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Calorie restriction and methionine restriction in control of endogenous hydrogen sulfide production by the transsulfuration pathway

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ABSTRACT

H_2S is a gas easily identified by its distinctive odor. Although environmental exposure to H_2S has been viewed alternately as therapeutic or toxic through the centuries, H_2S has recently regained recognition for its numerous beneficial biological effects. Most experiments documenting such benefits, including improved glucose tolerance, increased stress resistance, and even lifespan extension, are based on exposure of experimental organisms to exogenous sources of H_2S. However, appreciation is growing for the importance of H_2S produced endogenously by the evolutionary conserved transsulfuration pathway (TSP) in health and longevity. Recent data implicate H_2S produced by the TSP in pleiotropic benefits of dietary restriction (DR), or reduced nutrient/energy intake without malnutrition. DR, best known as the most reliable way to extend lifespan in a wide range of experimental organisms, includes various regimens aimed at either reducing overall calorie intake (calorie restriction, intermittent/every-other-day fasting) or reducing particular nutrients such as protein or the essential amino acid, methionine (methionine restriction), with overlapping functional benefits on stress resistance, metabolic fitness and lifespan. Here we will review the small but growing body of literature linking the TSP to the functional benefits of DR in part through the production of endogenous H_2S, with an emphasis on regulation of the TSP and H_2S production by diet and mechanisms of beneficial H_2S action.

1. Introduction

1.1. Dietary restriction

Dietary restriction (DR) encompasses a variety of regimens characterized by nutrient and/or energy restriction leading to generally beneficial, but reversible, adaptive changes on the organismal level. Because DR-related nomenclature is poorly defined, we will refer to regimens involving restriction of total food intake as calorie restriction (CR) in order to contrast them with regimens in which individual macronutrients such as protein, or specific amino acids such as methionine, are restricted (MetR) without enforced food restriction. CR and MetR result in overlapping phenotypes and associated benefits in multiple organisms, and as described below, may also share similar underlying mechanisms of benefits.

1.1.1. Calorie restriction

CR was originally identified as a lifespan extending regimen in rodents, and has been used as an experimental tool for nearly a century with which to study underlying mechanisms of the aging process. Functionally, CR regimens are diverse and organism specific; for example, in yeast reducing glucose the media from 2% to 0.5% extends chronological and replicative lifespan, while in rodents daily restriction of food by 40% or alternating days of fasting and ad libitum feeding (every-other-day fasting) represent two extremes of CR regimens leading to longevity extension, improved metabolic fitness and multiple stress resistance (Anson et al., 2005). In recent decades, evolutionarily conserved pathways involved in nutrient and energy sensing, including IIS, mTOR, AMPK, sirtuins, and GCN2 have been implicated in regulation of aging by CR, and associated benefits including stress resistance (Fontana et al., 2010). Because CR benefits are gained and lost rapidly upon the change from ad libitum to restricted feeding and vice versa, underlying mechanisms most likely involve adaptive changes linked to nutrient/energy restriction signal transduction pathways and downstream transcription factors including FOXO (Greer et al., 2007), NRF2 (Bishop and Guarente, 2007; Pearson et al., 2008), CREB (Mair et al., 2011) and ATF4 (Li et al., 2014). Nonetheless, evolutionarily conserved molecular requirements downstream of such transcriptional changes remain largely unresolved.

1.1.2. Methionine restriction

MetR also extends lifespan and stress resistance in yeast (Johnson and Johnson, 2014; Ruckenstuhl et al., 2014; Wu et al., 2013), flies (Troen et al., 2007), worms (Cabreiro et al., 2013) and rodents (Miller et al., 2005; Orentreich et al., 1993). In humans, it has been used to compliment cancer treatment (Thivat et al., 2007) and to improve metabolic fitness (Lees et al., 2014; Plaisance et al., 2011). Furthermore, MetR in

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yeast can be phenocopied by genetic manipulation of methionine biosynthetic pathways Met15/17/25 or Met2 and shMTR in human and mouse cells (Fig. 1), imparting multiple stress resistance phenotypes (Johnson and Johnson, 2014). In mammals, MetR benefits actually require combined methionine and cysteine restriction (Elshorbagy et al., 2013), and thus could be more accurately referred to as sulfur amino acid (SAA) restriction. Because MetR regimens in rodents are given on an ad libitum basis without enforced restriction of calorie intake, it is currently unclear to what degree SAA restriction and CR share underlying molecular mechanisms of protection despite clear phenotypic overlap (Lopez-Torres and Barja, 2008). Evidence in favor of mechanistic overlap comes from flies, in which CR-mediated lifespan extension can be specifically abrogated by essential amino acids (EAA) including Met, but not EAA lacking Met (Grandison et al., 2009); and in mice, where SAA abrogate benefits of stress resistance (Hine et al., in press) as discussed further below.

1.2. Hydrogen sulfide

H_2S gas is released into the environment from inorganic sources or produced by sulfate-reducing bacteria, and is thus found in varying concentrations from different sources including well-water, thermal baths and volcanoes. When present in high concentrations, H_2S blocks respiration by inhibiting cytochrome c oxidase and interfering with iron-dependent biochemical reactions. However, as is typical of hormetic compounds that are toxic at high doses, at lower doses H_2S has a number of beneficial effects, probably via a variety of different mechanisms (discussed below). Interestingly, although H_2S was in vogue for centuries past as a cure-all (Forster, 1994), it is currently viewed by environmental/regulatory bodies as hazardous with little to no acceptable level of exposure (WHO, 2003). Nonetheless, in biology and medicine, interest in H_2S has entered a renaissance since the recognition that it acts as a vasodilator, similar to nitric oxide (NO) and carbon monoxide (CO), and has a number of other benefits in health and medicine (Zhang et al., 2013).

1.2.1. Exogenous hydrogen sulfide benefits

Exposure to exogenous H_2S can induce a state of suspended animation in rats, allowing them to survive hypoxia over six hours without irreversible effects (Blackstone et al., 2005; Blackstone and Roth, 2007). H_2S can also protect against global ischemia associated with severe blood loss (Morrison et al., 2008). In yeast and worms, H_2S significantly extends median lifespan (Hine et al., in press; Miller and Roth, 2007). Furthermore, H_2S is beneficial against metabolic syndrome (Xue et al., 2013), cancer (Lee et al., 2011, 2014), neurodegeneration (Kida et al., 2011), and multiple stress resistance, including heat shock in worms (Miller et al., 2011) and oxidative stress and hypoxia in mammalian cells (Hine et al., in press; Wen et al., 2013).

1.2.2. Endogenous hydrogen sulfide benefits

H_2S is also produced endogenously by organisms including mammals via the transsulfuration pathway (TSP) via the tandem enzymatic activity of CBS and CGL (Kimura, 2011). The importance of endogenous H_2S production was first demonstrated in mice lacking CGL, the final

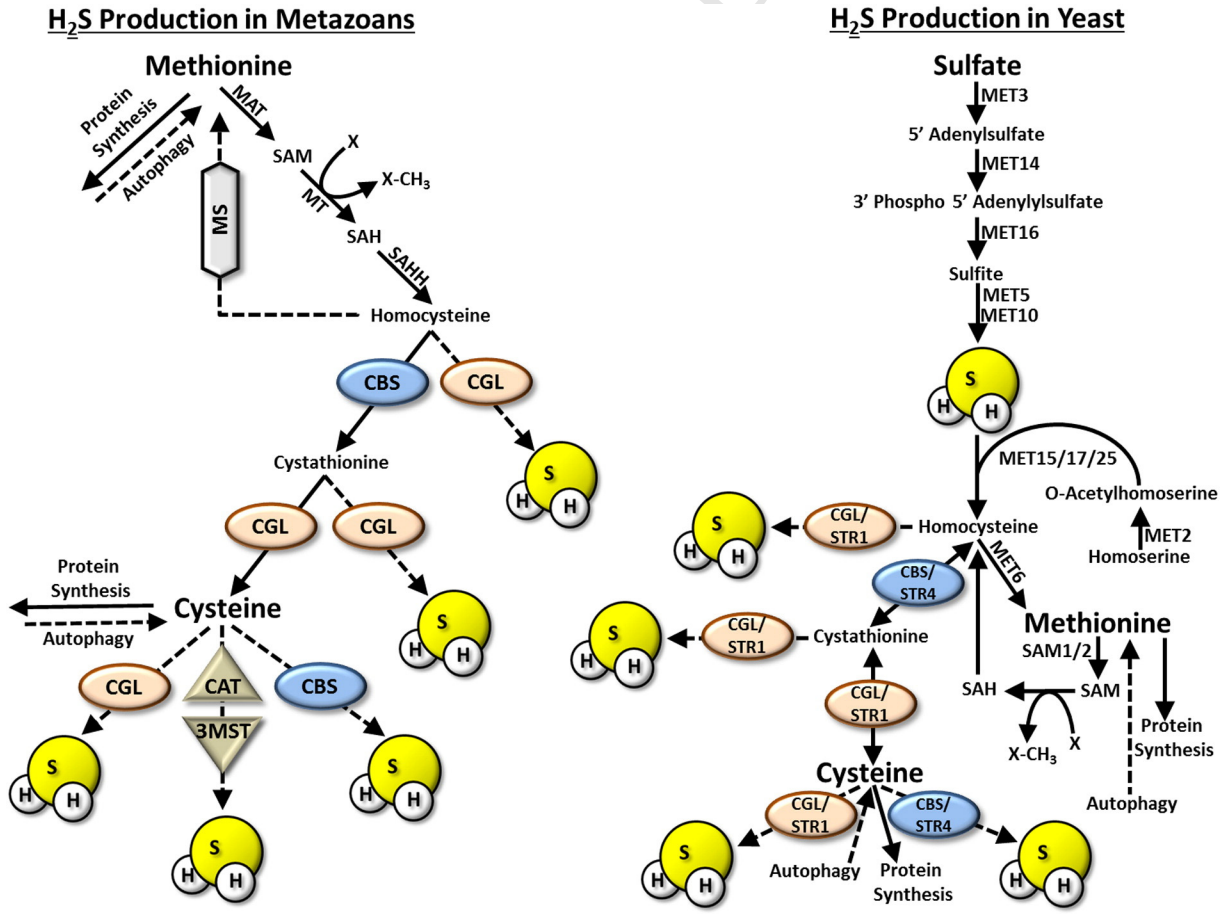

Fig. 1. Pathways of hydrogen sulfide production. Model of the transmethylation and transsulfuration pathway (TSP) in metazoans (left) and in yeast (right). Solid arrows trace canonical sulfur transfer from Met to Cys; metazoans, or from inorganic sulfate and/or Met to Cys; yeast, through various metabolites and downstream cellular processes via the enzymes Cystathionine Beta-Synthase (CBS)(STR4) and Cystathionine Gamma-Lyase (CGL)(STR1). Dotted arrows trace alternative pathways/usage of transmethylation products or TSP genes for production of H_2S. MAT: methionine adenosyl transferase, SAM: S-adenosylmethionine, SAH: S-adenosylhomocysteine, SAHH: S-adenosylhomocysteine hydrolase, and MS: methionine synthase.

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