S22-2 A search for antiamyloidogenic compounds based on a nucleation-dependent polymerization model

◯Hironobu NAIKI[1], Kazuhiro HASEGAWA[1], Kenjiro ONO[2], Masahito YAMADA[2]

[1]Univ. of Fukui, Fac. of Med. Sci., [2]Kanazawa Univ. Grad. Sch. of Med. Sci.

We have proposed that a nucleation-dependent polymerization model could explain the general mechanisms of amyloid fibril formation *in vitro*. Based on this model, we systematically demonstrated that several classes of organic compounds (e.g., wine-related polyphenols, non-steroidal anti-inflammatory drugs) not only inhibit the formation of Aβ amyloid fibrils from Aβ and their extension, but also destabilize Aβ amyloid fibrils dose-dependently *in vitro*. We found significant positive correlations of the effective concentrations (EC_{50}) of these compounds ranging from 10 nM to 10 μM, for the formation and destabilization of Aβ amyloid fibrils. We next investigated the anti-amyloidogenic effects of five flavonoids on Aβ amyloid fibrils *in vitro*. Oxidized flavonoids generally inhibited fibril formation significantly more potently than fresh compounds. By surface plasmon resonance (SPR) analysis, distinct association and dissociation reactions of myricetin (Myr) to Aβ amyloid fibrils were observed, in contrast to the very weak binding to the Aβ monomer. A significant decrease in the rate of fibril extension was observed when > 0.5 μM of Myr was injected into the SPR experimental system. These findings suggest that flavonoids, especially Myr exert an anti-amyloidogenic effect *in vitro* by preferentially and reversibly binding to the amyloid fibril structure of fibrils, rather than to Aβ monomers. This working model should prove useful not only for the rational development of preventives and therapeutics for Alzheimer's disease and other human amyloidosis, but also for understanding the basic mode of action of amyloid imaging compounds.