NMDA receptor-dependent glutamate release is controlled bypresynaptic JNK2

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Activation of c-Jun N-terminal kinase (JNK) signaling pathway is critical for neuronal death that occurs in different pathological conditions. JNKs can be activated via receptor tyrosine kinases, cytokine receptors, G-protein coupled receptors and ligand-gated ion channels, including the NMDA receptor. While JNK has been generally associated with postsynaptic NMDA receptors, its presynaptic role remains largely unexplored. Here, by means of biochemical and electrophysiological approaches, we demonstrate the presence of JNK at presynaptic level. Intriguingly, JNK controls NMDA-evoked glutamate release through a selective interaction with Syntaxin 1a (STX1a). Moreover, using knockout mice for single JNK isoforms in combination with molecular modeling studies, we conclude that JNK_2 is the critical player mediating this presynaptic event. Overall the present findings unveil a novel presynaptic role of JNK_2 under potentially excitotoxic conditions.