Stress-induced changes in crosstalk of S-palmitoylation and S-nitrosylation of proteins involved in synaptic plasticity

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Precise regulation of structural and functional synaptic integrity is critical for neuronal network connectivity and proper brain function. Essential aspects of the activity and localization of synaptic proteins are regulated by posttranslational modifications. It is believed that these processes may modulate structural alterations of individual synapses, thus determining the efficiency of neurotransmission. S-palmitoylation, a fully reversible covalent modification of cysteine side chain with palmitate, causes increase in the hydrophobicity and as a consequence modulates affinity of the protein to the cell membranes and membranous compartments. This has a strong impact on the sorting, localization and function of the target molecules. Due to the profound physiological roles of S-palmitoylation and S-depalmitoylation, those processes are tightly regulated not only enzymatically by acyltransferases and palmiotylthioestrases respectively but also through competitive modification of cysteine residue by distinct posttranslational modifications, such as S-nitrosylation. It is still not clear how this interplay is affected in the brain pathology such as stress related disorders and function of which synaptic proteins is regulated by this mechanism. Using a newly developed mass spectrometry based approach, for Palmitoylation And Nitrosylation Interplay MONItoring (PANIMoni), we analyzed endogenous S-nitrosylation and S-palmitoylation of the postsynaptic density proteins in the mouse model of chronic stress. Using this approach we performed differential analysis of the two posttranslational modifications to the level of single cysteine. Our results suggest that atypical mechanism of interplay between S-palmitoylation and S-nitrosylation of proteins involved in the synaptic transmission, protein localization and regulation of the synaptic plasticity might be one of the major events associated with chronic stress disorders.