CELLULAR AND MOLECULAR MECHANISMS UNDERLYING NEURONAL DEGENERATION IN ALZHEIMER’S DISEASE

The two major histopathological abnormalities in the brains of patients with Alzheimer’s disease (AD) are extensive extracellular deposits of amyloid β-peptide (Aβ) and degenerating neurons that contain abnormal hyperphosphorylated filaments composed mainly of the microtubule-associated protein tau (1). Aβ is a 40–42 amino acid peptide that is generated by proteolytic processing of a much larger, membrane-associated amyloid precursor protein (APP). A cleavage of APP in the middle of the Aβ sequence by an enzyme activity called α-secretase results in release of a secreted form of APP called sAPPα. Alternatively, APP can be cleaved at the N and C termini of the Aβ sequence by β-secretase and γ-secretase, respectively. A shift in processing of APP in favor of increased production of neurotoxic forms of Aβ, and decreased production of neuroprotective sAPPα, appears to play a seminal role in the initiation of the neurodegenerative process in AD (2). Indeed, mutations in the APP gene (located on chromosome 21), which are causally linked to a small percentage of cases of early-onset inherited AD, result in increased production of Aβ, particularly the highly neurotoxic long form of Aβ (Aβ1–42). Moreover, mutations in two other proteins called presenilin-1 (PS1; chromosome 14) and presenilin-2 (PS2; chromosome 1) that cause dominantly inherited early-onset forms of AD result in aberrant APP processing (3,4). PS1 and PS2 mutations enhance γ-secretase cleavage of APP and may thereby increase production of Aβ1–42 (5). PS1 mutations may also perturb calcium homeostasis in the endoplasmic reticulum (ER), which results in increased neuronal vulnerability to (age-related) increases in oxidative and energetic stress, and thereby promote a form of programmed cell death called apoptosis (4) (Fig. 1).
Studies of postmortem brain tissues from AD patients, and of experimental cell culture and animal models of AD, suggest that oxidative stress and perturbed regulation of intracellular calcium levels play central roles in the neurodegenerative process. Increased protein, lipid and DNA oxidation occur in association with neurofibrillary tangles and neuritic plaques, and are also increased in the cerebrospinal fluid of AD patients (see for review, ref. 6). Aβ can induce membrane lipid peroxidation in neurons, which impairs the function of ion-motive ATPases, and glucose and glutamate transporters, resulting in membrane depolarization and elevation of intracellular calcium levels; these alterations render neurons vulnerable to excitotoxicity and apoptosis (2). By impairing glucose transport, Aβ may contribute to the decreased glucose availability to brain cells and mitochondrial dysfunction documented in studies of AD patients (6,7). In