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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 have demonstrated that NRDC in the extracellular space enhances ectodomain cleavage of multiple membrane proteins. We also reported that nuclear NRDC regulates transcription of several target genes as a transcriptional coregulator. These results indicated that NRDC is a protease having localization-dependent multiple functions. 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. (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 HCN4 are impaired. (4) Gene knockdown of NRDC in primary rat ventricular myocyte led to the reduction of mRNA level of HCN4. (5) Chromatin immunoprecipitation-PCR analysis showed that NRDC binds to the promoter region of Cav3.1 and HCN4, suggesting the direct involvement of NRDC in transcriptional regulation of these ion channels. (6) Atrium-specific Nrdc–/– (Sarcolipin-Cre) showed mild bradycardia and reduced Cav3.1 mRNA expression. Together, our results indicated that NRDC in cardiomyocyte controls heart rate through the transcriptional regulation of ion channels critical for sinus automaticity.