Mild Cognitive Impairment (MCI) or early Alzheimer’s Disease (AD) is characterized by memory, learning and behavioral deficits indicative of synaptic dysfunction. Soluble, multimeric Aβ42 found in most afflicted individuals is directly toxic to synapses and post-synaptic dendritic spines. Aβ42 signaling activates calcineurin, a calcium dependent phosphatase. How Aβ42/calcineurin trigger synaptic and dendritic spine loss is unknown. We show that Aβ42 signaling in spines rapidly suppresses the cis-trans isomerase Pin1. Pin1 binds to Ser-Pro or Thr-Pro dipeptides and alters target protein conformation and function. Pin1 KO or inhibition in vitro or in vivo caused equivalent decreases in mature spine counts as Aβ42. Therefore, we propose that Pin1 blockade, induced by Aβ42/calcineurin signaling causes spine losses in early AD.