

A NOVEL REGULATORY MECHANISM OF GLYCOGEN METABOLISM IS INVOLVED IN NEURODEGENERATION

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Glycogen synthesis is normally absent in neurons. However, inclusion bodies resembling abnormal glycogen accumulate in several neurological diseases, particularly in progressive myoclonus epilepsy or Lafora disease. Mouse neurons have the enzymatic machinery for synthesizing glycogen, but it is suppressed by retention of muscle glycogen synthase (MGS) in the phosphorylated, inactive state. This suppression is further ensured by a complex of laforin and malin, which are the two proteins whose mutations cause Lafora disease. The laforin-malin complex causes proteasome-dependent degradation both of the adaptor protein targeting to glycogen, PTG, which brings protein phosphatase 1 to MGS for activation, and of MGS itself. Enforced expression of PTG leads to glycogen deposition in neurons and causes apoptosis. Therefore, the malin-laforin complex ensures a blockade of neuronal glycogen synthesis even under intense glycogenic conditions. These results explain the formation of polyglucosan inclusions in Lafora disease by demonstrating a crucial role for laforin and malin in glycogen synthesis.