THE CONTRIBUTION OF MICROGLIA TO THE ENHANCED SYNAPTIC ACTIVITY THAT PRECEDES AB-INDUCED NEURONAL DEATH

1)Spampinato SF. 2)Merlo S. 3)Beneventano M. 4)Sortino MA.

Catania University

Treatment of organotypic hippocampal cultures (OHC) with sub-lethal concentrations of Aβ 1-42 for a prolonged time leads to massive neuronal death, however preceded by an increase of synaptic proteins and activity, revealed by enhanced expression of synaptophysin (SYP) and increased vesicle unloading after labelling with the fluorescent membrane dye FM 1-43. Such effect, interpreted as an attempted compensatory response, is accompanied by a parallel increase of brain-derived neurotrophic factor (BDNF) expression whenever OHC are exposed to Aβ. The aim of this project was thus to dissect the events and mechanisms triggered by Aβ that lead to BDNF and SYP increase, to unmask potential effectors linking BDNF increase to SYP upregulation and to identify selective roles for glial and neuronal cells in this context.

BDNF expression was tested in neuronal SH-SY5Y cell line and pure astrocytes or pure microglial (pMG) cell cultures. Neuronal cells were exposed to Aβ 1-42 (0.5 µM) in the presence of conditioned medium from glial cultures challenged with Aβ 1-42 (CMA). Effects on neuronal viability, synaptic protein expression and synaptic activity were then tested. Treatment with 0.5 µM Aβ 1-42 increased microglial BDNF expression and release, but did not significantly affect BDNF expression directly on neurons or astrocytes, as by Western blot, ELISA and image cytofluorimetric analysis. When neurons were challenged with Aβ 1-42 in the presence of BDNF-enriched CMA from Aβ-treated pMG, SYP showed a significant increase. This effect was evidenced both at the mRNA and protein level, as by real-time quantitative PCR and Western blot. However, TrkB inhibitor GNF 5837 only partially prevented CMA+ Aβ 1-42 action on neuronal SYP levels, suggesting the contribution of other factors to the observed effect. Finally, MTT results show that increase of SYP expression is linked to neuroprotection at 24 h. These results support the idea that microglia take part to the response to Aβ challenge by favoring a compensatory increased neuronal activity that attempts to contrast synaptic derangement and neuronal death.

In summary, we here show that Aβ 1-42 selectively activates microglial cells to release factors providing neuronal protection. Modulation of microglial function may thus represent a strategy of intervention against Aβ insult.