The effect of SEA0400 on the calcium handling of mammalian ventricular myocytes

Péter Birinyi

DEPARTMENT OF PHYSIOLOGY

The Na^+/Ca^{2+} exchanger (NCX) plays a central role in Ca^{2+} handling of myocytes, it is the most important cellular mechanism in Ca^{2+} elimination. Among pathological circumstances it plays a role in the development of life threatening arrhythmias. With the selective blocking of NCX we can prevent the development of these arrhythmias. Many NCX blockers have been described in the literature, but all of them have proved to be applicable only to a limited extent for therapeutic application because of the absence of effective selectivity. According to studies the new NCX blocking molecule with a code number SEA0400, that has been recently syntetised, is held to be selective and therapeutically promising.

In the course of our experiments it was our aim to investigate the effect of SEA0400 on the surface membrane ionic currents, on the intracellular Ca^{2+} transient and on the features of the contractile answer in order to define the probable mechanism of the therapeutic effects of SEA0400, and in order to decide to what extent can we judge the compound to be a selective NCX-blocker. For our examinations we chose such preparates (cardiac myocytes isolated from canine and throbing guinea pig heart), which are very similar to human myocytes. We carried out our examinations with electrophysiological (patch-clamp) and optical (fluorimetric) methods. We established the following results:

1. The SEA0400 did not modify the amplitude of Ca^{2+} transient neither did it modify the left ventricular pressure or the cell shortening in myocytes from Langendorff-perfused guinea pig heart and canine left ventricule.
2. The SEA0400 failed to effect the Ca^{2+} release from HSR vesicules, the Ca^{2+} uptake from LSR vesicules, the gating features RyR2 receptors and Ca^{2+} sensibility of the concractile proteins of myocytes.
3. The SEA0400 blocked both the inward and the outward NCX current in a concentration-dependent manner on myocytes from canine left ventricule. The SEA0400 induced a stronger blocking effect on the outward than on the inward NCX current, the increased intracellular Ca^{2+} concentration decreased its effect.
4. The SEA0400 blocked the L-type Ca^{2+} current in a concentration-dependent manner in ten times bigger quantity of concentration than the NCX current.

On the basis of our results we think that applied in submicromolic concentration SEA0400 is such a relatively selective NCX-blocking molecule, which does not lead to the overloading of the cells with Ca^{2+} due to its special features (Ca^{2+} dependent dominantly reverse mode blocking). With higher concentration the increased NCX blocking is well compensated by the also increased blocking of I_{CaL}, which protects the cell from being overloaded by Ca^{2+}. Thus it is possible to block NCX effectively without increasing the Ca^{2+} loading of the cells. Due to the above mentioned features of SEA0400 it can play a major role in the therapy of pathological states of ischaemia/reperfusion.