Trapping the monomer of a non-amyloidogenic variant of transthyretin under mild conditions: its possible use against Familial Amyloidotic Polyneuropathy

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Transthyretin (TTR), a 55-kDa homotetramer rich in beta sheet, is responsible for the transport of thyroxine and retinol through blood and cerebrospinal fluid. Over 100 TTR point mutations were associated with a hereditary form of amyloidosis, named Familial Amyloidotic Polyneuropathy (FAP), which is characterized by the deposit of amyloid aggregates in peripheric nerves. These aggregates are formed after tetramer dissociation and partial unfolding of the monomers. The mutation T119M was identified in a family bearing the highly amyloidogenic mutation V30M and alleviates the symptoms of this aggressive mutation. Thus, the incorporation of a T119M monomeric subunit into a V30M tetramer could be a strategy to stabilize the heterotetramer inhibiting its aggregation. In the present study, we used high hydrostatic pressure (HHP) as a tool to produce monomers of T119M to be incorporated into V30M forming heterotetramers. Since T119M is a highly stable tetramer, the experiments were performed at pH 3.0 and 1ºC. However, at this pH, T119M monomers aggregate. This aggregation is blocked by the addition of glucose and manitol. Other pH values are being tested in order to find a condition where we could produce soluble monomers of T119M to be incorporated into V30M. Our results suggest that osmolytes could be useful to stabilize the monomers of T119M for therapeutical purposes.