ß-AMYLOID EFFECTS IN DIFFERENTIATION AND DEATH OF NEURAL PROGENITOR CELL-DERIVED NEURONS

Calafiore M[1], Giuffrida M.L.[1], Sortino M.A.[2] and Copani A[1].

[1]Department of Pharmaceutical Sciences, [2]Department of Experimental and Clinical Pharmacology, University of Catania, Catania.

Suspended neurospheres, obtained from the subventricular zone (SVZ) of adult mice, consist mainly of neural progenitor cells (NPCs) immunoreactive for nestin. These neurospheres also contain 18% astrocyte-like cells (nestin$^-$/GFAP$^+$), and 4% ependymal cells (CD4$^+$), whereas neuroblasts (PSA-NCAM$^+$) are virtually absent. We have previously shown that a 24-hour exposure to ß-amyloid (Aß) does not affect cell proliferation or apoptosis in the whole cell population, but increases the number of nestin$^+$ cells from about 50% to about 65%. The increase in nestin$^+$ cells in Aß-treated cultures is entirely accounted for by a population co-expressing nestin and DLX-2, an early marker of differentiation into a neuronal lineage. In addition, Aß dramatically increases the percentage of cells co-expressing DLX-2 and PSA/NCAM (1), which are the *in vitro* counterpart of migrating neuroblasts.
In order to test whether differentiated neuronal cells become sensitive to Aß toxicity, we have exposed plated neurospheres to 25 µM Aß(25-35) for 4 or 7 days. Before plating, some suspended neurospheres were treated with Aß for 24 hours. When added and mantained for 4 days to plated neurospheres, Aß reduced the basal apoptosis of MAP-2$^+$ cells both in naive neurospheres and in neurospheres pretreated with the peptide before plating. Seven days after plating, the number of apoptotic MAP-2$^+$ cells increased regardless of Aß pretreatment. Interestingly, in neurospheres pretreated with Aß, then plated and exposed to Aß for 7 days, the number of apoptotic MAP-2$^+$ cells did not differ from controls. Thus, mature MAP-2$^+$ cells were sensitive to Aß toxicity; however, about 15% of the cell population became resistent to Aß toxicity (following 7 days of treatment) if neurospheres were pretreated with the peptide before plating. Taking into consideration that 4 days of treatment with Aß reduced the basal levels of apoptosis of about the same extent (15% both in naive and Aß-pretreated neurospheres), these data indicate that Aß sustains the survival of a subpopulation of neuronal precursors the identity of which is currently unknown.

1. Calafiore M. et al. Neurobiol Aging. 2006 Apr; 27(4): 606-13.