RABIES VIRUS INFECTION INDUCES MITOCHONDRIAL DYSFUNCTION AND OXIDATIVE STRESS

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Our previous studies in an experimental model of rabies showed neuronal process degeneration in association with severe clinical disease. Cultured adult rat dorsal root ganglion (DRG) neurons infected with CVS-11 strain of rabies virus (RABV) showed axonal swellings and immunostaining for 4-hydroxy-2-nonenal
(4-HNE) indicating evidence of lipid peroxidation associated with oxidative stress and reduced axonal growth versus mock-infection. We have demonstrated that RABV infection alters a variety of mitochondrial parameters and increases reactive oxygen species production and mitochondrial Complex I activity vs. mock infection. We have hypothesized that a RABV protein targets the mitochondria and triggers its dysfunction. Mitochondrial extracts of MNA cells were analyzed with a proteomics approach. We have identified peptides belonging to the RABV nucleocapsid protein (N), phosphoprotein (P), and glycoprotein (G) and our data indicate that the extract was highly enriched with P. P was also detected by immunoblotting in RABV-infected purified mitochondrial extracts and in Complex I immunoprecipitates from the extracts, but not in mock-infected extracts. A plasmid expressing P in cells increased Complex I activity, whereas expression of other RABV proteins did not. We have analyzed recombinant plasmids encoding various P gene segments.
Expression of a peptide from amino acid 139-172 increased Complex I activity similar to expression of the entire P protein, whereas most peptides that did not contain this region did not increase Complex I activity. These results indicate that the RABV phosphoprotein interacts with Complex I in mitochondria causing mitochondrial dysfunction, oxidative stress, and neuronal process degeneration in experimental rabies.