A pathological hallmark of Alzheimer's disease (AD) is an accumulation of insoluble plaque containing the amyloid-β (Aβ) peptide of 40-42 amino acid residues. Soluble oligomeric species of the Aβ peptide are believed to play a role in the pathophysiology of AD. Recently, we reported that cellular Prion Protein (PrP\textsuperscript{c}) is a high-affinity receptor for Aβ oligomers and mediates the deleterious action of Aβ oligomers. However, the signal transduction pathways downstream of Aβ/PrP\textsuperscript{c} have not been investigated yet. Herein we demonstrate that Aβ oligomer binding to PrP\textsuperscript{c} induces Fyn activation and subsequent NR2B phosphorylation. This pathway induces the short-term increases in surface NR2B receptors level and excitotoxicity, followed by dendritic spine loss. We also show that altered network activity and epileptiform discharges observed in APP transgenic mice are PrP\textsuperscript{c}-dependent. Our findings point to a downstream pathway of Aβ -PrP\textsuperscript{c} complexes that may contribute to AD pathogenesis.