

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

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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 β-amyloid (Aβ) 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 Aβ-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, Aβ 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 Aβ toxicity, we have exposed plated neurospheres to 25 μM Aβ(25-35) for 4 or 7 days. Before plating, some suspended neurospheres were treated with Aβ for 24 hours. When added and maintained for 4 days to plated neurospheres, Aβ 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 Aβ pretreatment. Interestingly, in neurospheres pretreated with Aβ, then plated and exposed to Aβ for 7 days, the number of apoptotic MAP-2⁺ cells did not differ from controls. Thus, mature MAP-2⁺ cells were sensitive to Aβ toxicity; however, about 15% of the cell population became resistant to Aβ toxicity (following 7 days of treatment) if neurospheres were pretreated with the peptide before plating. Taking into consideration that 4 days of treatment with Aβ reduced the basal levels of apoptosis of about the same extent (15% both in naive and Aβ-pretreated neurospheres), these data indicate that Aβ 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.