
# $NA^+/CA^{2+}$ EXCHANGER IN HUMAN IPSC DERIVED CARDIOMYOCYTES: FUNCTIONAL EVIDENCE AND RELEVANCE FOR BEATING BEHAVIOR

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The $Na^+/Ca^{2+}$-exchanger (NCX) plays an important role in cellular calcium homeostasis. Under physiological conditions NCX removes $Ca^{2+}$ from the cell lumen of excitable cells and is involved in regulatory processes. Under pathological conditions, NCX can reverse direction and contribute to cell damage by $Ca^{2+}$ overloading. These critical functions have fueled the debate over the pharmacological potential of NCX since many years. Inhibition of the reversed mode of NCX is thought to be beneficial in ischemia/reperfusion injury. Moreover, inhibition of NCX has been proposed to exhibit an anti-arrhythmic effect and implications for safety screening are discussed.

Human iPSC derived cardiomyocytes (hiPSC-CMs) are an evolving model system in cardiac research. We investigated NCX function in hiPSC-CMs. By developing a suitable sensor based method (SSM based electrophysiology) we recorded specific NCX current responses of high amplitude. These currents showed similar calcium affinity compared to NCX1 expressed in HEK cells and were sensitive to nickel, KB-R7943 and SEA0400. The beating behavior of hiPSC-CMs was further investigated using an impedance based system. We observed a significant increase in beating rate as a long term effect when inhibiting NCX with SEA0400.

These findings clearly demonstrate the presence of functional NCX in hiPSC-CMs which until now has been poorly investigated. The observed increase in beating rate after inhibition of NCX is to some extent in disagreement with other studies. However, previous studies have employed different methods using non-human systems and usually investigate short term effects of up to one hour. Further investigation is necessary, but at this time we can state that we have found an intriguing new combination of tools which will help to generate new insights into the physiology and pharmacology of NCX.