**Epigenetic drugs limiting neurodegeneration: any perspective in rehabilitation?**

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The mechanisms underlying the neuronal resilience to trauma and ischemia, as well as the processes driving neuronal plasticity in rehabilitation, remain mostly undefined to date.

By focusing on the complexity of transcriptional activity in neuronal cell death, it emerged that epigenetic mechanisms modulating the acetylation of histone and transcription factors finely tune the expression of genes in brain ischemia. Ischemia-induced modifications of histone H3 and NF-κB/RelA were corrected by the therapeutic association of the sirtuin 1 activator, resveratrol, and the histone deacetylase inhibitor, MS-275. When administered to mice subjected to focal brain ischemia, the drug combination elicited a potent and synergistic neuroprotection by reducing infarct volume and neurological deficits. The drugs displayed a wide therapeutic window as they were effective when administrated within 7 h from the ischemia onset. The neuroprotection resulted from changes in the acetylation state of both RelA and histones associated to promoters of NF-kB-target genes. Under the treatment, RelA shifted from the pro-apoptotic (Bim and DMT-1) to anti-apoptotic (Bcl-xL) genes (Lanzillotta et al., Neurobiol Dis 2013). Moreover, association of resveratrol and MS-275 increased the acetylation of H3 and H4 histones at the promoter of brain-derived neurotrophic factor (BDNF), a condition that cooperatively increases BDNF expression. BDNF has emerged as a key facilitator of neuroplasticity involved in motor learning and rehabilitation after injury. Thus the efficacy of epigenetic drugs let us envisage new therapeutic frontiers to stabilize BDNF expression during exercise and neuroplasticity in post-injury recovery.