Calcium, beta-2-microglobulin and the disease called DRA

DRA (or dialysis related amyloidosis) is a disease in which a serum protein called beta-2-microglobulin (beta2m) precipitates in the form of amyloid fibrils within the bone joints of people suffering from kidney disease (as an unexplainable consequence of their undergoing hemodialysis).

Nobody understands how, or why, beta2m is agreeable to depositing into amyloid fibrils as a consequence of dialysis, since it is an extremely soluble and stable protein *in vitro* which does not aggregate under any sorts of physiological conditions. Certain non-physiological conditions (e.g., very acidic pH), however, have previously been discovered to cause precipitation of beta2m into amyloid fibrils *in vitro*.

We have discovered that at serum concentrations of calcium and beta2m, at physiological pH, the binding of calcium to beta2m causes the latter's precipitation into micro-aggregates. Increasing beta2m concentrations under such conditions leads to large scale precipitation of beta2m into amorphous aggregates that transform into amyloid aggregates over a timescale of weeks. Addition of calcium chelators, such as EDTA, causes facile reversal of amorphous aggregates into micro-aggregates or even soluble, monomeric beta2m. However, amyloid aggregates remain unaffected. Putative sites of calcium binding were identified.

We have thus explained how beta2m forms aggregates, and shown that DRA results from the increase in the concentration of amorphous, calcium-bound, beta2m micro-aggregates [which probably exist as natural a mechanism for the mopping up and recycling/destruction of beta2m in the kidney] through hemodialysis.

We have proposed that use of calcium chelators during hemodialysis could prevent DRA.

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