cardiac electrophysiology

Mouse hearts are similar to human hearts in many respects, making them invaluable as model systems for the study of human arrhythmic syndromes. Firstly, the SA and AV nodes as well as the His-Purkinje system are structurally similar [52]. Secondly, the same patterns of depolarization and repolarization are observed in both species, with depolarization spreading from endocardium to epicardium and from apex to base, and repolarization from epicardium to endocardium and from base to apex [53]. Thirdly, the transmural conduction velocities (CVs) are nearly identical in mouse and human hearts [53]. Fourthly, apex-base and endocardium–epicardium repolarization gradients are present in both species [54]. Finally, the upstroke of the action potential in both mice and humans is attributed to I_{Na}, making mouse hearts especially suitable for studying changes in CV [55]. Readers who are interested in the electrophysiological mechanisms of arrhythmogenesis are directed to these review articles [56–58].

However, it must also be recognized that mice do show some important differences in their cardiac electrophysiology [51,53,59]. Firstly, the basal heart rate in the mouse is around 600 bpm, which is ten times greater than that observed in the human [60]. Secondly, the morphology of the mouse and human ventricular action potentials is different, with the mouse ventricular action potential having a shorter duration and lacking a plateau phase [61]. This has been attributed to different expression levels of repolarizing potassium channels. Thus, I_{to} is the major repolarization current with I_{Kr} and I_{Ks} having a diminished role in mice [62], whereas I_{Kr} and I_{Ks} are the major repolarization currents in humans [63]. Additional differences between mouse and human electrophysiology lead to difficulties in extrapolating data obtained from mice to humans and interpreting the mouse electrocardiogram [64]. Other species such as guinea pigs [65–71] and rabbits [72,73] may be better models for studying cardiac repolarization, as their ion currents are similar to those found used by human hearts.

The critical mass hypothesis posited that heart size must be sufficiently large to support fibrillation [74]. Because the wavelength of the excitation, given by ERP x CV, must be smaller than the available path length to allow re-entry [75], mouse hearts were originally thought to be too small to sustain re-entrant pathways. However, reconstruction of activation pattern [64] and mapping studies [19,76,77] have both shown that re-entry can take place. Bearing these limitations in mind, mouse models have provided significant advances in our understanding of cardiac electrophysiology. It is made possible by monophasic action potential (MAP) and bipolar electrogram (BEG) techniques to examine local activation and repolarization patterns [78–81]. Fig. 2 shows an experimental setup for recording left ventricular epicardial MAPs from isolated, Langendorff-perfused mouse hearts during right ventricular pacing. The study of congenital ion channelopathies has provided much insights into the general mechanisms by which disturbances in action potential conduction and repolarization generate arrhythmias, whereas that of heart failure and atrial fibrillation have identified pathological processes underlying disease progression with time and age [82]. These conditions will be discussed in turn.

4. Catecholaminergic polymorphic ventricular tachycardia (CPVT)

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited, cardiac ion channelopathy characterized by adrenaline-

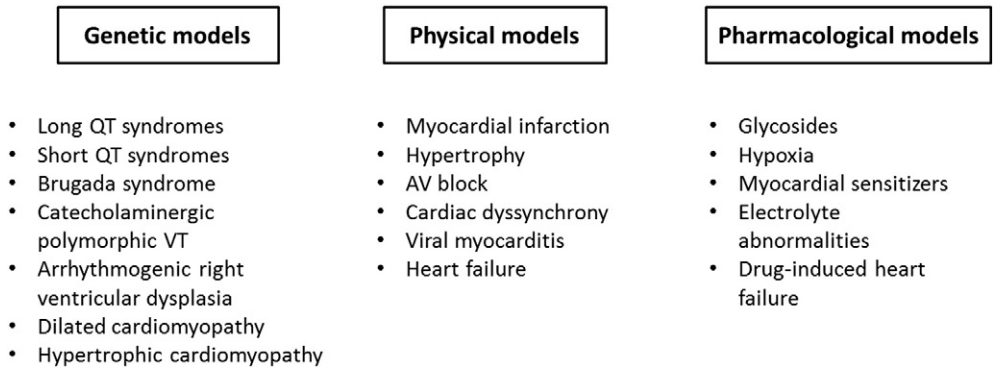

Fig. 1. Genetic, physical and pharmacological models in mouse hearts.