THE ROLE OF THE Na^+/Ca^{2+} EXCHANGER (NCX) ISOFORMS IN CELLULAR ANOXIA AND CEREBRAL ISCHEMIA: MOLECULAR AND PHARMACOLOGICAL CHARACTERIZATION.

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NCX plays a relevant role in controlling $[Na^+]_i$ and $[Ca^{2+}]_i$ in many pathophysiological states like anoxic conditions. The NCX can shift from a less active (reduced) to a more active (oxidized) state in presence of redox agents. The trivalent iron salts $K_3Fe(CN)_6$ and $FeCl_3$ and SNP that, besides to donate NO, releases Fe^{3+}, increased the NCX activity as a Na^+efflux-Ca^{2+} influx (reverse mode) pathway and reduced C6 glioma cells hypoxic injury. Conversely, Bepridil and CB-DMB, two inhibitors of NCX, counteracted the protective effect of Fe^{3+}. This neuroprotective role played by the NCX working in the reverse mode was also confirmed in conditions of in vivo cerebral ischemia induced by pMCAO. Intracerebroventricular infusion of $FeCl_3$ and SNP, caused almost a 50% reduction of the cerebral infarct volume. By contrast, NCX inhibition by Bepridil and CB-DMB produced an increase of the infarctual volume. Analogously, the intracerebral perfusion of GLUcosylated form of the eXchange Inhibitory Peptide (GLU-XIP), a synthetic 20 aminoacid peptide with a sequence the same as the endogenous XIP located on the intracytoplasmic "f" loop, caused an enlargement of the infarct volume. Collectively, these results suggest that NCX may be an interesting molecular target to develop in the future new neuroprotective agents for stroke.