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Exercise prevents hyperhomocysteinemia in a dietary folate-restricted mouse model

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ABSTRACT

Hyperhomocysteinemia is a condition that results from altered methyl group metabolism and is associated with numerous pathological conditions. A number of nutritional and hormonal factors have been shown to influence circulating homocysteine concentrations; however, the impact of exercise on homocysteine and methyl group balance is not well understood. Our hypothesis was that exercise represents an effective means to prevent hyperhomocysteinemia in a folate-independent manner. The purpose of this study was to determine the influence of exercise on homocysteine metabolism in a dietary folate-restricted mouse model characterized by moderate hyperhomocysteinemia. Female outbred mice (12 weeks old) were assigned to either a sedentary or free-access wheel exercise group. Following a 4-week acclimation period, half of the mice in each group were provided a folate-restricted diet for 7-weeks prior to euthanasia and tissue collection. As expected, folate-restricted sedentary mice exhibited a 2-fold increase in plasma total homocysteine concentrations; however, exercise completely prevented the increase in circulating homocysteine concentrations. Moreover, exercise reduced plasma homocysteine concentrations 36% within the group fed only the control diet. The prevention of hyperhomocysteinemia by exercise appears, at least in part, to be the result of increased folate-independent homocysteine remethylation owing to a 2-fold increase in renal betaine homocysteine S-methyltransferase. To our knowledge, this is the first report demonstrating the prevention of hyperhomocysteinemia by exercise in a dietary folate-restriction model. Future research will be directed at determining if exercise can have a positive impact on other nutritional, hormonal, and genetic models of hyperhomocysteinemia relevant to humans.

1. Introduction

The maintenance of the folate-dependent one-carbon pool and methyl group metabolism is essential for optimization of health. Perturbations of these interrelated metabolic pathways have been implicated in a number of diseases, including cancer development, cardiovascular disease, neural tube defects, and cognitive disorders [1-4]. Homocysteine is an important intermediate in methyl group metabolism and is partially dependent on folate/B_{12} for its metabolism. Hyperhomocysteinemia, a condition that can result from a lack of methyl group donors, cofactors, and/or relevant genetic anomalies, has been shown to be an independent risk factor in the development of cardiovascular disease [5].

Homocysteine is a product of transmethylation reactions involving S-adenosylmethionine (SAM), the activated form of

Abbreviations: BHMT, betaine-homocysteine S-methyltransferase; MS, methionine synthase; SAM, S-adenosylmethionine.

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methionine, in which a methyl group is donated to a number of acceptors, including proteins, lipids, and nucleic acids (Fig. 1) [6]. Homocysteine can be remethylated back to methionine by folate-dependent or -independent mechanisms, or undergo irreversible catabolism by transsulfuration. Folate-dependent remethylation utilizes folic acid in its most reduced form to transfer a methyl group to homocysteine and generate methionine via the vitamin B_{12}-dependent enzyme methionine synthase (MS). Conversely, folate-independent remethylation of homocysteine utilizes the enzyme betaine-homocysteine S-methyltransferase (BHMT) and a methyl group from betaine, a compound derived from the oxidation of choline. Transsulfuration of homocysteine by the vitamin B_6-dependent enzymes cystathionine β-synthase and cystathionine γ-lyase leads to irreversible catabolism and the eventual formation of cysteine. Thus, homocysteine balance and the prevention of hyperhomocysteinemia are dependent on a number of substrates, cofactors, and the proper expression and function of key enzymes.

As the regulation of homocysteine balance is vital to maintain optimal health, the establishment of homocysteine management-based therapies is necessary to prevent or treat diseases related to hyperhomocysteinemia. Recent studies examining the role of exercise as a potential means to reduce circulating homocysteine concentrations have been inconclusive, owing in large part to the variations in study design and exercise regimes [7-15]. Moreover, discrepancies within these human studies, including B-vitamin and subject training status, as well as variations in mode, intensity, and duration of test exercises, limit the strength of their conclusions [16,17]. Mechanistically, reductions in homocysteine concentrations by exercise may be related to increased protein turnover owing to increased plasma methionine concentrations during exercise, followed by reduced concentrations below basal levels after exercise [18-21]. This fluctuation in methionine availability for methyl group metabolism may be due, in part, to the increased need of methionine for muscle anabolism, potentially resulting in diminished homocysteine production [17,21]. However, exercise also increases the demand of vitamin B_6 to support increased muscle catabolism, thereby potentially limiting its availability for transsulfuration and subsequently resulting in homocysteine accumulation [22].

Our hypothesis was that exercise represents an effective means to prevent hyperhomocysteinemia in a folate-independent manner. This was based on our previous research demonstrating that a gluconeogenic state and related hormonal alterations, similar to what is exhibited as a function of exercise, results in reduced homocysteine concentrations via enhanced folate-independent remethylation of homocysteine, as well as increased catabolism [23-26]. The aim of the present study was to assess the influence of voluntary exercise on homocysteine balance using a folate-restricted mouse model of hyperhomocysteinemia. This moderate hyperhomocysteinemia model was utilized to represent populations that experience poor folate absorption or intake, as well as individuals with relevant polymorphisms

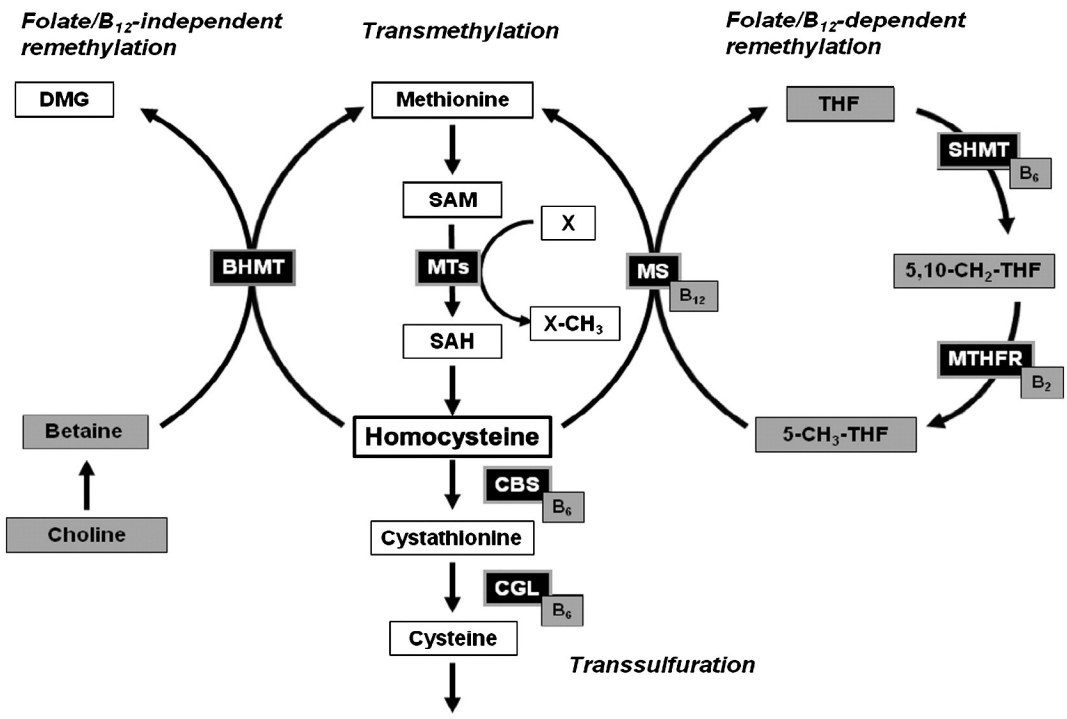

Fig. 1 – Methyl group and homocysteine metabolism. Enzymes are shown in black boxes, whereas vitamin substrates and/or cofactors are shown in gray boxes. Abbreviations: CBS, cystathionine β-synthase; DMG, dimethylglycine; MTs, methyltransferases; MTHFR, 5,10-methylene-THF reductase; SAH, S-adenosylhomocysteine; SAHH, SAH hydrolase; THF, tetrahydrofolate; X, methyl acceptor. In addition to THF, this series of interrelated pathways are dependent on a number of other B-vitamins, including riboflavin [B_2], vitamin B_6, and vitamin B_{12}.