Poster P.10.81

A NEW EXPLOITATION OF A PORPHYRIN WITH ANTI-PRION PROPERTIES: CHARACTERIZATION OF THE MECHANISM OF ACTION AND PRECLINICAL STUDIES IN MOUSE MODELS OF GENETIC PRION DISEASE

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Genetic prion diseases are invariably fatal neurodegenerative disorders caused by mutations in the gene encoding the cellular prion protein (PrPC), a cell surface glycoprotein expressed at the highest levels by neurons in the CNS. Mutant PrPC molecules tend to misfold and aggregate, leading to neuronal dysfunction and death; they can also acquire an infectious conformation (PrPSc or prion) which propagates by inducing misfolding of native PrPC. Promising therapeutic strategies include blocking PrPC to PrPSc conversion or depleting the substrate for PrPSc formation by reducing endogenous (mutant and wild-type) PrPC level. We identified a metal-porphyrin (VA01) with a remarkable anti-prion activity. The aims of this project were: 1) to characterize the mechanism of action of VA01; 2) to study its pharmacokinetic properties; and 3) to test its therapeutic efficacy in transgenic mouse models of genetic prion disease.
We applied NMR spectroscopy and other biophysical techniques to clarify at the molecular level the mechanism of action of VA01. We found that VA01 binds to recombinant human PrP (HuPrP) with micromolar affinity, and the binding is influenced by the coordinated metal. Thermal melt circular dichroism spectroscopic studies and analytical ultracentrifugation sedimentation velocity experiments indicated changes in HuPrP stability, size and shape upon VA01 binding. These results suggest that VA01 alters PrP structure disfavoring conversion to PrPSc. Consistent with this, VA01 inhibited PrPSc formation in vitro, as assayed by PMCA (protein misfolding cyclic amplification), and reduced PrPSc levels in prion-infected cells and organotypic cerebellar cultures. Pharmacokinetics studies in rodents demonstrated that VA01 crosses the blood brain barrier (BBB) and is active in vivo when administered intraperitoneally; however, the amount of VA01 that reached the brain and its biological activity in the CNS were variable. Therefore, before testing the therapeutic efficacy of VA01 in genetic prion disease models, we needed to improve its brain penetration. Towards this aim, we loaded VA01 in functionalized nanoparticles which show a remarkable ability to cross the BBB and deliver drugs to the CNS.

Una nuova applicazione di una porfirina ad attività antiprionica: caratterizzazione del meccanismo d'azione e studi preclinici in modelli murini di malattie da prioni di origine genetica

Malattie da prioni genetiche

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