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Creatine supplementation decreased homocysteine plasma levels in rats but not humans: A critical review with meta-analysis

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ABSTRACT

Background: Increasing evidence has shown that an elevated a level of homocysteine (Hcy) in the blood is related to several diseases. Over the last few years, studies have demonstrated creatine (Cr) synthesis and Hcy formation are metabolically connected; and Cr supplementation can decrease Hcy blood levels in different situations. This data however is inconsistent and still controversial.
Objective: The aim of this critical review with meta-analysis was to discuss and ascertain the effects of Cr supplementation on blood Hcy levels.
Method: A review was conducted according to the PRISMA guidelines using PubMed Discuss and Scielo online databases to identify relevant studies through November 2015. RevMan was used to calculate the effect size of the change in Hcy plasma/serum concentration from baseline to post-supplementation with Cr vs. placebo groups. Weighted mean differences were calculated using random effect models.
Results: Cr supplemented trials were divided into two subgroups according to whether the experimental design included animals or humans participants. Overall, 14 studies were included in the meta-analysis. The six rodent included studies reported decreased plasma Hcy concentration after Cr supplementation with a mean effect size equal to −2.43 μmol/l (95% CI: 3.60, −1.26, $P < 0.01$). The humans studies involved 483 participants (242 Cr and 241 placebo supplemented subjects) and indicated no changes in plasma Hcy concentration after Cr supplementation compared to placebo (0.09 μmol/l, 95% CI: −0.47, 0.66, $P = 0.18$).
Conclusions: Our data demonstrated Cr supplementation is effective in decrease Hcy blood concentration in rats; the same effect however, is not demonstrated humans studies. Human and rats particularities in Hcy metabolism and poorly controlled humans studies may contribute to the divergence of results.

Contents

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1. Introduction

Homocysteine (Hcy) is a sulfur amino acid synthesized in the liver as a byproduct of methionine metabolism [1]. Hcy has recently gained attention in the literature due to its association with several diseases that may increase the risk of mortality [2,3]. Humphrey et al. [4] demonstrated that each increase of 5 μmol/l in plasma Hcy concentration increased the risk of cardiovascular events by approximately 20%. Bostom et al. [5] demonstrated elevated blood Hcy concentration is independently associated with an elevated risk of mortality (54% for all-cause mortality and 52% for cardiovascular mortality).

Creatine (Cr) occurs naturally in food, especially in meat and fish. In human omnivores, one-half of Cr required is provided in the diet and the remainder is endogenously synthesized [6]. Recent studies have shown Cr synthesis and Hcy formation are metabolically connected (Fig. 1) [7,8]. Cr synthesis involves the reversible transfer of the amidino group of arginine to glycine to form guanidinoacetic acid (GAA) and ornithine in a reaction catalyzed by the enzyme arginine: glycine amidinotransferase (AGAT), which is very active in kidneys. Next, the irreversible transfer of a methyl group from S-adenosylmethionine (SAM) to GAA is catalyzed by the enzyme guanidinoacetate N-methyltransferase (GAMT) in the liver [6] and Cr is formed. SAM acts primarily as a universal methyl donor in the synthesis of several others methylated compounds such as neurotransmitters (adrenaline, noradrenaline), DNA, RNA, phosphatidylcholine and others. A byproduct of these methylation reactions is S-adenosylhomocysteine, which is hydrolyzed to adenosine and Hcy. Thus, Cr synthesis and Hcy formation are metabolically linked by methyl metabolism. Previous studies have shown that Cr supplementation downregulates AGAT activity [7,9] and the endogenous synthesis of Cr; because Cr synthesis is responsible for a considerable consumption of SAM (at least 40%) and Hcy formation [7,10], Cr supplementation leads to reduced Hcys formation in rats [7,10–12]. There have only been a small number of studies regarding the effect of Cr supplementation in humans, and the results from these studies were quite inconsistent.

Given the inconsistence of the published data, it is important to investigate whether Cr supplementation modulate Hcy metabolism in different situations. The increasing number of published studies allows us to apply strict methodological analysis and summarize the main results. Thus, we propose a meta-analysis approach to provide a statistical summary of comparable studies in order to consolidate a quantitative review of the effects of Cr supplementation on blood Hcy concentration.

2. Methods

2.1. Search approach and study selection

This review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement guidelines [13,14]. The PubMed database was searched for English-language articles, using the combination of

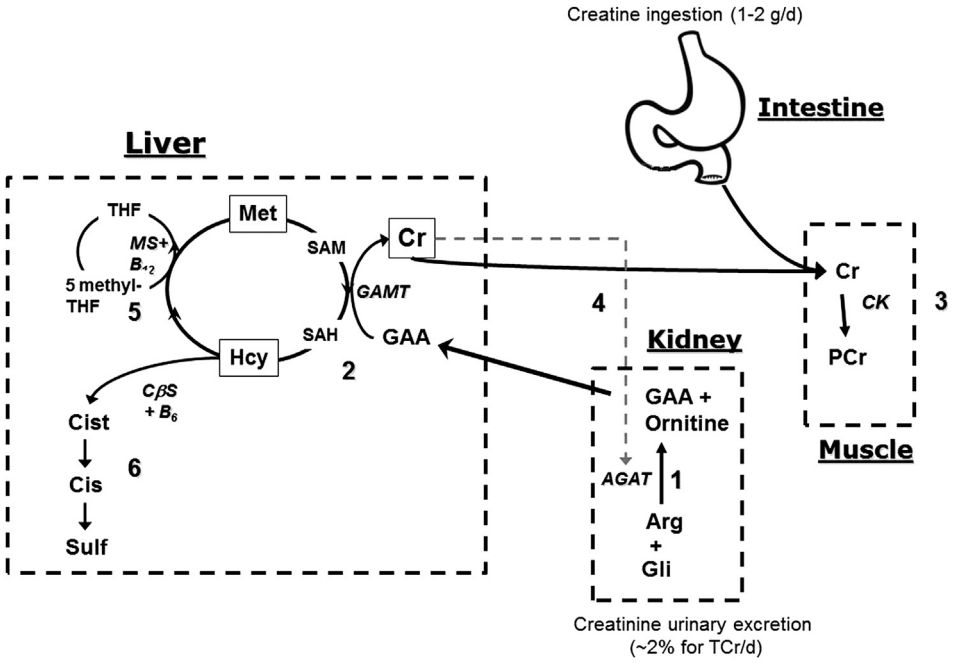

Fig. 1. Schematic presentation of the interaction of Hcy and Cr metabolism in rats. 1) action of kidney L-arginine: glycine amidinotransferase AGAT for guanidineacetic acid (GAA) formation as the first step of Cr synthesis; 2) the irreversible transfer of a methyl group from S-adenosylmethionine (SAM) to GAA is catalyzed by the enzyme guanidinoacetate N-methyltransferase (GAMT) in the liver; 3) Cr/PCr muscle system; 4) an increase in Cr intake down-regulates kidney AGAT in reaction 1 and decreases methyl flux for Hcy formation (reaction 2); 5) remethylation pathway; 6) transsulfuration pathway. THF, tetrahydrofolate; MS, methionine synthase; GNMT, glycine N-methyltransferase; GAMT, guanidinoacetate methyl-transferase; CbS, cystathionine-b-synthase; GSH, reduced glutathione.