## ACUTE INCREASE OF GLUTAMATE RELEASE INDUCED BY NERVE GROWTH FACTOR : INVOLVEMENT OF EXTRA- AND INTRACELLULAR CALCIUM

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Nerve growth factor (NGF) was found to increase glutamate release in the developing visual cortex. We investigated the cellular mechanisms of this effect and its dependence on extracellular and intracellular $Ca^{2+}$. The NGF-induced enhancement of glutamate release from superfused rat visual cortex synaptosomes required mild depolarization. Removal of external $Ca^{2+}$ during depolarization with 15 mM $K^+$ only halved the effect of NGF on glutamate release. NGF increased $[Ca^{2+}]_i$ in $K^+$-depolarized synaptosomes preloaded with fura-2AM both in the presence and in the absence of external $Ca^{2+}$. The effects of NGF on glutamate release and $[Ca^{2+}]_i$ elevation were prevented by an anti-TrkA receptor monoclonal antibody. NGF increased synaptosomal inositol (1,4,5)-triphosphate ($InsP_3$) during depolarization and the $InsP_3$ receptor antagonist heparin abolished the effect of NGF on evoked glutamate release both in the presence and in the absence of external $Ca^{2+}$. The effect of NGF on the evoked glutamate release in $Ca^{2+}$-free medium was abolished by dantrolene, a ryanodine receptor blocker, by CGP 37157, a blocker of the mitochondrial $Na^+/Ca^{2+}$ exchanger and by pretreatment of synaptosomes with caffeine. NGF significantly increased the depolarization-induced activation of $Ca^{2+}$/calmodulin-dependent protein kinase II (CaMKII) and the subsequent phosphorylation of synapsin I in the absence of external $Ca^{2+}$ and the NGF effect on evoked glutamate release was inhibited by the CaMKII inhibitor KN-93. Thus, the effect of NGF on evoked glutamate release is linked to an increase in $[Ca^{2+}]_i$ contributed by both $Ca^{2+}$ entry and mobilization from InsP3-sensitive, ryanodine-sensitive and mitochondrial stores and to the subsequent activation of CaMKII.