

## THE ROLE OF THE REVERSE $\text{Na}^+/\text{Ca}^{2+}$ EXCHANGER AND THE $\text{Ca}^{2+}$ -DEPENDENT $\text{K}^+$ -CURRENT IN SINUS-NODE PACEMAKING

Norbert Nagy<sup>1,2</sup>, Noémi Tóth<sup>1</sup>, Axel Loewe<sup>3</sup>, Jozefina Szlovák<sup>1</sup>, Zsófia Kohajda<sup>2</sup>, Gergő Bitay<sup>1</sup>, Szilvia Déri<sup>1</sup>, Jouko Levijoki<sup>4</sup>, Julius Gy. Papp<sup>1,2</sup>, András Varró<sup>1,2</sup>

<sup>1</sup>Department of Pharmacology and Pharmacotherapy, Albert Szent-Györgyi Medical School, University of Szeged, Hungary

<sup>2</sup>ELKH-SZTE Research Group of Cardiovascular Pharmacology, Szeged, Hungary

<sup>3</sup>Institute of Biomedical Engineering, Karlsruhe Institute of Technology (KIT), Karlsruhe, Germany

<sup>4</sup>Orion Pharma, Espoo, Finland

Sinus node (SN) pacemaking is driven by a close interaction of surface membrane ion-channels and intracellular  $\text{Ca}^{2+}$ -handling. The reverse mode of the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger (NCX) and the small-conductance  $\text{Ca}^{2+}$ -activated  $\text{K}^+$ -channel ( $\text{I}_{\text{SK}}$ ) could be important players of this system, however, the exact roles of these components are not fully clarified.

Whole-cell and perforated patch-clamp experiments were performed on rabbit SN cells supplemented with fluorescent  $\text{Ca}^{2+}$ -tracking. NCX was assessed by specific block with 1  $\mu\text{M}$  ORM-10962,  $\text{I}_{\text{SK}}$  was inhibited by apamin. The ECG R-R intervals were obtained by Langendorff-perfusion method.

Active reverse NCX caused larger  $\text{Ca}^{2+}$ -transient amplitude due to larger SR  $\text{Ca}^{2+}$ -content. Spontaneous action potential (AP) frequency was enhanced in the presence of active reverse NCX. When reverse NCX was facilitated by 1  $\mu\text{M}$  strophanthine the  $\text{Ca}^{2+}_{\text{i}}$  and spontaneous rate increased. ORM-10962 applied prior to strophanthine prevented  $\text{Ca}^{2+}_{\text{i}}$  and AP cycle change. SK2 channel expression was verified by immunoblot technique in rabbit SN cells and patch-clamp experiments revealed apamin-sensitive current. However, we found no change in the action potential parameters nor in the ECG R-R interval after application of 100 nM apamin.

Our results indicate that the reverse NCX activity may provide additional  $\text{Ca}^{2+}$ -influx that could increase SR  $\text{Ca}^{2+}$ -content, leading to enhanced pacemaking activity. Therefore, the reverse mode of the NCX may contribute in normal SN pacemaking increasing the robustness of the automaticity. In contrast, our data indicate that  $\text{I}_{\text{SK}}$  has no role in SN pacemaking under normal condition.

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