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Investigating Pathological Mechanisms of Depression as Risk Factors for Alzheimer's Disease

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While therapeutic intervention of Alzheimer's disease (AD) is important, we should pay more attention to prevent elderly suffering from this memory-robbing disease. It has been predicted that an increase of AD pathological factors may start 30 years before clinical symptoms of cognitive impairment. Therefore, it is important to prevent dementia and AD. Epidemiological studies have revealed that depression is a risk factor leading to the development of AD. The aim of our study is to elucidate the biological mechanisms of how depression leads to cognitive impairment and even to AD.

We have used corticosterone as a model agent for depression and oligomeric β-amyloid (Aβ) peptide as a toxic agent for AD. Immunoreactivity for α-tubulin, tau and phospho-tau (pS396, pS404) was examined in primary cultures of hippocampal neurons prepared from embryonic day 18 rats. Phosphorylation of tau protein was examined by both Western-blot and immunofluorescent staining. Morphological changes of cytoskeleton were examined using immunocytochemical analysis or live cell imaging technique with confocal microscopy by transfecting a mCherry-actin/GFP-tubulin into neurons. Both corticosterone and Aβ peptide induce aggregation and subsequent loss of synaptic proteins, aggregation of tubulin and phosphorylation of tau protein. Altered post-translational modification and aggregation of microtubules were found in neurons after treatment with exposure to Aβ peptide or corticosterone. Aggregation of actin forming actin rods was also observed. All these events were reversed by taxol – a microtubule-stabilizing agent. Therefore, depression may prime neurons to be susceptible to Aβ toxicity. This explains why depression can be a risk factor for developing cognitive impairment in AD.

Our research has helped explain why some factors reported by epidemiological studies can be risk factors for AD. As AD-like pathology starts to develop 30 years before any cognitive impairment, advancement of our knowledge of the mechanisms of risk factors can help the scientific community develop ways to prevent progression to AD.

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