

Abstract Proof

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Abstract

TITLE: NEUROFILAMENT PROTEIN ADDUCT FORMATION IN SPINAL CORD FRACTIONS OF 2,5-HEXANEDIONE INTOXICATED RATS

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ABSTRACT BODY: Axon atrophy associated with 2,5-hexanedione (HD) neurotoxicity may be mediated by lysine reaction and pyrrole adduction on neurofilament (NF) proteins, causing disrupted insertion of these subunits into the cytoskeletal polymer and their subsequent loss (Tox. Appl. Pharmacol. 199: 20-34, 2004). In this study, mass spectral (MS) analysis was used to identify NF protein adducts in low speed (P1) and high-speed (P2,S2) Triton fractions of spinal cord from HD-exposed rats (175 mg/kg/d x 101 d) exhibiting moderate neurotoxicity (gait score = 3.1 ± 0.3). Proteins in each fraction were separated by SDS-PAGE and subjected to in-gel tryptic digestion. LC-ESI-MS/MS and/or MALDI-TOF MS were used to analyze tryptic peptides. Specific pyrrole adduct formation was noted in NF-H and -M of the P1 and P2 fractions, whereas adduction of NF-L was found in S2 fractions only. Although sequence coverage for each protein was not complete (40-60%), adduct levels appeared to be highest in NF-H protein (7-9 mol adduct/mol protein), with adducts clustered primarily in the C-terminal KSP and KEP "tail" domains. The P2 fraction also contained adducts in a "rod" domain peptide (residues 105-113) of NF-H. For NF-M, one adducted tail sequence was present in P1 and P2 fractions and one rod domain adduct was present in P1 only. NF-L adducts were present in the amino-terminal "head", rod, and tail regions in S2 fractions only. Thus, as noted in our previous in vitro studies, the formation of NF protein adducts is limited and specific. These data support our hypothesis that pyrrole adduction in the NF rod and tail domains inhibits subunit polymerization and modifies interfilament interactions, respectively, thus shifting the mass equilibrium toward the more soluble, mobile NF phase. Reduction in axon caliber occurs as a consequence of increased mobile phase transport and loss of NF proteins at the nerve terminal. (Supported by NIEHS grant ESO7912-08).