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AGEING IS ASSOCIATED WITH CHANGES IN STRUCTURE AND ION CHANNEL EXPRESSION WITHIN THE ATRIOVENTRICULAR CONDUCTION AXIS

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Introduction The inferior nodal extension (INE), compact atrioventricular (AV) node and penetrating/His bundle (PB) form the AV conduction axis and are responsible for delay and propagation of the action potential from the atria to the ventricles. With ageing, dysfunction in these tissues results in prolongation of the PR interval and first, second and third degree AV block. The only treatment is implantation of permanent pacemakers, which are known to be associated with various complications. Previous studies have described age-related structural and functional changes in the AV conduction axis, but detailed examination of morphological changes (such as fibrosis and hypertrophy) as well as changes in ion channel expression with ageing have not been investigated.

Methods We have compared the regions of the AV conduction axis (INE, compact AV node, CN, proximal PB, PPB and distal PB, His bundle) from 3 (n=9) and 24 (n=8) months old male rats (humanely killed in accordance with UK Animals Scientific Procedures Act 1986). From the survival curve, 3 months old rats correspond to 20 years old humans, whereas 24 months old rats correspond to ~70 years old humans. Morphological characteristics of these tissues were studied using serial cryosections and Masson's trichrome (MT) and picrosirius red (PR) histological stains and light and polarised microscopy. The expression of the ion channel HCN4 (responsible for pacemaking) and the gap junction channels Cx43 and Cx40 (responsible for electrical coupling between cardiac cells) was studied using immunofluorescence and confocal microscopy on sister sections to those used for histology. Qualitative signal intensity of these channels was measured using Volocity software. Statistical analysis was performed with SPSS version 20.1.

Results At the structural level, we observed significant changes with ageing. MT staining showed that the cells of INE, CN, PPB and His bundle are more loosely packed and irregularly arranged in older animals. Age-dependent cellular hypertrophy was confirmed by a statistically significant increase in cell size across all regions of the AV junction. With ageing, total collagen content estimation showed a statistically significant increase in thin (but not in thick) collagen fibres in the CN, PPB and His bundle. Immunohistochemistry revealed a decrease in Cx43 expression in the INE (P=0.003), PPB (P=0.005), His bundle (P=0.02), but an increase in Cx40 expression in the INE (P=0.01) and CN (P=0.005) with ageing. There was also trend to downregulation of HCN4 expression especially in the His bundle (P=0.051).

Conclusion Ageing is associated with structural changes of the AV junction tissues, which include fibrosis, hypertrophy and changes in Cx43 and Cx40 and possibly HCN4 expression. Our current findings may explain the prolongation of the PR interval with ageing observed in our previous study.

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