16.4.1.2 Alzheimer's Disease

The number of individuals with Alzheimer's disease (AD) is dramatically increasing with the aging of the population. Analyses of genetic background and animal models suggest a pivotal role of amyloid β peptide (Aβ) and neurofibrillary tangles in AD, although the biological basis of AD is still poorly understood. One key hallmark of the AD brain is the inflammatory processes that exert neurotoxicity during aging.[92,93] Excessively activated microglia and astrocytes in the brain accelerate amyloid plaque formation. Microglial activation along with increased inflammatory cytokines and chemokines may deteriorate neuronal loss and accelerate progression of AD. This extensive innate immune gene activation accompanies brain aging, increasing vulnerability to cognitive decline and neurodegeneration.[93]

There are several recent investigations supporting the anti-inflammatory role of PPARs in AD and brain aging. Among the three PPAR isotypes, PPARγ showed prominent effects on the delay of AD onset. The initial studies exploring the roles of PPARγ in AD were based on people with long-term intake of non-steroidal anti-inflammatory drugs (NSAIDs) and PPARγ ligands.[94,95] Long-term NSAID treatment reduces AD risk, and it was suggested that PPARγ stimulation may be involved in this beneficial effect.[96] Various *in vivo* and *in vitro* investigations further demonstrated the anti-inflammatory roles of PPARγ activation.[97] In addition, PPARγ agonists have been demonstrated to directly suppress the Aβ-mediated activation of microglia and prevent neuronal cell death.[98] Further, animal and clinical studies using pioglitazone and rosiglitazone demonstrated the role of PPARγ activation in the prevention of AD.[97,99] Although the beneficial effects of PPARγ agonists on AD are clear and evident, the underlying molecular mechanisms must be elucidated in future studies. Interestingly, recent studies revealed the beneficial role of PPARβ/δ on AD. Activation of PPARβ/δ agonists reduced the amyloid burden and exerted neuroprotective effects in a mouse model of AD.[100,101]

16.4.1.3 Inflammatory Bowel Diseases

Inflammatory bowel diseases (IBD) are generally thought to be diseases of young individuals. However, IBD among the elderly are becoming common with growing incidence and prevalence rates.[102] Compared with younger IBD patients, dysregulation of the immune system and chronic inflammation play more important roles in older-onset IBD.[103] In this respect, the age-associated increase in inflammation should be considered as an important factor for older-onset IBD. PPARs are broadly associated with onset and progression of IBD.

PPARγ exerts its most powerful effects on suppression of IBD. Natural and synthetic ligands of PPARγ reduce colitis in experimental animal models.[104,105] Furthermore, cell-specific deletion of PPARγ in epithelial cells, macrophages, and T cells has demonstrated the role of PPARγ in a colitis model.[106–108] In addition, PPARγ also maintains antibacterial effects of