Experimental and computational elucidation of the inhibition of myoglobin aggregation by polyethylene glycol

Francisco Pereira[*], Andreia Barbosa[*], Tarsila Castro[**] and João Carlos Marcos[*]

**Center of Chemistry, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal*

***CEB- Centre of Biological Engineering, University of Minho, Campus de Gualtar, 4710-057, Braga, Portugal*

Several pathologies, namely neurodegenerative disorders like Alzheimer, Parkinson and Huntington's diseases are triggered by protein unfolding or misfolding, and its consequent aggregation[1]. Although each disease has specific and different proteins involved, it is believed that the process is similar in all of them. At the molecular level it appears that the unfolding or misfolding of specific proteins leads to the exposure of hydrophobic patches that interact with each other originating the formation of pathological aggregate[2]. Some compounds are known to reduce or eliminate protein aggregation. For instance, polyethylene glycol (PEG) has been described to have contradictory effects on protein stabilization [3,4]. In this work, myoglobin was used as a model protein to elucidate the impact of PEG on protein aggregation. Experimentally, it was found that PEG reduces the thermal stability of myoglobin, but its aggregation is reduced with intermediate molecular weight polymers. Computer simulations using molecular dynamics further elucidate these results at the molecular level. It was shown that intermediate molecular weight polymers aggregate and decrease the interactions between denatured myoglobin chains preventing their aggregation. Although the utilization of PEG itself as a drug poses significant problems, the disclosure of this shielding mechanism may pave the way to the design of more efficient drugs against the devastating disease referred above.

References

1. Koopman, M.B. (2022) How do protein aggregates escape quality control in neurodegeneration? *Trends in Neurosciences* 45, 257
2. Scheres, S.H.W. *et al.* (2023) Molecular pathology of neurodegenerative diseases by cryo-EM of amyloids. *Nature* 621, 701–710
3. Parray, Z.A. *et al.* (2017) Characterization of intermediate state of myoglobin in the presence of PEG 10 under physiological conditions. *International Journal of Biological Macromolecules* 99, 241–248
4. Yamamoto, E. *et al.* (2017) Protein refolding is improved by adding nonionic polyethylene glycol monooleyl ethers with various polyethylene glycol lengths. *Biotechnology Journal* 12, 1600689