SMALL MOLECULES ENHANCE TRANSTHYRETIN STABILITY AND DECREASE AMYLOIDOGENICITY: A NEW STRATEGY TO PREVENT SYSTEMIC AMYLOIDOSIS

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Transthyretin (TTR) is a tetrameric plasmatic protein involved in amyloidogenic diseases such as familial amyloidotic polyneuropathy and senile systemic amyloidosis. The precise mechanism that leads this protein to aggregate presupposes its dissociation into a misfolded monomer. Previous studies have demonstrated that some small molecules bind TTR in its thyroxin binding channel enhancing tetramer stability and preventing fibril formation. In this work, we chose four compounds, namely Sulindac, Ketoconazole, Chlorpromazine and Propranolol, which share similarities with thyroxin and evaluated their effects on tetramer stability and on amyloidogenicity. High hydrostatic pressure (HHP) and acidic pH were used as perturbing agents in combination with spectroscopic techniques to evaluate tetramer dissociation and aggregation. Our results show that these compounds were able to stabilize the wild-type TTR against HHP and inhibit fibril formation, either induced by a cycle of compression-decompression or by acidic pH. Also, the crystallographic structure of TTR bound to Sulindac is being refined by our group. Our next step is to characterize the morphology of the aggregates formed in the presence of these small compounds by atomic force microscopy (AFM). These data give new clues about TTR stability and amyloidogenicity being helpful to formulate new therapeutic strategies against this disease.