DEFICIENT DIETARY FOLIC ACID AND SYSTEMIC DSP-4 INDUCED LOCUS COERULEUS LOSS ASSESSED AS NEURODEGENERATIVE COGNITIVE MODEL IN ADULT CB57/J6 MICE

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Dietary deficiency of folic acid (FA) shortened nerve lengths as much as 50% in hippocampal dentate gyrus (DG). Locus coeruleus (LC) is largest noradrenergic nucleus in central nervous system with neurogenic projections widely dispersed in the brain and, notably, a major norepinephrine source in the DG and frontal cortex (FC). For 16 weeks, adult CB57/J6 mice (N=66) were provided 4 dietary/DSP-4 treatments: NFCS (n=16, normal FA control, saline injected [0.2 mg FA/kg BW]); NFCD (n=18, normal FA, DSP-4 injected (50 mg DSP-4/kg BW); FADS (n=16, FA deficient, saline injected); and, FADD (n=16, FA deficient, DSP-4 injected). NE in FC was measured in addition to significant loss of LC neurons; astrocytes, calcium signaling, and embryonic neurons using, respectively, immunohistochemical methods for tyrosine hydroxylase (TH), GABA fibrillary acidic protein (GFAP), parvalbumin (PV), doublecortin (DCX) were analyzed. Confirmation of phenotypic cognitive behavior with Nesting Behavior; decreased distance traveled with Novel Object Recognition (NOR); and, decreased rearing and latency to explore to the center of the field in Open Field Testing (OFT) were enumerated between NFCS and FADD ($p<0.05$). Elevated plasma homocysteine (Hcy) and decreased methyltransferase activity ($p<0.05$) established folic acid deficiency between NFCS and FADS/FADD. Results support that grievous injury to the LC noradrenergic system via systemic NE specific neurotoxin DSP-4 disrupts motor activity, contextual learning and memory, and perhaps significantly, the supportive cellular environment for the LC and efficient dispersion of NE. Understanding the molecular mechanisms underlying LC degeneration during disease progression or aging is yet to be fully understood.