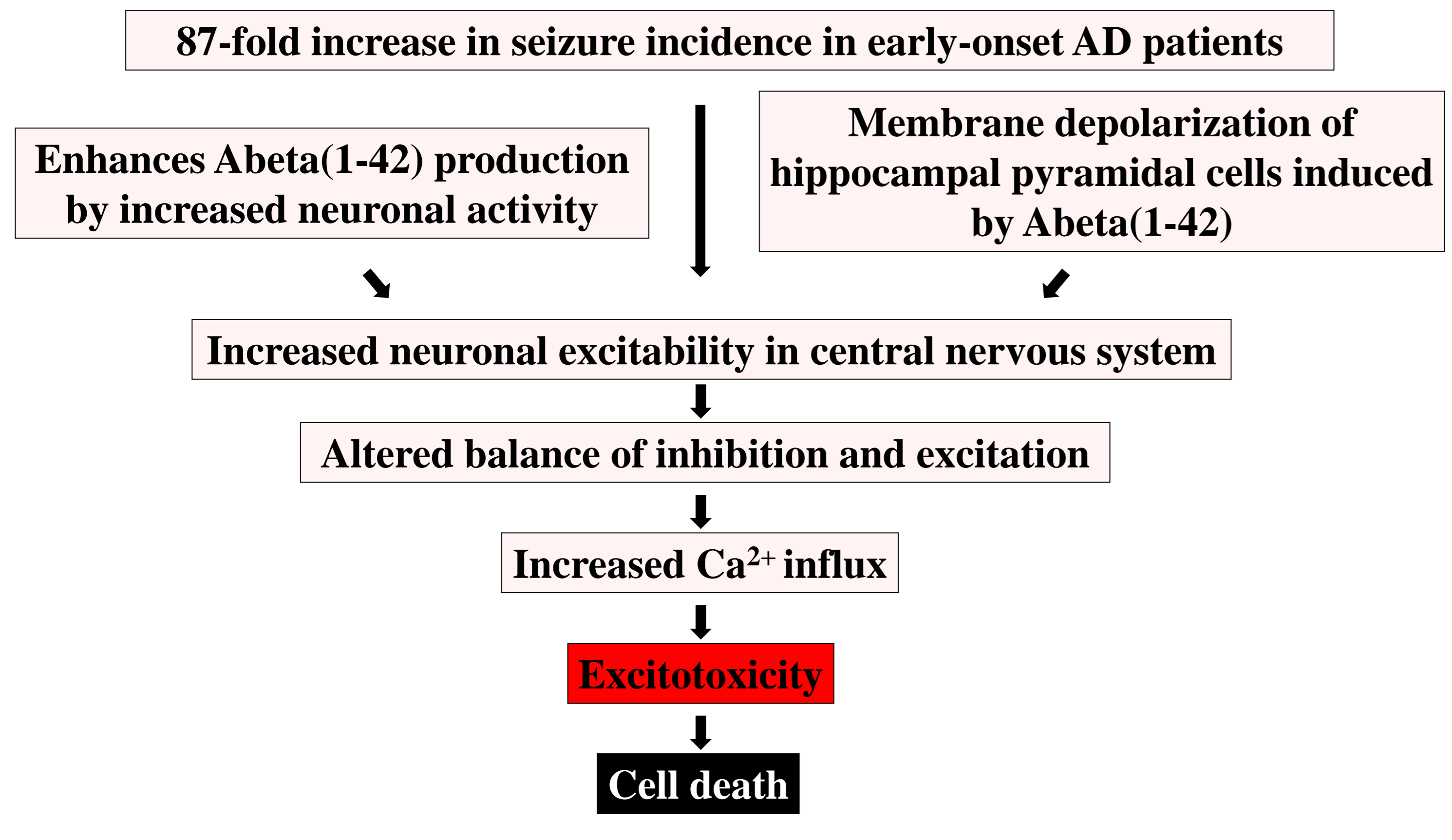


ABETA(1-42) INDUCES IMPAIRMENT OF LTP AND SPIKING RATE IN THE CA1: ROLE OF GLUTAMATE REUPTAKE INHIBITION

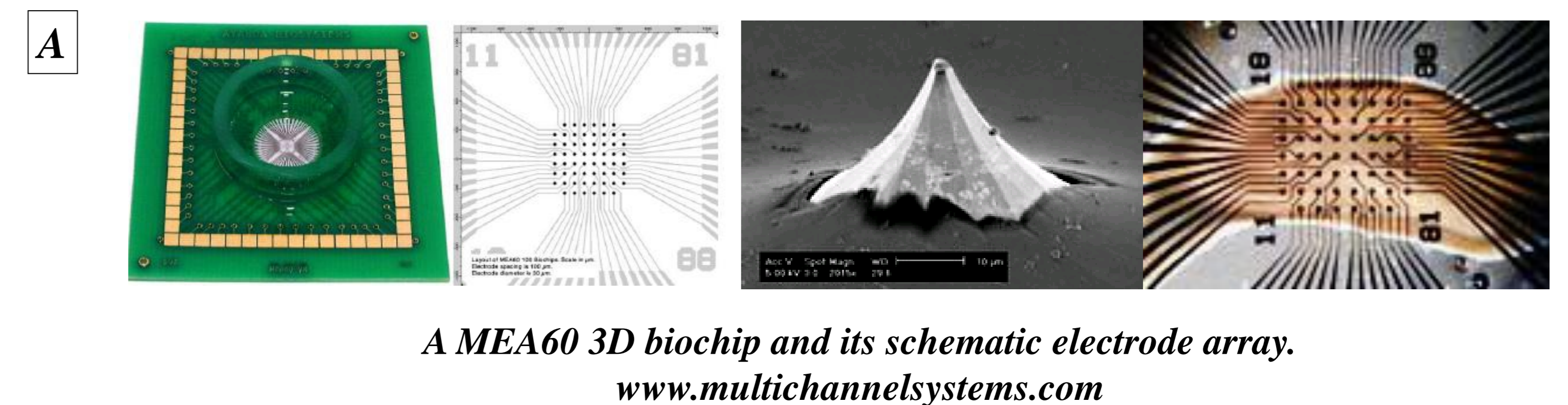
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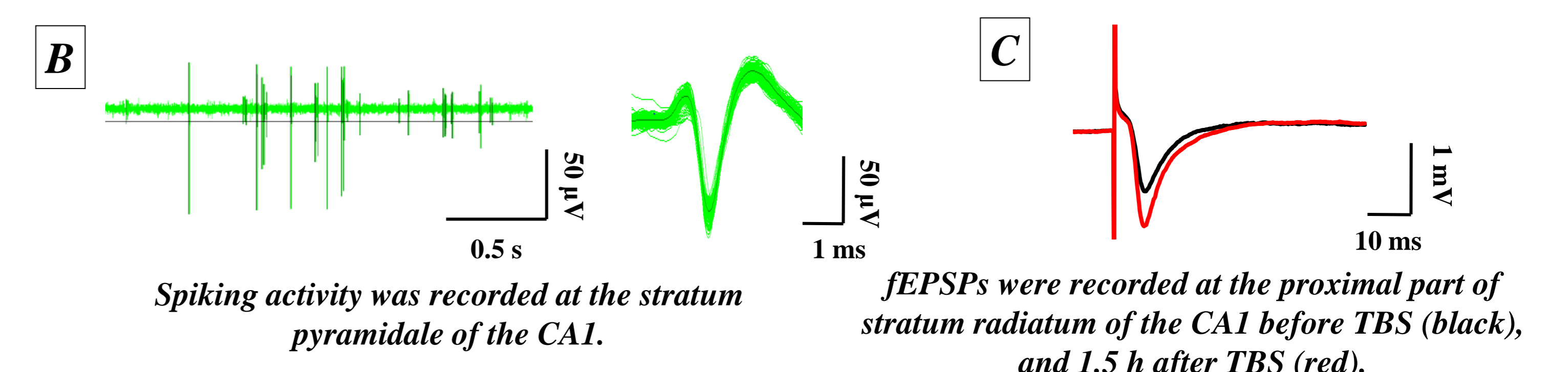
Early AD is associated with increased probability of seizures. Abeta(1-42) itself was shown to induce hyperexcitability by a still unknown mechanism. Increased excitability induced by Abeta(1-42) may result in a vicious cycle leading to massive neuronal loss:



Our goal was to investigate Abeta(1-42) induced impairment of long-term potentiation (LTP) and spiking rate on acute hippocampal slices by Multi-electrode array (MEA) (A): how does Abeta(1-42) induce neuronal hyperexcitation?

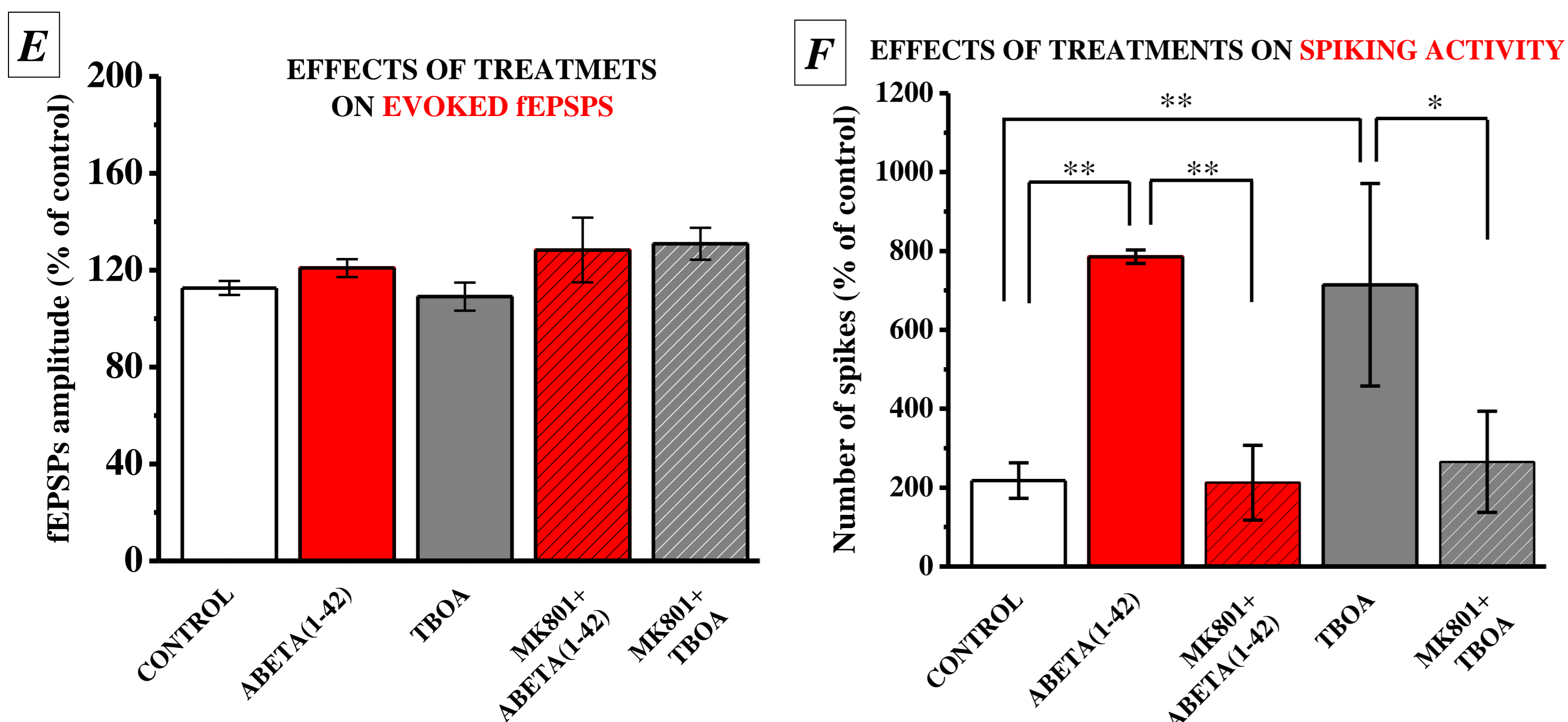


Here, we applied Abeta(1-42) and the following compounds onto murine hippocampal slices (n=5-10): a blocker of glutamate-uptake (TBOA), an antagonist of NMDA receptor (MK801) and an antagonist of AMPA receptor (CNQX). Spiking activity (B) and field excitatory postsynaptic potentials (fEPSPs) (C) were recorded from the CA1. LTP was induced by theta-burst stimulation (TBS), and neuronal discharges were recorded before TBS and 1.5 h after TBS. P * < 0.05; ** < 0.01; *** < 0.001.



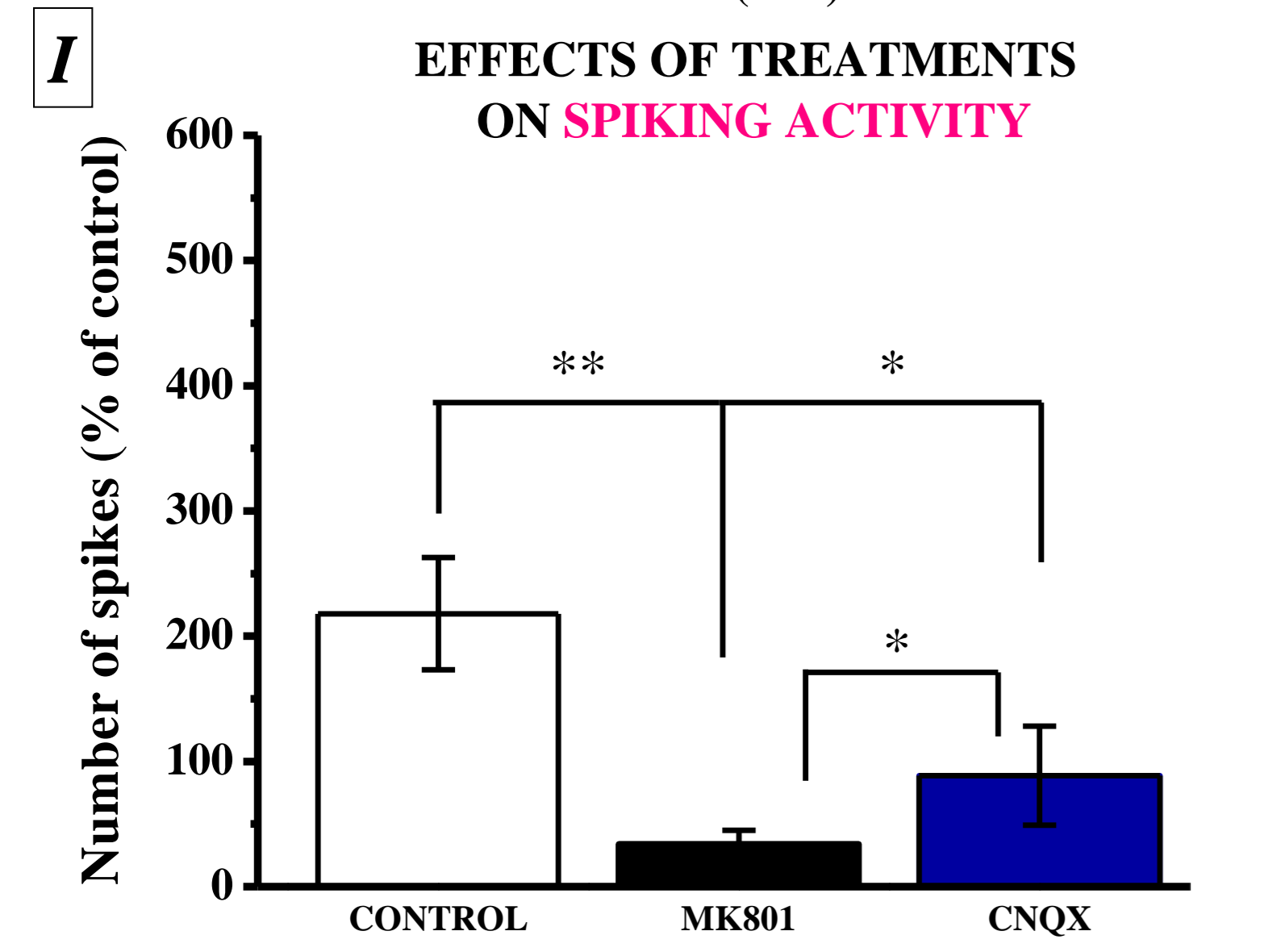
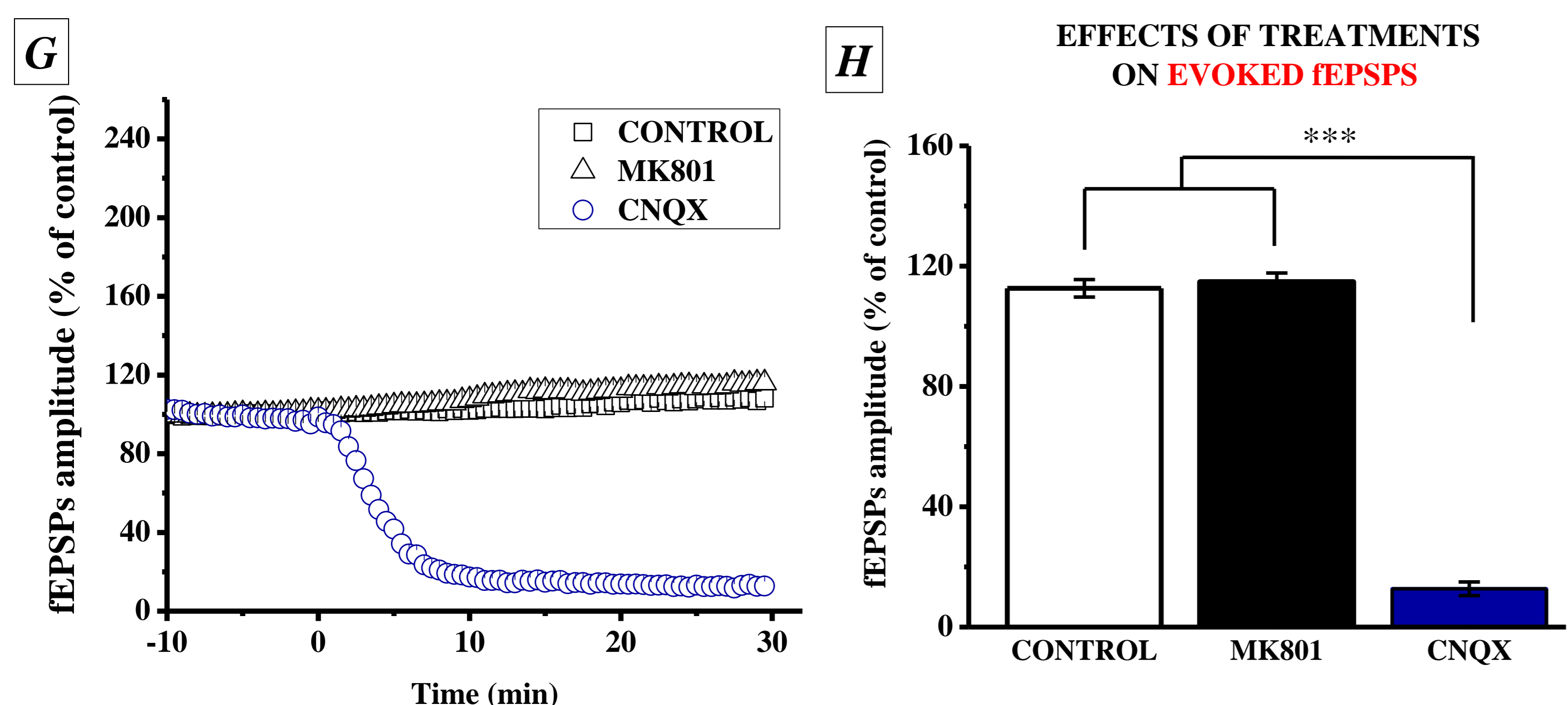
Abeta(1-42) was synthesized at the Department of Medical Chemistry, University of Szeged, Hungary. The aggregation state of the Abeta(1-42) used was verified by transmission electron microscopy (TEM) (D) and dynamic light scattering studies. On the basis of these methods, we used oligomer Abeta(1-42) for our investigation.

BOTH ABETA(1-42) AND TBOA INDUCED HYPEREXCITATION IS NMDA RECEPTOR DEPENDENT



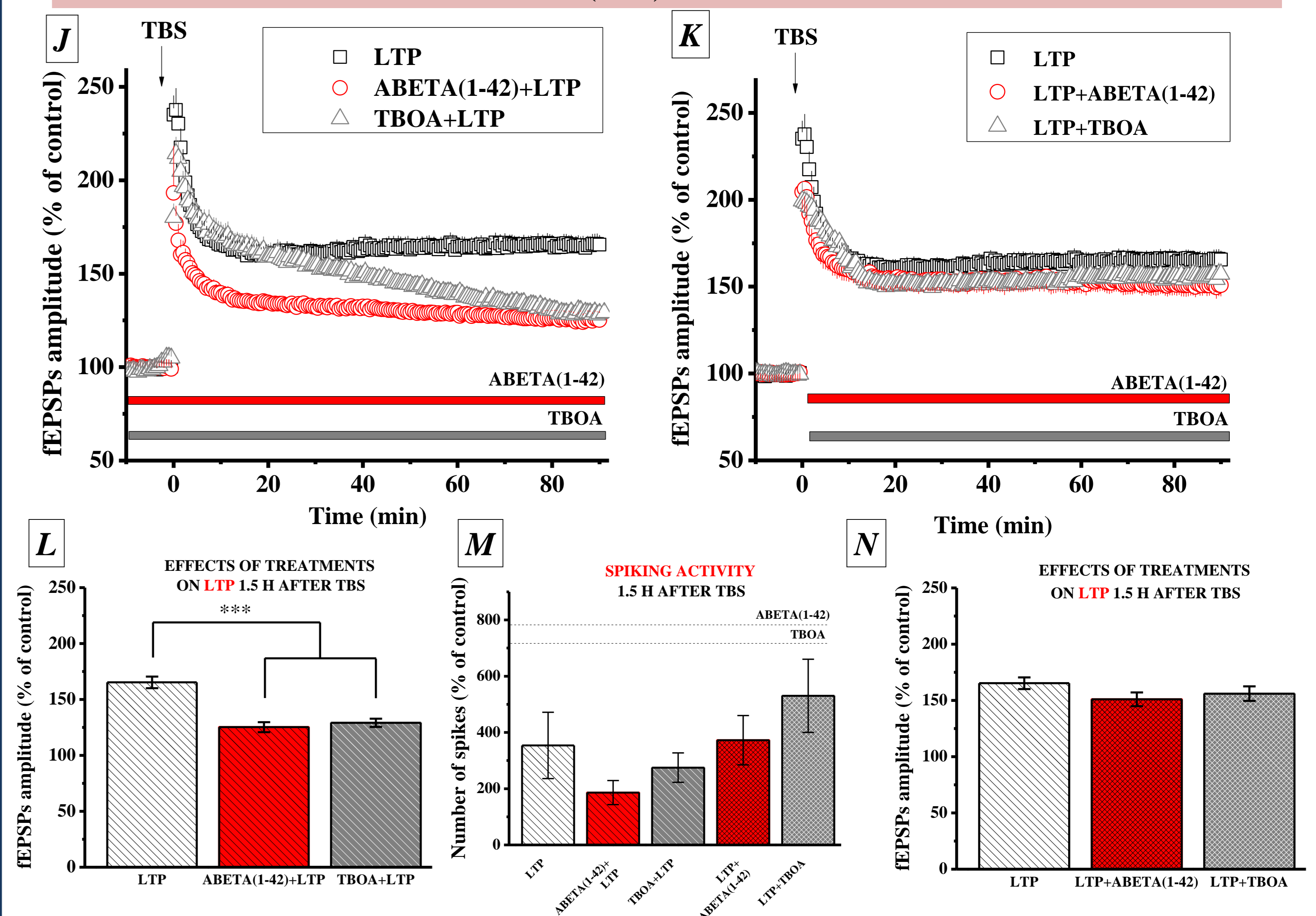
We have found that both Abeta(1-42) and TBOA induced a massive enhancement of spiking activity without altering the evoked fEPSPs. This effect was NMDA receptor dependent, since the blocking of NMDA receptors with MK801 prevented hyperexcitation (E, F).

THE EVOKED fEPSPs ARE SYNAPTIC AMPA RECEPTOR DEPENDENT AND THE SPIKING ACTIVITY REQUIRES EXTRASYNAPTIC NMDA RECEPTOR ACTIVATION

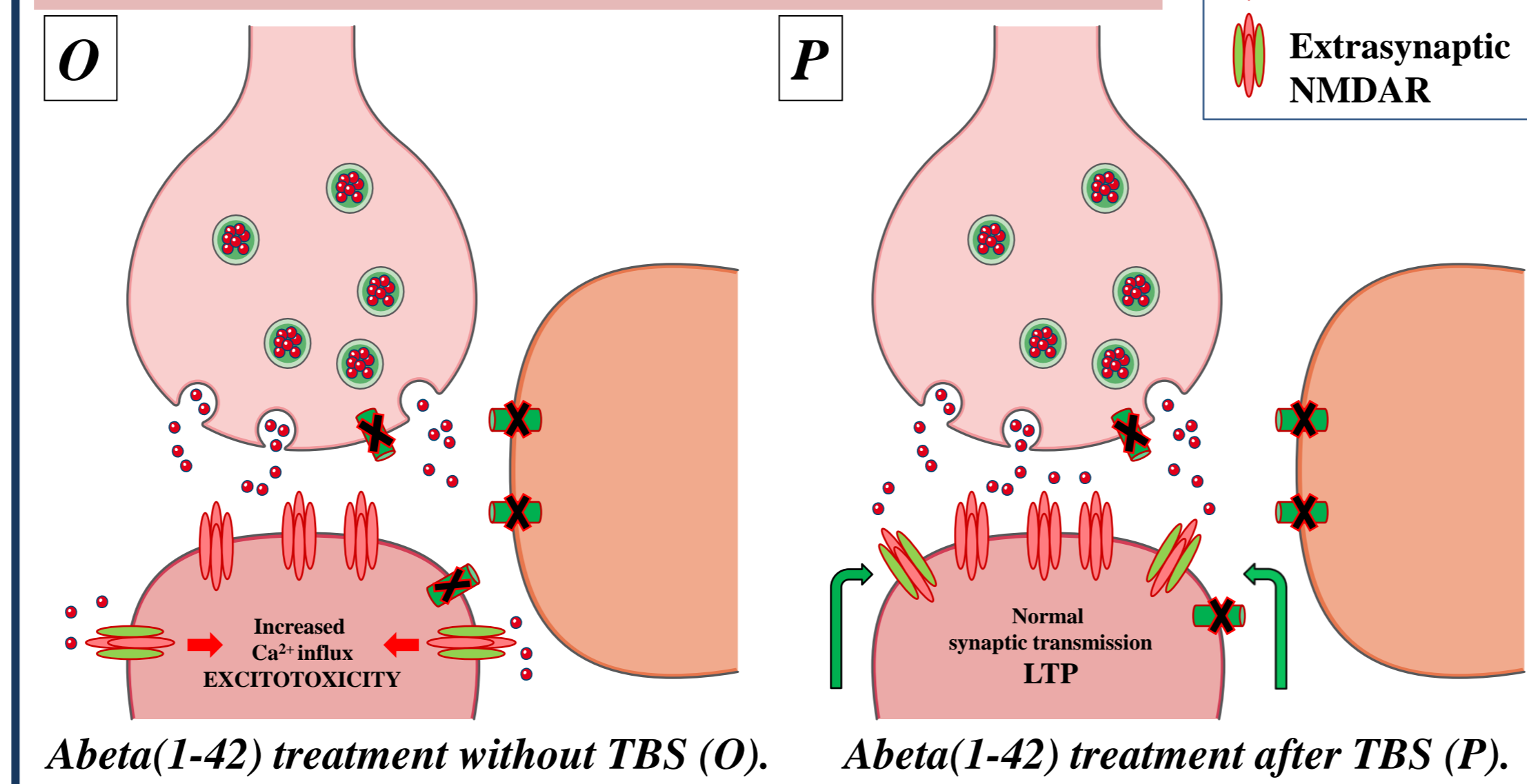


In presence of CNQX and using Mg²⁺-free ACSF, we have also shown that the evoked fEPSPs are AMPA receptor dependent (G, H), but the spiking activity requires NMDA receptor activation (I).

LTP INDUCTION PREVENTS ABETA(1-42) OR TBOA INDUCED HYPEREXCITATION



LTP INDUCTION INVOLVES LATERAL MOVEMENT OF NMDARS FROM AN EXTRASYNAPTIC SITE TO THE SYNAPSE



Abeta(1-42) induced LTP damage and hyperexcitation were mimicked by the excitatory amino-acid transporters (EAATs) inhibitor TBOA. Block of EAATs leads to increased glutamate at the synaptic cleft and subsequent spillover and activation of extra- or perisynaptic NR2B-enriched NMDARs, which play a major role in LTD induction and cell death pathway activation (O). Notably, inducing LTP prevents the hyperexcitation caused by overspilled glutamate, most probably by relocating extrasynaptic NMDA receptors to the synaptic compartment (P).

WE CONCLUDE THAT OLIGOMER ABETA(1-42) DISTURBS SYNAPTIC PLASTICITY BY ALTERING GLUTAMATE RECYCLING AT THE SYNAPSE.