LETTERS TO THE EDITOR

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Not so fast! Sick sinus syndrome is a complex and incompletely understood disease that might prove hard to model in animals

We read with great interest the paper by Herrmann et al.1 describing the effects of inducible HCN4-positive cell deletion in the mouse. This novel study using Cre-lox P adds to their previous work using this system to knock down HCN4 expression in adult mice and is a valuable contribution to unravelling the complexities of sinoatrial node (SAN) function and disease.1 The authors claim that their DTA/KiT mouse represents an accurate analogue of human sick sinus syndrome (SSS). For example, in the DTA/KiT mouse, following HCN4-positive cell deletion, there is a marked cell loss and fibrosis in the SAN. Literature is cited that agrees age-related degenerative fibrosis is the primary pathological mechanism of SSS. However, careful analysis of the published literature casts doubt on fibrosis as the primary or isolated pathology in this disease. Fibrosis of the SAN with age is not a regular finding. For example, Alings et al.2 ruled out fibrosis in the SAN of the aged human and cat and we observed a down-regulation (not up-regulation) of fibrosis genes in the SAN of the aged rat.1 In contrast, there is clear evidence of electrical remodelling in the pathology of SSS. An area of slow action potential upstroke velocity extends into the peripheral SAN with advancing age in the cat and rabbit.3,4,5 This suggests an age-dependent down-regulation of Na+, in fact, this has been demonstrated in the aged rat.3 In the aged rat, there is also an age-dependent down-regulation of RyR2 (important component of the Ca2+ clock mechanism of pacemaking) in the SAN.6,7 In the aged guinea pig, there is an age-dependent down-regulation of Cx43 and Cav1.2 in the SAN.8 In the aged mouse, there is an age-dependent down-regulation of a wide range of ion channels.9 The age-dependent electrical remodelling of the SAN can potentially explain the SAN dysfunction in the elderly, without the need to invoke fibrosis.

Herrmann et al.1 claim that the spectrum of arrhythmias displayed in the DTA/KiT mouse following HCN4-positive cell deletion matches that seen in human SSS. The DTA/KiT mouse, following HCN4-positive cell deletion, showed a phenomenon analogous to the ‘bradycardia–tachycardia syndrome’, a hallmark of SSS in patients. However, the ‘bradycardia–tachycardia syndrome’ in patients has been attributed to alternating periods of atrial fibrillation and SAN dysfunction,10 a feature not identified in the study of Herrmann et al.1. The DTA/KiT mouse, following HCN4-positive cell deletion, displayed ventricular tachycardia (VT). Herrmann et al.1 assert that VT is often seen as a late feature of SSS. A literature search by us revealed no reports of this. Extreme bradycardia in the human can lead to VT as an escape rhythm. This is usually monomorphic VT due to triggered automaticity or re-entry. The electrocardiogram shown in the paper of Herrmann et al.1 shows polymorphic VT of the type normally seen in long-QT states.

As with previous work from this group,11 this mouse model uses a ubiquitous Cre promoter. A recently published HCN4 knockout mouse using the cardiac-specific αMHC Cre promoter resulted in a different phenotype to the HCN4 knockout with the ubiquitous Cre promoter.11,12 Questions remain as to the tissues targeted by the ubiquitous Cre promoter. Furthermore, the technique used by Herrmann et al.1 is expected to knock out all HCN4-expressing cells and not just those of the SAN—this will include the cells of the atrioventricular ring tissues, the retroaortic node, the atrioventricular node, the His bundle, and the Purkinje fibres.

The paper from Herrmann et al.1 raises an intriguing opportunity to study cardiac conduction system disease. However, many differences exist between this model and idiopathic SSS, and so, the results should be interpreted with caution.

References

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