Oligomeric Aβ intermediates increase intacellular Ca^{2+} levels, possibly through cell membrane destabilization (Demuro et al., 2005). Increased intracellular Ca^{2+} promoted by oligomeric Aβ induces the activity of the Ca^{2+}/calmodulin (CaM)-dependent phosphatase calcineurin. Active calcineurin dephosphorylates/***inactivates*** CREB, thus leading to reversible impaired synaptic plasticity and decreased memory function; through prolonged exposure to oligomeric amyloids neurons become dyshomeostatic and eventually a CaN-dependent apoptotic pathway involving dephosphorylation/***activation*** of the pro-apoptotic BAD is allowed to progress and contributes neurodegenerative-dependent cognitive deficits.

SUPPLEMENTARY FIGURE LEGENDS

Figure S1. Confirming previously published evidence (Demuro et al., 2005), our preparation of Aβ oligomers, but not monomers or fibrils, increases intracellular Ca^{2+} levels in SY5Y cells. Graph showing a 35-minute time course of Ca^{2+} dependent fluorescence recorded and averaged from 19 fluo-3 loaded SY5Y human neuroblastoma cells in response to consecutive application of Aβ42 monomers, fibrils, and oligomers (2μM for 10 min each). Cells were challenged with ionomycin (2μM) at the conclusion of the experiment. Error bars = ± 1 S.E. Images on top depict the response of 3 individual cells at the time points indicated by the corresponding number on graph. Warmer colors correspond to a higher level of fluorescence.

Figure S2. Depolarization of SY5Y cells by KCl induces CaN activity and decreases pCREB and pBAD levels. SY5Y cells were treated with 100 mM KCl for the indicated times and collected for measurement of CaN activity (A, 15 min time point only) and pCREB/CREB and pBAD/BAD levels by Western blot (B, top). Intensity of specific bands on western blot were analyzed and the result expressed as ratio between phosphorylated protein and the corresponding total protein in the same sample (B, bottom).

Figure S3. pCREB and pBAD levels are reduced in the CNS of AD patients. Western blot analysis of total protein extracts from the pre-frontal cortex of adult, aged and AD subjects. Membrane was re-probed for total CREB, total BAD and NeuN to control for protein loading. When blots were analyzed densitometrically (not shown), there was an evident (albeit only marginally statistically significant) reduction of pCREB and pBAD in both the aged and AD group (as compared to adult) when band density was normalized to total CREB and total BAD. On the other hand, there was a significant reduction of pCREB and pBAD in the AD group when band density was normalized to NeuN. Whether this represents a selective, more pronounced reduction of pCREB and pBAD in neurons in AD brains as compared to age-matched subjects remains to be established.