

Metalloprotease nardilysin controls heart rate through the transcriptional regulation of ion channels critical for sinus automaticity.

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Nardilysin (NRDC; N-arginine dibasic convertase) is a metalloprotease of the M16 family. We reported that NRDC is a protease having localization-dependent multiple functions; an enhancer of ectodomain shedding in the extracellular space and a transcriptional coregulator in the nucleus. NRDC-deficient mice (*Nrdc*^{-/-}) showed wide range of phenotypes such as hypomyelination, hypothermia, and bradycardia. In this study, we have explored a role of NRDC in the regulation of heart rate, and obtained the following results. (1) Pharmacological blocking of autonomic nervous system revealed that an intrinsic heart rate of *Nrdc*^{-/-} was significantly reduced compared with that of wild-type mice. (2) In *Nrdc*^{-/-} hearts, mRNA levels of Cav3.1 and HCN1/4, ion channels responsible for sinus automaticity, were significantly reduced. (3) Funny (If) current and T-type Ca current measured in the sinus node cells were markedly reduced in *Nrdc*^{-/-} cells, indicating that the functions of Cav3.1 and HCN1/4 are impaired. (4) Gene knockdown of NRDC in primary rat ventricular myocyte led to the reduction of mRNA level of HCN1/4. (5) Chromatin immunoprecipitation-PCR analysis showed that NRDC binds to the promoter region of Cav3.1 and HCN1/4, suggesting the direct involvement of NRDC in transcriptional regulation of these ion channels. (6) Atrium-specific *Nrdc*^{-/-} (obtained by mating *Nrdc* floxed mouse with Sarcoplipin-Cre mouse) showed mild bradycardia and reduced Cav3.1 mRNA expression. (7) In silico simulation model of human iPS cell-derived sinus node cells recapitulated the bradycardia in NRDC-deficient cells. Together, our results indicated that NRDC in cardiomyocyte controls heart rate through the transcriptional regulation of ion channels critical for sinus automaticity.