

Opposing roles for NF- κ B/Rel factors p65 and c-Rel in the modulation of neuron survival elicited by glutamate and interleukin-1 β

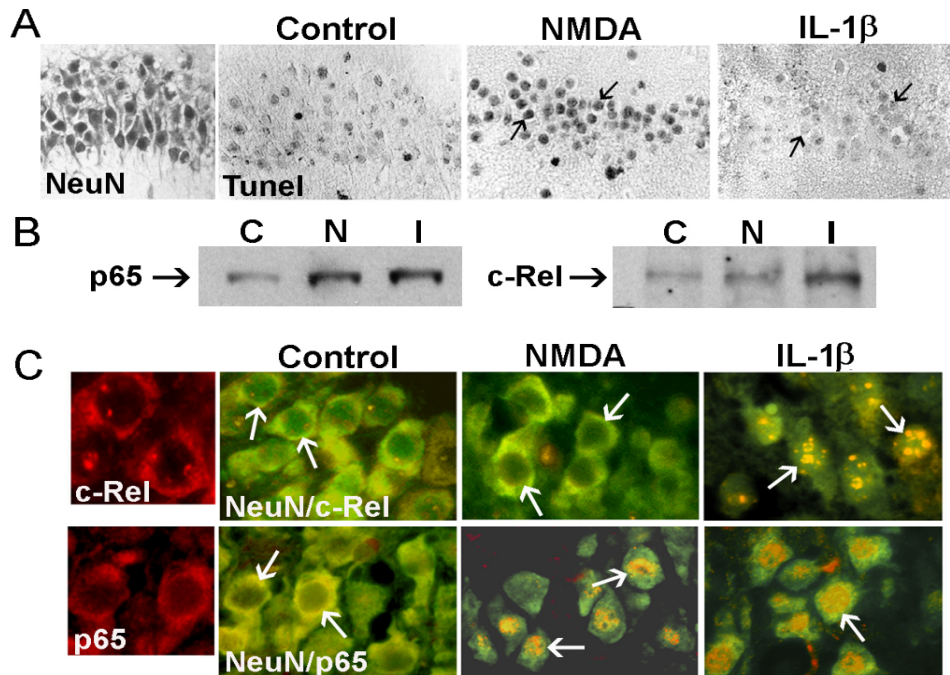
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The nuclear transcription factors NF- κ B/Rel have been shown to function as key regulators of either cell death or survival in neuronal cells. Here, we investigated whether selective activation of diverse NF- κ B/Rel family members might lead to distinct effects on neuron viability. Both in cultured rat cerebellar granule cells and in mouse hippocampal slices, we examined NF- κ B/Rel activation induced by two opposing modulators of cell viability: interleukin-1 β (IL-1 β) that promotes neuron survival and glutamate that can elicit toxicity. IL-1 β produced a prolonged stimulation of NF- κ B/Rel factors by inducing both I κ B α and I κ B β degradation. Glutamate produced a delayed and transient activation of NF- κ B/Rel, associated with a brief loss of I κ B α . Moreover, IL-1 β activated p50, p65 and c-Rel subunits of NF- κ B/Rel, while glutamate activated only p50 and p65 proteins. Inhibition of NF- κ B/Rel protein expression by antisense oligonucleotides in cerebellar granule cells showed that p65 was involved in glutamate-mediated cell death while c-Rel was essential for IL-1 β -preserved cell survival. Furthermore, depletion of c-Rel in cultured neurons as well as in hippocampus from the c-Rel^{-/-} mice converted IL-1 β effect into toxicity. These findings suggest that, within a single neuron, the balance between cell death and survival in response to external stimuli may rely on activation of distinct NF- κ B/Rel proteins.

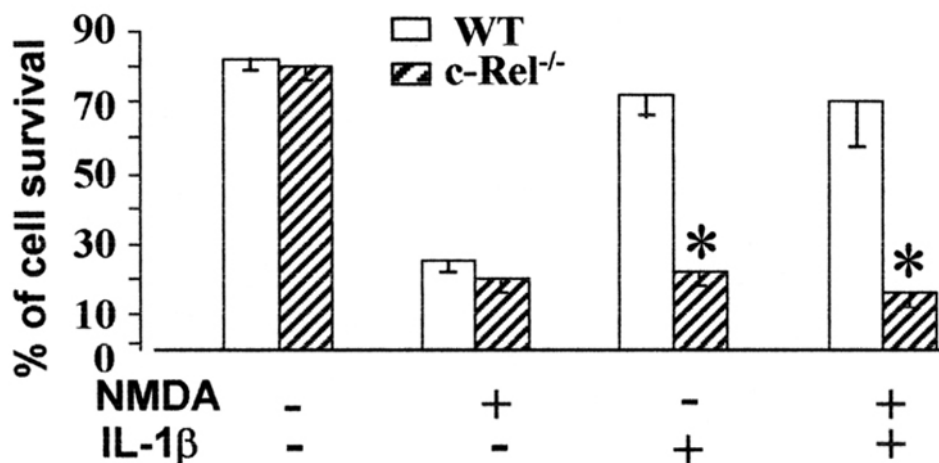
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Effect of NMDA and IL-1 β on neuron survival and NF- κ B/Rel activation in CA1 region of hippocampal slices from C57BL/6 mice. After 15 min exposure to NMDA (100 μ M) hippocampal slices were left to recover for 35 min in fresh buffer. Exposure to IL-1 β (1000 U/ml) was maintained for the entire period (50 min).

(A) Immunohistochemistry and TUNEL-labelling in CA1 region of mouse hippocampal slices. Scale bar, 20 μ m (B) Western blot analysis of p65 and c-Rel protein in nuclear extracts of hippocampal slices. The NMDA treatment increased the nuclear amount of p65 subunit, while IL-1 β stimulation increased the nuclear levels of both p65 and c-Rel. Blots reprobed with an anti α -tubulin antibody indicated equal amounts of proteins in the different lanes (data not shown). (C) Antibodies to NeuN (Cy-2 green) and c-Rel or p65 (both Cy-3 red) demonstrate colocalization. The nuclear localization of NF- κ B proteins shows that NMDA stimulation activates only p65 subunit, while IL-1 β exposure promotes nuclear translocation of both p65 and c-Rel proteins



IL-1 β (1000 U/ml) elicits neuroprotection against NMDA (100 μ M)-mediated excitotoxicity in hippocampal slices from wild-type mice (WT), but exerts toxicity in slices from c-Rel^{-/-} mice (c-Rel^{-/-}). Quantitative analysis of NMDA and IL-1 β -induced cell loss in CA1 hippocampal region of WT and c-Rel^{-/-} mice. * P< 0.05 vs the corresponding values of WT group.