DISSECTION OF PRION PROTEIN AND HEPARIN INTERACTION SITES

Vieira, TCRG[1]; Gomes, MPB[1]; Foguel, D[1]; Cordeiro, Y[2]; Silva, JL[1].

[1]IBqM, [2]Faculdade de Farmácia, UFRJ, RJ, Brasil.

Transmissible spongiform encephalopathies are a group of fatal diseases, which affect mammals, caused by an abnormal isoform of the prion protein (PrP). Conversion of cellular PrP (PrP^C) into the pathological conformer, PrP^{Sc}, involves contact between both isoforms and probably requires a cellular factor, such as a glycosaminoglycan. Though direct interaction between PrP and heparin has been recorded, little is known about the structural features implicit in this interaction. In the present work, we used light-scattering and circular dichroism (CD) measurements to provide information on the binding sites of heparin in the full-length recombinant PrP (rPrP 23-231). A PrP construct lacking a portion of the N-terminal domain (rPrP ?51-90) was also utilized. We found that the Far-UV CD ellipticity values of rPrP 23-231 decrease in the presence of heparin, followed by an increase in light scattering. However, heparin caused no changes on the rPrP ?51-90 structure. These results indicate that heparin binding site in PrP is restricted from amino acid 51 to 90. We also investigated heparin sulfation groups important for interaction using modified heparins. While standard heparin interacted with rPrP 23-231, inducing partial unfolding leading to oligomerization, modified heparins containing only 6-O-sulfated or 2-O-sufated groups made no changes in the protein secondary structure. On this basis it may be inferred that these two sulfate groups play important role in prion-heparin interaction.

Support: CNPq, PRONEX, FAPERJ