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Hyperhomocysteinemia due to a short-term folate deprivation is related to electronmicroscopic changes in the rat brain.

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Elevated plasma homocysteine is thought to be an independent risk factor for cerebrovascular and neurodegenerative disorders, but the underlying mechanisms are unknown. The strong association of plasma homocysteine with cerebrovascular disease may be due to the homocysteine-induced vascular injury leading to stroke and also participate in the ensuing neurotoxic response in the brain. We investigated the effects of folate deprivation on plasma folate, vitamin B-12 and homocysteine, and its cerebrovascular and neurotoxic effects. Plasma folate, vitamin B-12 levels were analyzed by a radioimmunoassay. Plasma homocysteine levels were measured by a HPLC-fluorescence detection method. Cerebrovascular and neurotoxic effects of hyperhomocysteinemia were analyzed by immunohistochemical and electronmicroscopic methods. Two levels of folic acid (0 mg and 4mg/kg diet) diets were fed to six-month-old male Sprague Dawley rats for 8 weeks. Dietary folate deprivation caused a decrease in the plasma folate from 155.8±13.1ng/ml to 19.5±3.2ng/ml. Plasma homocysteine was increased by 317% from 6.15±0.9 μmol/L to 19.5±2.7 μmol/L. Dietary folate deprivation did not cause a significant increase in the plasma vitamin B-12 levels. Plasma folate, but not vitamin B-12, was negatively correlated with plasma homocysteine ($r=-0.6144$, $p=0.0042$). Dietary folate deprivation-induced hyperhomocysteinemia for 8 weeks caused a decrease in the immunoreactivity of the hippocampal neuronal heme oxygenase-1(HO-1), an important biomarker for the oxidative stress. This result indicates that the neuroprotective effects via antioxidative activities in the hippocampal neurons are diminished by folate deprivation-induced hyperhomocysteinemia. Electronmicroscopic examinations of the central nervous system demonstrated a hippocampal neuronal cell damage in the folate-deprived rats. The cytoplasmic swelling and mitochondrial degeneration in the endothelium, perivascular fibrosis-collagen like amorphous substances, and pericyte degeneration are found in the cerebrocortical microvascular wall of folate-deprived rats. Homocysteine neurotoxicity through deterioration of blood brain barrier-function may contribute to the pathogenesis of hyperhomocysteinemia by folate deprivation. These morphologic evidences might be helpful for elucidating the underlying mechanism for cerebrovascular- and neuro-pathogenesis of folate deficiency.