# Differential deregulation of astrocytic calcium signaling by Amyloid beta, IL-1b, TNFa and LPS.

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Alzheimer's disease (AD) is a devastating neurological disorder that affects increasing number of people in elderly worldwide. The amyloid beta (Abeta) hypothesis of AD is the most popular and the most studied one to explain pathogenetic mechanisms of the disease. Neuroinflammation is an integral part of the AD pathogenesis and plays an important role in sensitizing neurons to the toxic effects of amyloid beta. Growing body of evidence suggest that reactive astrocytes, and specifically, deregulation of astrocytic calcium signaling, plays a pivotal role in the early synaptic dysfunction and the memory impairment. Little (if anything) is known about very early astrocytic activation, whether it is induced by toxic Abeta peptide or, alternatively, the pro-inflammatory environment, created by activated microglia, plays a pivotal role. Previously we have shown that Abeta deregulates calcium homeostasis via activation of calcineurin (CaN) and NF-kB in hippocampal astrocytes. We therefore treated primary cultured hippocampal astrocytes with nanomolar [Abeta], the major brain pro-inflammatory cytokines, TNFa and IL-1b, and the bacterial antigen LPS as a classic activators of glial cells. In stimulated astrocytes we investigated i) changes in mRNA levels of the key components of the astrocytic calcium signaling (mGluR5, IP3R1 and IP3R2); ii) degradation of IkBa as a marker of the NF-kB activation. We report that all four activating agents induced degradation of IkBa and therefore activation of NF-kB, although there was a clearly distinct pattern of changes in expression of the calcium signaling genes. Specifically, in hippocampal astrocytes: Abeta induced up-regulation of all three target genes. On the other hand, both IL-1b and TNFa down-regulated all three studied genes, while LPS had a major effect on mGluR5, although down-regulation of IP3R1 and IP3R2 was less prominent. The results obtained by real-time PCR were then confirmed in calcium imaging experiments. Ab, in line with our previuosly published results, increased mGluR5-mediated calcium transients, although both cytokines and LPS strongly suppressed calcium signals mediated by mGluR5. Experiments are now underway to investigate which of these changes are mediated by CaN-NF-kB axis and/or the other signaling routes are involved.