Prolonged activation of NMDA receptors promotes dephosphorylation and alters postendocytic sorting of GABAB receptors

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Slow and persistent synaptic inhibition is mediated by metabotropic GABAB receptors (GABABRs). GABABRs are responsible for the modulation of neurotransmitter release from presynaptic terminals and for hyperpolarization at postsynaptic sites. Postsynaptic GABABRs are predominantly found on dendritic spines, adjacent to excitatory synapses, but the control of their plasma membrane availability is still controversial. Here, we explore the role of glutamate receptor activation in regulating the function and surface availability of GABABRs in central neurons. We demonstrate that prolonged activation of NMDA receptors (NMDA-Rs) leads to endocytosis, a diversion from a recycling route, and subsequent lysosomal degradation of GABABRs. These sorting events are paralleled by a reduction in GABABR-dependent activation of inwardly rectifying K+ channel currents. Postendocytic sorting is critically dependent on phosphorylation of serine 783 (S783) within the GABABR2 subunit, an established substrat