FOLIC ACID PREVENTS LINE-1 HYPMETHYLATION IN RATS WITH HYPERHOMOCYSTEINEMIA

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Objectives LINE-1 (Long Interspersed Nuclear Elements-1) hypomethylation has been associated with risk of cardiovascular disease. Increased plasma homocysteine (Hcy) is an independent risk factor for cardiovascular disease. However, it is still unclear whether plasma Hcy can be approached as a modifiable risk factor for atherosclerosis, since the results regarding the effect of Hcy-lowering treatment on cardiovascular risk are contradictory. Our study was designed to determine whether Hcy is associated with LINE-1 hypomethylation and whether folic acid supplementation can prevent this process in rats with hyperhomocystinemia (HHcy).

Methods 36 healthy 6-week-old Wistar male rats, weighing (160 ± 10 g), after being fed adaptable for one week, were randomly divided into control group (n=12), HHcy group (n=12), folic acid treatment group (n=12). The control group was fed with AIN-93G...
diet. The Hhcy group was fed with high-methionion diet, consisting of AIN-93G diet plus 1.7% methionion. The folic acid treatment group was fed with high-methionion plus folic acid-rich diet, consisting of AIN-93G diet plus 1.7% methionion and 0.008% folic acid. After be maintained for 18 weeks on the previously described diets, the Hcy and folic acid concentrations in the plasma was measured with the IMX assays. The thoracic aorta was harvested for morphology (electron microscopy). The DNA methyltransferase activity was determined using EpiQuik DNA Methyltransferase (DNMT) Activity/Inhibition Assay Kit. The methylation status of LINE-1 was assessed by the combined bisulphite restriction analysis (COBRA) method.

**Results** A high methionine diet for 18 weeks is sufficient to induce Hhcy. Folic acid supplementation to the rats fed with the high-methionine diet prevented an elevation Hcy levels in the plasma (p<0.01) and morphological changes in the thoracic aorta. Compared with the Control group, the Hhcy group had decreased DNA methyltransferase activity and LINE-1 methylation status (p<0.01, p<0.05). After folic acid supplementation, the lowering of Hcy levels was accompanied by a marked elevation of DNA methyltransferase activity and LINE-1 methylation status in aorta (p<0.05, p<0.05).

**Conclusions** Our findings indicate that folic acid supplementation prevents LINE-1 hypomethylation in rats with Hhcy.