**SYNERGISTIC ASSOCIATION OF VALPROATE AND RESVERATROL REDUCES BRAIN INJURY IN ISCHEMIC STROKE**

1)Lara faggi LF. 2)Giuseppe pignataro GP. 3)Edoardo parrella EP. 4)Annamaria lanzillotta AL. 5)Vanessa porrini VP. 6)Mariana mota MM. 7)Marina benarese MB. 8)Paolo tonin PT. 9)Lucio annunziato LA. 10)Pierfranco spano PS. 11)Marina pizzi MP.

*Università degli studi di Brescia*

Different studies demonstrated that histone deacetylation and modification of NF-kB/RelA acetylation occur during brain ischemia. We previously demonstrated that, sub-threshold doses of resveratrol, a sirtuin 1 activator, and MS-275, a class I HDAC inhibitor, elicited neuroprotection in a mouse model of MCAO. In the present work, we replace MS-275 with valproate, an antiepileptic drug also reported as a class I HDACs inhibitor.

In cortical neurons exposed to 3h of OGD, 24h of treatment with 100 μM valproate resulted neuroprotective per se, while in association with resveratrol it was active at 1μM. In mice subjected to 60 minutes of MCAO the association of resveratrol 680 μg/kg and valproate 200 μg/kg significantly reduced the infarct volume as well as the neurological deficits. Single treatments at the same doses had no effects, while at the higher doses, resveratrol 6,8 mg/kg or valproate 20 mg/kg limited the infarct volume but did not reduce the neurological deficits.

In accordance with the effect observed by combining resveratrol and MS-275, the association of resveratrol and VPA restored the acetylation levels of histone H3 (K9/18) reduced after OGD exposure. Moreover, the application of resveratrol and VPA reversed the OGD-mediated increase in the RelA(K310) acetylation. Finally, ChIP assays in cortical neurons exposed to OGD demonstrated that the addition of resveratrol (3 μM) and valproate (1 μM), totally impaired the RelA binding at the Bim promoter as well as the promoter–specific H3 (K9/18) acetylation.

We can conclude that valproate and resveratrol may represent a promising ready-to-use strategy for the therapy of post-ischemic brain damage.