Extracellular Phosphorylation of a Receptor Tyrosine Kinase Controls Synaptic Localization of NMDA Receptors and Regulates Pathological Pain

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Extracellular phosphorylation of proteins was suggested in the late 1800s when it was demonstrated that casein contains phosphate. More recently, extracellular kinases that phosphorylate extracellular serine, threonine, and tyrosine residues of numerous proteins have been identified. However, the functional significance of extracellular phosphorylation of specific residues in the nervous system is poorly understood. Here we describe a single extracellular tyrosine whose inducible phosphorylation may represent an archetype for a new class of mechanism mediating protein-protein interaction and regulating protein function. We show that synaptic accumulation of GluN2B-containing N-methyl-D-aspartate receptors (NMDARs) and pathological pain are controlled by ephrin-B-induced extracellular phosphorylation of a single tyrosine (p*Y504) in a highly-conserved region of the fibronectin type III (FN3) domain of the receptor tyrosine kinase EphB2. Ligand-dependent Y504 phosphorylation modulates the EphB-NMDAR interaction in cortical and spinal cord neurons. Furthermore, Y504 phosphorylation enhances NMDAR localization and injury-induced pain behavior. By mediating inducible extracellular interactions that are capable of modulating animal behavior, extracellular tyrosine phosphorylation of EphBs may represent a previously unknown class of mechanism mediating protein interaction and function. Importantly, our study defines a specific extracellular phosphorylation event as a mechanism driving protein interaction and suggests that phosphorylation of FN3 domain-containing proteins is an underappreciated mechanism contributing to the development and function of the nervous system and synapse.