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COMMENTARY

ORM-10103: a significant advance in sodium-calcium exchanger pharmacology?

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The sodium-calcium exchanger (NCX) is an electrogenic transporter that is widely expressed in different tissues. In the heart, the NCX plays important roles in calcium ion homeostasis, excitation-contraction coupling and the electrophysiological properties of cardiac myocytes. Precise determination of the roles of the NCX has somewhat been hampered by a lack of selective small molecule inhibitors. In this issue of the *BJP*, Jost and colleagues present data on a new NCX inhibitor, ORM-10103, which has submicromolar EC_{50} values against cardiac forward and reverse exchange activity. The compound exhibits improved selectivity over existing small molecule NCX inhibitors and, in particular, appears to be without effect on L-type calcium channels at high concentrations. ORM-10103 could therefore have significant value for studies of the (patho)physiological roles of the NCX in the heart. Further pharmacological studies are required to investigate the actions of ORM-10103 on cardiac cells and tissues and to determine its effects on non-cardiac NCX isoforms.

LINKED ARTICLE
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Abbreviations
CICR, Ca^{2+}-induced Ca^{2+} release; DAD, delayed after-depolarizations; EAD, early after-depolarizations; EC, excitation–contraction; I_{CaL}, LTCC, L-type Ca^{2+} channels; NCX, sodium-calcium exchanger; NCLX, sodium/lithium-calcium exchanger; SR, sarcoplasmic reticulum

Sodium-calcium exchanger (NCX) proteins, encoded by the *SLC8* gene family, are secondary active exchangers expressed in most mammalian tissues; they influence a wide range of physiological processes from insulin secretion, to neuronal function and calcium regulation and excitation–contraction (EC) coupling (Khananshvili, 2013). Different NCX isoforms encoded by *SLC8A1*, *A2* and *A3* are expressed in different tissue types and control cell membrane Ca^{2+} fluxes, while the *SLC8B1*-encoded sodium/lithium-calcium exchanger (NCLX) is located in the membrane of mitochondria where it contributes to the regulation of energy metabolism (Khananshvili, 2013). The function of native NCX has perhaps been most widely studied for the NCX1 isoform expressed in the heart, where with each heartbeat, Na^+ and Ca^{2+} cycling are particularly important, the former for excitation, the latter for contraction. The regulation of these two ions is intimately connected through several mechanisms in cardiac myocytes, but the most direct and efficient link is provided by sarcolemmal NCX, with preferential localization in the t-tubules of ventricular myocytes, along with other proteins involved in EC coupling (Scriven and Moore, 2013).

The major role of the sarcolemmal NCX in cardiac myocytes is, in principle, well established as maintaining Ca^{2+} homeostasis by rebalancing the levels of cytoplasmic Ca^{2+} entering the cell via the L-type Ca^{2+} channels (LTCC) at each heartbeat, hence contributing to diastolic function (Bers, 2002). In addition, the NCX operates an electrogenic exchange with net charge movement in the direction of Na^+ (commonly ascribed to a 3 Na^+ : 1 Ca^{2+} stoichiometry), thereby contributing to action potential morphology (Blaustein and Lederer, 1999) and in cardiac pacemaker cells to generating diastolic depolarization (Bogdanov *et al.*, 2001). Acute and chronic changes in NCX activity have been described in the pathophysiology of cellular arrhythmic

events (early after-depolarizations – EADs and delayed after-depolarizations – DADs), ischaemia-reperfusion injury, hypertrophy and heart failure (Pott *et al.*, 2011).

The rate of Na^+-Ca^{2+} exchange operated by NCX depends on the transmembrane gradients of Na^+ and Ca^{2+} and membrane voltage (Blaustein and Lederer, 1999). Because there are substantial variations in these parameters in different species, cardiac locations and diseases, the precise contribution of NCX activity to cardiac function remains unclear.

The study of the (patho)physiological roles of the NCX has been hindered by the lack of selective NCX inhibitors that can readily be applied in experimental settings. Non-selective inhibitors include the inorganic cations nickel and cadmium, and compounds such as amiloride, bepridil and amiodarone. Selective block has been achieved using peptides engineered to bind to cytoplasmic regulatory sites, such as XIP and FRCRCFa. However, their intracellular sites of action make them unsuitable for studies in intact tissue and certainly inadequate for therapeutic purposes (Doggrell and Hancox, 2003; Khananshvili, 2013). An advance in the development of NCX blockers was provided by three compounds, KB-R7943, SEA0400 and SN-6. All these compounds show a significantly higher degree of selectivity for NCX at low doses, possibly in a mode-dependent manner, although this latter point is controversial. Selectivity is still an issue, however. These drugs inhibit several ion currents, including I_{CaL} the Ca^{2+} current carried by the LTCC, with significant confounding consequences. Changes in Ca^{2+} entry via LTCC, even if very small, can be massively amplified by the Ca^{2+}-induced Ca^{2+} release (CICR) system, with consequences that can overshadow NCX blockade (Doggrell and Hancox, 2003; Khananshvili, 2013).

In this issue of the *British Journal of Pharmacology*, Jost and colleagues describe a novel NCX blocker, ORM-10103, with significantly improved selectivity for NCX (Jost *et al.*, 2013). This compound is mode-independent with similar, submicromolar, EC_{50} values for inward and outward NCX current. When applied to canine ventricular myocytes at a relatively high concentration of 10 μM, ORM-10103 had no effect on I_{CaL}. The compound is also without effect on several other ion transporters, including voltage-gated Na^+ channels, Na^+/K^+ pump and the main K^+ channels, with the exception of the rapid delayed rectifier current, I_{Kr}, which is slightly reduced by the drug at 3 μM. The authors also demonstrated that this compound prevented pharmacologically induced EADs and DADs, implicating the NCX in these events and pointing to possible antiarrhythmic applications of ORM-10103.

This study is important because the availability of a selective NCX inhibitor could help address a number of unresolved questions regarding cardiac NCX function. These include to what extent is the NCX able to contribute to the process of CICR in normal physiology; how much does it contribute to Na^+ regulation and to the membrane potential during the normal functioning of the heart; could selective NCX inhibition be curative in cardiac pathologies? In the case of heart failure, it is plausible that the demonstrated increase in NCX activity in the presence of reduced sarcoplasmic (SR) Ca^{2+} uptake can lead to SR and cytoplasmic Ca^{2+} depletion (Pogwizd *et al.*, 2001), but confounding factors such as an increase in cytoplasmic Na^+ levels and action potential prolongation also point to reduced NCX-mediated Ca^{2+} extrusion. Importantly, would NCX blockade lead to cytoplasmic Ca^{2+} accumulation and diastolic dysfunction? Finally, would an NCX inhibitor with improved selectivity be a better treatment than the combined LTCC and NCX block with SEA0400, already successfully exploited to treat EADs and DADs in experimental models of arrhythmias (Bourgonje *et al.*, 2013)?

While the current discovery of ORM-10103 is exciting, several aspects require careful consideration. The inhibition of I_{Kr} has been proposed to be a positive aspect by Jost *et al.* (2013), as this may prevent the shortening of the action potential that is expected following NCX blockade. In some settings, however, this action could potentially be a confounding factor as this effect can influence arrhythmogenicity by affecting membrane repolarization, also indirectly altering NCX activity. The compound's effects on other ion transporters and receptors need to be investigated and studies on Ca^{2+} regulation remain to be performed. It will be particularly interesting to see the effects of ORM-10103 on CICR and during hypertrophy and heart failure where the relative contribution of different factors to NCX function can be predicted to have discordant results. It will also be valuable to know whether and how ORM affects pacemaker cell function. Taking a wider perspective, it will also be important to determine whether ORM-10103 inhibits other NCX isoforms or the NCLX, and if so, what its relative potency is against the different isoforms. Nevertheless, although there is much further work that can be performed, it is clear that the discovery of ORM-10103 is important as the compound promises to provide a powerful pharmacological tool to manipulate NCX, better to understand its role in physiology and disease.

Conflict of interest

None.

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