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Circadian Regulation of Blood Pressure and Heart Rate by Na^+/Ca^{2+} Exchanger

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Summary

In mammals, including humans, blood pressure and heart rate are known to exhibit a circadian rhythm, and it has been suggested that abnormal circadian rhythm is a factor in the onset of hypertension and ischemic heart disease. Recently, we have found that Na^+/Ca^{2+} exchanger-mediated intracellular Ca^{2+} oscillation is primarily involved in the formation of circadian rhythm in the suprachiasmatic nucleus (SCN), which is the central clock. In fact, NCX2-deficient mice ($NCX2^{+/-}$) and NCX2/3 double-deficient mice ($NCX2^{+/-}$;$NCX3^{-/-}$) exhibited disturbed behavioral rhythms due to abnormal circadian rhythms. NCX is a bidirectional transporter that is controlled by membrane potential and transmembrane gradients of Na^+ and Ca^{2+}, and is involved in the maintenance of intracellular Ca^{2+} homeostasis and the formation of Ca^{2+} signals. In this study, we examined the role of NCX in circadian rhythm control of blood pressure and heart rate using various NCX-deficient mice (systemic and organ-specific). In systemic $NCX1^{+/-}$ and $NCX2^{+/-}$ mice, the circadian rhythm of blood pressure was normal, comparable to wild-type control mice. In vascular smooth muscle-specific NCX1-deficient mice, a significant decrease in blood pressure was observed, but the circadian rhythm of blood pressure was normal. On the other hand, in systemic $NCX3^{-/-}$ mice, enhanced blood pressure was significantly suppressed during the active phase compared to wild-type control mice, and the onset of the active phase under the dark condition tended to be slightly earlier. Thus, $NCX3^{-/-}$ mice exhibited abnormal circadian rhythm of blood pressure. This result indicates that NCX3 plays an important role in maintaining normal circadian rhythm of blood pressure, suggesting the importance of NCX3-mediated Ca^{2+} signaling in the circadian clock center (SCN). Further studies on disease models using $NCX3^{-/-}$ mice will provide new insights into the relationship between circadian rhythm abnormalities and the onset of cardiovascular diseases.