Cellular Polyamines Promote Amyloid-Beta (A beta) Peptide Fibrillation and Modulate the Aggregation Pathways

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The cellular polyamines spermine, spermidine, and their metabolic precursor putrescine, have long been associated with cell-growth, tumor-related gene regulations, and Alzheimer's disease. Here, we show by in vitro spectroscopy and AFM imaging, that these molecules promote aggregation of amyloid-beta (A beta) peptides into fibrils and modulate the aggregation pathways. NMR measurements showed that the three polyamines share a similar binding mode to monomeric A beta(1-40) peptide. Kinetic ThT studies showed that already very low polyamine concentrations promote amyloid formation: addition of 10 mu M spermine (normal intracellular concentration is similar to 1 mM) significantly decreased the lag and transition times of the aggregation process. Spermidine and putrescine additions yielded similar but weaker effects. CD measurements demonstrated that the three polyamines induce different aggregation pathways, involving different forms of induced secondary structure. This is supported by AFM images showing that the three polyamines induce A beta(1-40) aggregates with different morphologies. The results reinforce the notion that designing suitable ligands which modulate the aggregation of A beta peptides toward minimally toxic pathways may be a possible therapeutic strategy for Alzheimer's disease.
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