High-frequency field stimulation of primary neurons enhances ryanodine receptor-mediated Ca2+ release and generates hydrogen peroxide, which jointly stimulate NF-?B activity

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Neuronal electrical activity increases intracellular Ca2+ concentration and generates reactive oxygen species. Here, we show that high frequency field stimulation of primary hippocampal neurons generated Ca 2+ signals with an early and a late component, and promoted hydrogen peroxide generation via a neuronal NADPH oxidase. Hydrogen peroxide generation required both Ca2+ entry through N-methyl-D-aspartate receptors and Ca2+ release mediated by ryanodine receptors (RyR). Field stimulation also enhanced nuclear translocation of the NF-?B p65 protein and NF-?B -dependent transcription, and increased c-fos mRNA and type-2 RyR protein content. Preincubation with inhibitory ryanodine or with the antioxidant N-acetyl L-cysteine abolished the increase in hydrogen peroxide generation and the late Ca2+ signal component induced by electrical stimulation. Primary cortical cells behaved similarly as primary hippocampal cells. Exogenous hydrogen peroxide also activated NF-?B-dependent transcription