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Review

Metabolic adaptations to methionine restriction that benefit health and lifespan in rodents

Carmen E. Perrone *, Virginia L. Malloy, David S. Orentreich, Norman Orentreich

Orentreich Foundation for the Advancement of Science, Inc., Cold Spring-on-Hudson, NY 10516, United States

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ABSTRACT

Restriction of dietary methionine by 80% slows the progression of aged-related diseases and prolongs lifespan in rodents. A salient feature of the methionine restriction phenotype is the significant reduction of adipose tissue mass, which is associated with improvement of insulin sensitivity. These beneficial effects of MR involve a host of metabolic adaptations leading to increased mitochondrial biogenesis and function, elevated energy expenditure, changes of lipid and carbohydrate homeostasis, and decreased oxidative damage and inflammation. This review summarizes observations from MR studies and provides insight about potential mediators of tissue-specific responses associated with MR's favorable metabolic effects that contribute to health and lifespan extension.

1. Introduction

Aging is, in itself, the most significant risk factor for a range of prevalent diseases including cardiovascular disorders, cancer and diabetes (Anderson and Weindruch, 2012). Because of increasing healthcare challenges, there is a need to find ways to improve health with advancing age. A potential mechanism to achieve this goal is dietary restriction. Early studies conducted by McCay et al. (1935) showed that restriction of calories without malnutrition increased mean and maximal survival in rats. Later studies revealed that caloric restriction (CR) also delayed the onset of age-dependent pathologies and these observations led investigators to examine whether specific dietary nutrients were implicated in the early development of diseases (reviewed in McDonald and Ramsey, 2010). In rodents, mineral and lipid restriction did not extend lifespan (Iwasaki et al., 1988), while the effect of carbohydrate restriction remained unequivocal (Khorakova et al., 2012). Although not as efficacious as CR, protein restriction (PR) in the absence of CR produced a small but significant increase in lifespan extension in Fischer 344 (F344) rats possibly by mitigating two age-associated pathologies: chronic progressive nephropathy and cardiomyopathy (Maeda et al., 1985). The restriction of essential amino acids was also reported in rodents. In Long–Evans rats fed diets in which tryptophan levels were decreased by 30%, the maximum lifespan was extended by 23%; however, these studies were hampered by early mortality with 50% of the tryptophan restricted rats dying within the first year (Ooka et al., 1988). Benefits of tryptophan restriction were also observed in mice, in which median and maximal survival was increased by 6% and 10%, respectively (De Marte and Enesco, 1986). These studies served as the impetus to examine dietary restriction of another essential amino acid, methionine. Methionine restriction (MR) was shown to be a more robust model of amino acid restriction since it increased medium and maximal lifespan by 30% and 40%, respectively, and caused no significant early mortality (Orentreich et al., 1993). Studies conducted over the last decade suggest that the beneficial effects associated with MR could be utilized to understand processes that increase vulnerability to disease. Such studies are presented here.

Abbreviations: ACC, acetyl-CoA carboxylase; Ahcy, adenosylhomocysteinase; AT, adipose tissue; ATGL, adipose triglyceride lipase; AMPK, AMP-activated protein kinase; Bhmt, betaine-homocysteine *S*-methyltransferase; CR, caloric restriction; CBS, cystathionine β-synthase; Ccl7, chemokine (C-C motif) ligand 7; CF, control-fed; Cth, cystathionase; Ccr2 and Ccr5, chemokine (C-C motif) receptors 2 and 5; FGF21, fibroblast growth factor 21; F344, Fischer 344; FRL, free radical leak; Gclm, glutamine–cysteine ligase; Gpd2, glycerophosphate dehydrogenase 2; Gnmt, glycine *N*-methyltransferase; GH, growth hormone; IGF-1, insulin-like growth factor-1; Lbp, lipopolysaccharide binding protein; Mat1a, methionine adenosyltransferase 1 alpha; Mtr, methionine synthase; MR, methionine restriction; 8-oxo-dG, 8-oxo-deoxyguanosine; PPARs, peroxisome proliferator-activated receptors; PGC1, peroxisome proliferator-activated receptor coactivator 1; PR, protein restriction; ROS, reactive oxygen species; SAH, *S*-adenosylhomocysteine; SAM, *S*-adenosylmethionine; Sirt1, sirtuin 1; Scd1, stearoyl-CoA desaturase-1; TG, triglyceride; TNFα, tumor necrosis factor-alpha; UCP1, uncoupling protein-1; WAT, white adipose tissue.

* Corresponding author at: Cell Biology Laboratory, Orentreich Foundation for the Advancement of Science, Inc., 855 Route 301, Cold Spring-on-Hudson, NY 10516, United States. Tel.: +1 845 265 4200x235; fax: +1 845 265 4210.

E-mail addresses: perrone@orentreich.org, perronecepr@yahoo.com (C.E. Perrone).

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2. Dietary methionine restriction and lifespan

The concept that dietary MR could significantly extend survival in rodents was first introduced by Orentreich et al. (1993). Orentreich's initial studies demonstrated that the inception of MR early in life increased median and maximal lifespan by 30 and 40%, respectively (Fig. 1a). Later studies showed that MR initiated at 12 months of age also increased both median and maximum lifespan in CB6F1 mice, suggesting that, at least in this model, MR can have beneficial effects when imposed later in life (Sun et al., 2009). MR animals have markedly lower body weight relative to age-matched control-fed (CF) animals (Fig. 1b and c). This specific response to reduced methionine intake was questioned because MR rats consume less food compared to CF rats but are slightly hyperphagic when food consumption is adjusted for lower body weight (Fig. 1d). Indeed, increasing the energy density of the MR diet failed to increase growth (Orentreich et al., 1993). Further evidence that the MR effects are not due to CR was shown in long-term studies in which CF rats were fed allotments of food consumed by MR rats (i.e. pair fed, PF) (Malloy et al., 2006). Although growth was attenuated in the PF animals, key serum markers of adiposity and insulin sensitivity were comparable to CF rats. Moreover, the median and maximum lifespan of PF rats was not significantly increased. These effects of MR are also unrelated to protein deficit as these animals consume more protein than CF rats when corrected for either total body weight or lean body mass (Malloy et al., 2006).

Chronic MR results in lower serum insulin-like growth factor-1 (IGF-1) levels in both rats (Fig. 2a) and mice (Malloy et al., 2006; Miller et al., 2005). Several lines of evidence point to the relationship between the growth hormone (GH)/IGF-1 axis and insulin with effects on disease and longevity. Ames dwarf mice are GH-deficient and have markedly reduced circulating IGF-1 levels (Bartke et al., 2001). Like MR animals, Ames dwarf mice are long-lived, smaller than age-matched controls, and remain insulin sensitive (Bartke et al., 2001; Brown-Borg et al., 1996). Furthermore, GH deficiency has been shown to delay aging and mortality in rodents through enhanced mitochondrial function, resistance to oxidative stress, and increased latency to neoplastic disease (Brown-Borg et al., 2001; Ikeno et al., 2003). Studies have also shown that Ames dwarf mice have altered methionine metabolism relative to their wild-type littermates (Uthus and Brown-Borg, 2006), i.e., the flux of methionine through the transulfuration pathway is markedly enhanced in these mice. Indeed, the expression of genes encoding key methionine metabolism enzymes, i.e., methionine adenosyltransferase 1 alpha (*Mat1a*), glycine *N*-methyltransferase (*Gnmt*), betaine-homocysteine *S*-methyltransferase (*Bhmt*), adenosylhomocysteinase (*Ahcy*) and cystathionase (*Cth*) were all significantly upregulated in the Ames dwarf mouse relative to wild-type animals. Conversely, the expression of methionine synthase (*Mtr*) was markedly decreased in the dwarf mouse.

Like other animal models of lifespan extension, MR also attenuates the expected age-dependent increase in both basal insulin and glucose levels in aging rats (Fig. 2b and c) and mice (Malloy et al., 2006; Miller et al., 2005). More importantly, the response to oral glucose challenge was preserved in MR rats. While the glycemic responses to a glucose load were not different between young, mature adult or older CF and MR rats at 7, 30 and 90 weeks, respectively, the area under the curve for insulin following a 60-minute glucose tolerance test was reduced over 60% in 30 week-old rats relative to CF (Malloy et al., 2006). This response was also conserved in 90 week-old MR rats (Malloy et al., 2006). A consequence of impaired insulin response is dyslipidemia, one of a cluster of abnormalities associated with the metabolic syndrome. Aging-associated increase of adiposity in both humans and

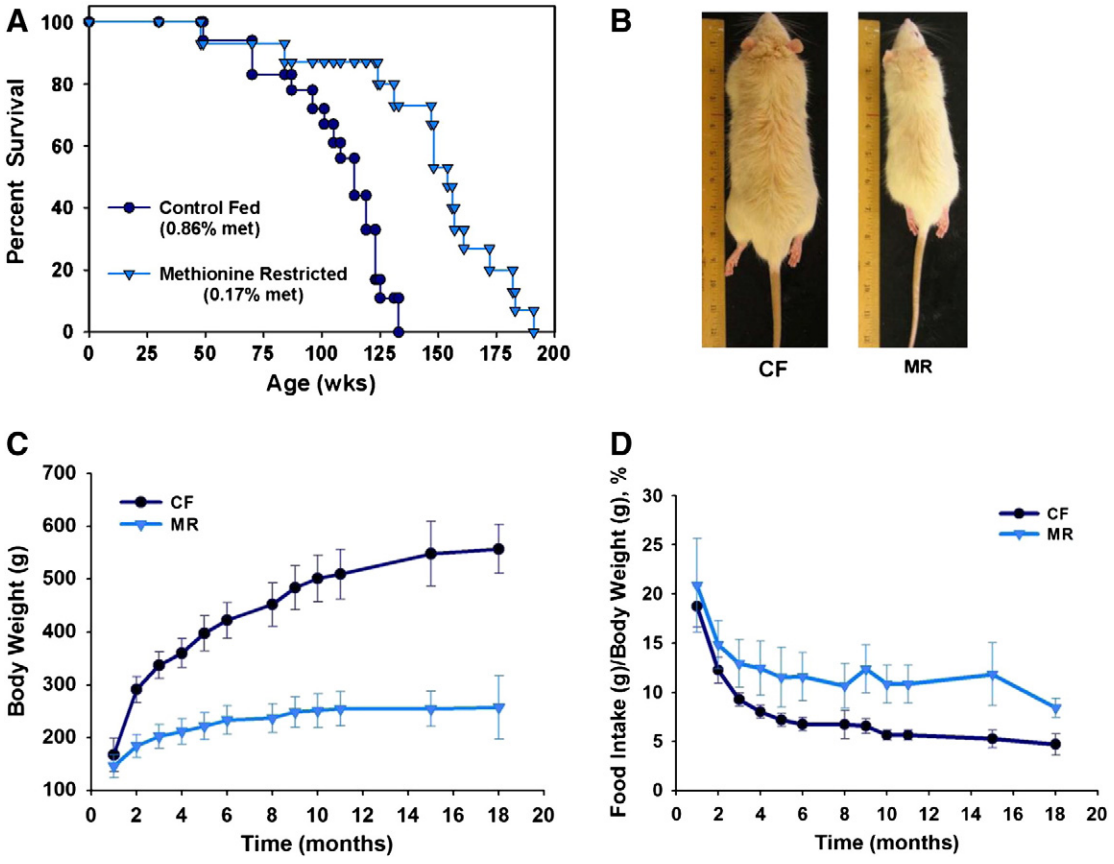

Fig. 1. MR increases median and maximal lifespan in F344 rats (panel A). Although MR significantly decreases body weight gain in rats (panels B and C), food consumption adjusted for total body weight shows that MR rats are hyperphagic (panel D) and, therefore, MR-mediated reduction in body weight is not a response to decreased caloric intake. Data is expressed as the mean ± SEM.