Interactions between prion inhibitors and prion protein

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POSTER

In prion disease, a fatal neurodegenerative disorder, the cellular form of the prion protein (PrP^{C}) is converted to the disease isoform (PrP^{Sc}). Although currently no effective therapies or treatments exist, most likely due to the incomplete understanding of prion disease pathogenesis, many studies target enhancing PrP clearance or redistribution/sequestration, suppressing PrP expression, or decreasing PrP conversion. Some antiprion compounds that have been rigorously tested include 2-aminothiazoles and quinacrine. 2-aminothiazoles work by affecting prion conversion or by reducing clearance, while quinacrine has its mechanism of action by reducing the protease resistance of PrP aggregates or by inhibiting the conversion of PrP^{C} to PrP^{Sc}. By combining the effective structures of these two antiprion compounds, novel 2-aminothiazole derivatives were synthesized and have been found theoretically to have potential anti-prion properties. In this study, we aim to verify the theoretical binding dissociation and EC50 values of these compounds and determine whether they are still prion inhibitors in more biological systems. Since both 2-aminothiazoles and quinacrine affect prion conversion, perhaps these novel compounds exert their inhibitory effect by sequestering PrP^{C} through direct binding or by causing an internalization of PrP^{C} in cells so less seed is available for conversion. We used cell toxicity assays to determine compound toxicity and surface plasmon resonance (SPR) to detect binding affinities. Confocal microscopy was used to detect PrP^{C} localization in an N2a neuroblastoma cell line after a 24hr treatment with 100 µM of each compound, while $CuSO_4$ and glycine was used as a positive control for internalization.