S22-3 Analysis of Aβ metabolic mechanism and identification of a novel therapeutic target for Alzheimer disease

◯Nobuhisa IWATA[1]
[1]Riken

Aggregation and accumulation of amyloid-β peptide (Aβ) in the brain are triggering events leading to the pathological cascade of Alzheimer's disease (AD). Aβ accumulates in AD brains and forms amyloid plaques, which consist mostly of amino-terminally truncated and/or modified Aβs, among which Aβ3pyroglutamate (Aβ3pE) is a major product. Thus, the accumulated species of Aβ are different from those secreted from neurons. Aβ3pE-42 is more easily self-aggregated (250-fold), and is more resistant to proteolytic degradation (4-fold) than Aβ1-42. Therefore, Aβ3pE appears to act as a seed for the formation of oligomers and amyloid plaques. Aβ is physiologically degraded via the neprilysin (NEP)-mediated pathway. However, if NEP activity is low, a compensatory metabolic pathway is up-regulated, in which exopeptidases, such as aminopeptidase or dipeptidyl peptidase, and glutaminyl cyclase (GC) may be involved, generating Aβ3pE. GC is up-regulated by Aβ aggregate-induced inflammatory responses, such as gliosis, and reduced activity of NEP promotes gliosis and consequently further up-regulates GC. Therefore, up-regulation of NEP may have the potential not only to increase Aβ degradation, but also to prevent inflammatory responses and Aβ3pE formation by down-regulating GC. In addition, inhibition of Aβ3pE formation appears to be a novel target for therapy and prevention of AD. Development of a GC inhibitor is in progress.