Epigenetic Regulation of NCXs Expression As A Pharmacological Strategy To Intervene In Stroke

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During stroke the isoform 1 and 3 of the sodium–calcium exchanger (NCX), a plasma membrane protein regulating cellular calcium and sodium homeostasis in the brain, have a neuroprotective role (Annunziato L et al., 2004). Specifically, ncx1 and ncx3 knocking-down increases infarct volume after brain ischemia and partially reverts ischemic preconditioning–induced neuroprotection (Pignataro et al., 2004 and 2011). Stroke-induced NCX1 down-regulation occurs, through the RE1–Silencing Transcription factor (REST)/Specificity protein (Sp) 3/Histone deacetylase (HDAC) 1 and HDAC2 complex whereas brain ischemic preconditioning- ncreases NCX1 expression through the hypoxia-inducible factor 1 (HIF-1)/Sp1/histone acetyl-transferase p300 complex, by epigenetic mechanism. Notably, the HDAC class I inhibitor MS-275 exerts a neuroprotective effect by preventing cell death during oxygen and glucose deprivation (OGD), and this effect is abolished by the small interfering RNA (siRNA) of NCX1 (Formisano L et al., 2013 and 2015). Regarding NCX3 isoform we found that the Downstream Regulatory Element Antagonist Modulator (DREAM)/HDAC4/HDAC5 complex reduced NCX3 gene and protein after stroke, by deacetylating ncx3 promoter sequence. In addition, HDAC class II inhibition by MC1568 treatment prevented OGD-induced neuronal death, by blocking NCX3 reduction. Therefore, NCX1 and NCX3 isoforms might represent new molecular targets by which epigenetic drugs inhibiting HDACs reduce neuronal cell death after stroke.

References:

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