Effects of streptozotocin-induced type I diabetes mellitus on the sinoatrial-node of the rat heart

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Introduction
It has been estimated that 5 million people will suffer from diabetes in the UK by 2025.5 Cardiovascular complications are common in type 1 diabetes mellitus (T1DM). There is increased risk of bradyarrhythmias, atrioventricular block and bundle branch block as a result of dysfunction of the cardiac conduction system (CCS).1 The CCS is responsible for the generation and transmission of electrical activity in the heart (Figures 1 and 2) and consists of the sinoatrial node (SAN, the primary pacemaker), atrioventricular node (AVN), bundle of His (HS), right and left bundle branches (RBB, LBB) and right and left Purkinje fibres (RPFs; UFPs). In the rat streptozotocin (STZ)-induced model of T1DM, in vivo ECG recordings have shown a significant (P<0.05) decrease in heart rate (HR) and prolongation of the QRS complex, evidence of dysfunction of the CCS (Figures 8-10).

Methods and Results

Figure 6: A and B show Masson’s trichrome stained whole tissue sections from one control rat heart and one T1DM heart at the level of the SAN. C and D show low magnification confocal images of adjacent tissue sections immunostained for HCN4 and Cx43 at the level of the SAN. E and F show high magnification confocal images at the level of the SAN - HCN4 signal is in red and HCN4 is in green. G and H show high magnification confocal images at the level of the SAN - HCN4 signal is in red and HCN4 is in green (G and H). Scale bar = 50 μm.

Figure 7: HCN4 expression was significantly reduced in the SAN in T1DM hearts. RyR2 expression was significantly decreased as the SAN in T1DM hearts. Figure 8: ECG recordings from control and T1DM hearts. (n=12).

Figure 10: Beating rate of ex vivo SAN preparations; rates reduced by 56% on application of 1mM caffeine and 90% on application of 1mM caffeine and 2mM Ca²⁺.

Figure 11: This figure shows that no sera able to record funny current (IC) was able to block RyR2 (Ca²⁺) channel activity in isolated SAN cells. The block of IC was tested at three different concentration levels of block (n=12).

Figure 12: Schematic diagram showing the sinoatrial node involved in the propagation potential and pacemaker activity. Figure 13: Schematic shows the sinoatrial node involved in the propagation potential and pacemaker activity. Figure 14: Schematic shows the sinoatrial node involved in the propagation potential and pacemaker activity.

References

Conclusion
1. Downregulation of RyR2 in the SAN could be a compensatory mechanism to regulate heart rate in T1DM.
2. HCN4 decrease in T1DM rats could be a compensatory mechanism to regulate heart rate in T1DM.
3. Complex interplay between membrane currents and Ca²⁺ clock signalling may increase risk of bradyarrhythmias.

Acknowledgement
The British Heart Foundation supported this work.

Data availability statement
All data relevant to the study are included in the article.

Conflicts of interest
The authors declare no competing interests.

Figure 1: Schematic diagram showing the sinoatrial node involved in the propagation potential and pacemaker activity.