

Does spinophilin play a role in alteration of NMDAR phosphorylation?

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Normal brain function requires proper organization of downstream signaling pathways. This organization can be modulated by protein phosphorylation. Protein phosphorylation is a balance of phosphatases, such as protein phosphatase 1 (PP1), and kinases such as protein kinase A (PKA) and cyclin dependent kinase 5 (CDK5). Proper targeting of these proteins is critical for their normal function and is perturbed in various disease states. Spinophilin is critical in targeting PP1 to various substrates making it important in regulating the phosphorylation state and thus the function of various proteins including glutamate receptors, such as AMPARs and NMDARs. NMDARs are abundant postsynaptic proteins that are critical for normal synaptic communication. It has been reported that NMDAR phosphorylation modulates channel function. Here we aim to understand if spinophilin regulates NMDAR phosphorylation and function as well as the mechanisms by which the spinophilin NMDAR interaction are altered. Specifically, we have found that the presence of spinophilin decreases the abundance of PP1 bound to NMDAR. This affect was not observed when a PP1 binding-deficient spinophilin mutant (F451A) was expressed. Furthermore, activation of endogenous PKA and/or overexpression of PKA catalytic subunit robustly increased the association between spinophilin and GluN1 and C-terminal tail of the GluN2B subunit of the NMDAR. Conversely, these associations are decreased when CDK5 is present. Our future studies will evaluate the role of spinophilin in regulating the phosphorylation state of the NMDAR. Taken together, our data demonstrate that spinophilin can associate with multiple subunits of the NMDAR in HEK293 cells and that protein kinases can biphasically modulate these associations.