Genetic Approaches for the Treatment of Bradycardias

Since the identification of the hyperpolarisation-activated cyclic nucleotide channel 4 (HNC4), a major constituent of the pacemaker current (I_f) in the sinoatrial node, as a modulator of heart rate,[1] several genetic causes of sinus bradycardia by means of mutations in ion channel encoding genes have been described. They may result in isolated sick sinus sydrome or other arrhythmia and cardiomyopathy syndromes.[2,3]

Gene 'therapy' strategies using gene transfer vectors have, therefore, been attractive as an alternative method for treating bradycardia syndromes, and non-viral methods, including the revolution of CRISPR gene editing technology, are also becoming available.

Genetics may be of service in treating bradycardias in other ways too. Very recently, one heterozygous mutation, *KCNJ3* c.247A>C, p.N83H, was identified as a novel cause of hereditary bradyarrhythmias.[4] *KCNJ3* encodes the inwardly rectifying potassium channel Kir3.1, which combines with Kir3.4 (encoded by *KCNJ5*) to form the acetylcholine-activated potassium channel (I_{KACh}channel) with specific expression in the atrium. Studies on patients with sporadic AF also identified another five rare mutations in *KCNJ3* and *KCNJ5*, suggesting the relevance of both genes to these arrhythmias.[4]

More importantly, in this study, NIP-151, a benzopyran derivative and selective I_{KACh} channel blocker, effectively inhibited the mutant I_{KACh} channel and up-regulated heart rate in a zebrafish model. Thus, pharmacological blockade of I_{KACh} channels appears as a promising, safe therapy for increasing heart rate or preventing AF in patients with sick sinus syndrome and gain-of-function mutations in the I_{KACh} channel.

I believe that a new era is beginning for the treatment of conduction disorders in humans. Perhaps the possibility of treating sick sinus syndrome and AV block without any invasive pacing procedure is not very far away. The cardiology community is eagerly awaiting clinical implementation of this possibility. ■

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