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Effect of proteasomal inhibition by MG-132 on inclusion body formation in astrocytes

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The small heat shock proteins (sHSPs), HSP25/27 and alpha B-crystallin, are more prominent in glia than in neurons, act as molecular chaperones and specifically interact with cytoskeletal elements. They represent prominent constituents in inclusion bodies originating in astrocytes and oligodendrocytes, and have been described to be involved in Alexander's disease, a human neurodegenerative disorder with astrocytic inclusions called Rosenthal fibres (RF). These protein aggregates also contain GFAP (glial fibrillary acidic protein) and ubiquitin, indicating that inclusion body formation might be causally related to an impairment of the ubiquitin proteasome pathway (UPS).

In the present study, we have examined if defects in the UPS system contribute to the protein aggregation process in astrocytes. Cultured astrocytes, prepared from the brains of newborn rats, were treated with the proteasomal inhibitor MG-132 (5 μM). Under control conditions, astrocytes constitutively express high levels of HSP25, but only very low amounts of alpha B-crystallin. Treatment with MG-132 for 24 h caused the upregulation of HSP25 and alpha B-crystallin, which both were increasingly found in the detergent insoluble fraction. Indirect immunofluorescence analysis displayed small aggregates of HSP25 throughout the cytoplasm and in the perinuclear region. These aggregates also contained alpha B-crystallin and ubiquitin. Furthermore, the disassembly of the microfilament system was observable, while GFAP intermediate filaments and microtubules remained largely intact, and only disassembled at later times of treatment (48 h). The effects of MG-132 were reversible and did not cause apoptotic cell death, as observed in oligodendrocytes. After 24 h in the absence of MG-132, the cytoskeleton was reorganized and the protein aggregates were almost completely removed, and HSP25 was diffusely present and alpha B-crystallin remained in small aggregates throughout the cytoplasm.

Hence, proteasomal inhibition leads to HSP induction and the formation of inclusion bodies, as observed in neurodegenerative diseases. In astrocytes these aggregates are not toxic, and their formation might be a rescue mechanism to protect cells from unwanted interactions with amyloid proteins.