Recent studies have demonstrated that certain presenilin (Ps) mutations can alter the site of APP cleavage and subsequently increase the Aβ42/Aβ40 ratio. These mutations additionally reduce the catalytic efficiency of γ-secretase, favouring the production of peptides of longer lengths, such as Aβ42. Because of their key role in APP cleavage, γ-secretase and its catalytic core, presenilin, have become attractive therapeutic targets for Alzheimer’s disease.

**TAU TANGLES**

Growing evidence suggests that APP and Ps mutations are associated not only with amyloid plaques, but also with neurofibrillary tangles (NFTs). NFTs are aggregates of hyperphosphorylated tau proteins that accumulate in brain regions critical to cognitive function. Responsible for stabilizing microtubules, tau supports the neuronal cytoskeleton and facilitates axonal transport. However, following aberrant modifications, tau triggers the synaptic loss and neuronal death characteristic of Alzheimer’s. According to recent research, the Aβ peptides comprising amyloid plaques may also contribute to the formation of NFTs. In particular, Aβ activates caspases involved in programmed cell death, or apoptosis. Caspase activation induces cleavage of tau at its carboxy-terminus, and the resulting tau fragments assemble more rapidly into filaments. Further conformational changes initiate and accelerate tau phosphorylation and aggregation. Tangled and twisted, the filaments impede axonal transport and impair neuronal function, ultimately leading to the potentiation of caspase-mediated apoptosis. Given the significant role of NFTs in neurodegeneration, studies continue to investigate the therapeutic potential of inhibiting abnormal hyperphosphorylation and disassembling filament aggregates.

**REFERENCES**