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Research Paper

Low sulfide levels and a high degree of cystathionine β-synthase (CBS) activation by S-adenosylmethionine (SAM) in the long-lived naked mole-rat

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ABSTRACT

Hydrogen sulfide (H_2S) is a gaseous signalling molecule involved in many physiological and pathological processes. There is increasing evidence that H_2S is implicated in aging and lifespan control in the diet-induced longevity models. However, blood sulfide concentration of naturally long-lived species is not known. Here we measured blood sulfide in the long-lived naked mole-rat and five other mammalian species considerably differing in lifespan and found a negative correlation between blood sulfide and maximum longevity residual. In addition, we show that the naked mole-rat cystathionine β-synthase (CBS), an enzyme whose activity in the liver significantly contributes to systemic sulfide levels, has lower activity in the liver and is activated to a higher degree by S-adenosylmethionine compared to other species. These results add complexity to the understanding of the role of H_2S in aging and call for detailed research on naked mole-rat transsulfuration.

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1. Introduction

Hydrogen sulfide (H_2S) is a gasotransmitter playing a role in many physiological and pathological processes e.g. inflammation, apoptosis, cellular energetics, vascular contractility. Known molecular mechanisms underlying H_2S effects include activation of ion channels, regulation of second messengers (cAMP, cGMP, free calcium) levels, and protein sulfhydration [1]. In mammals, H_2S is produced mainly by two enzymes of the evolutionarily conserved transsulfuration pathway, cystathionine β-synthase (CBS, EC 4.2.1.22) and cystathionine γ-lyase (CSE, EC 4.4.1.1), as well as 3-mercaptopyruvate sulfurtransferase (MST, EC 2.8.1.2).

CBS is a key regulatory enzyme at the intersection of the transsulfuration pathway and methionine cycle, controlling the flux of methionine into transsulfuration (Fig. 1B). In the canonical reaction CBS catalyses condensation of homocysteine and serine to form cystathionine and water. However, when cysteine is used instead of serine, cystathionine and H_2S are produced. CBS is a pyridoxal 5'-phosphate and heme dependent enzyme consisting of three structural domains: (i) N-terminal heme binding domain, (ii) catalytic core, and (iii) C-terminal regulatory domain with an autoinhibitory function (Fig. 1A). Binding of a universal methyl group donor S-adenosylmethionine (SAM) to the regulatory domain activates and stabilizes the enzyme [2,3].

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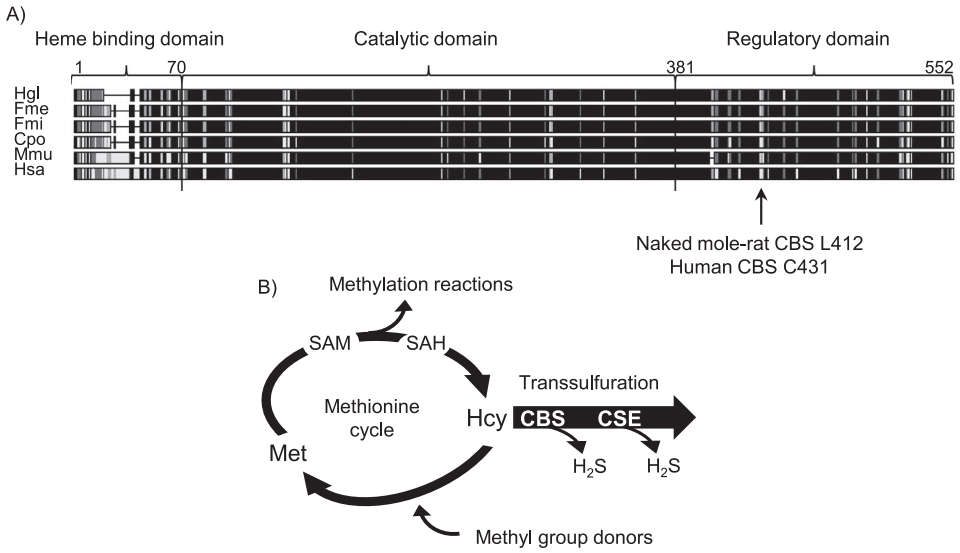

Fig. 1. CBS – an H_2S producing enzyme. (A) Six-species CBS sequence alignment. CBS consists of three domains. The mole-rat C412L substitution is located in the regulatory domain. Hgl – *H. glaber*, Fme – *F. mechowii*, Fmi - *F. micklemi*, Cpo – *C. porcellus*, Mmu – *M. musculus*, Hsa – *H. sapiens* (B) A simplified scheme showing the role of CBS in sulfur metabolism. Met – methionine, hcy – homocysteine.

Although there is increasing evidence that H_2S is implicated in aging and lifespan control, its exact role in these processes is still not clear. Exogenous H_2S increases lifespan in *Caenorhabditis elegans* [4]. Moreover, CBS is required for the life-prolonging effect of caloric restriction in *Drosophila* [5], and increased H_2S production in models for diet-induced longevity was observed [6]. In contrast, a decrease in CBS protein levels and activity in response to methionine and isocaloric protein restriction, respectively, was shown [2,7].

Importantly, sulfide concentration in naturally long-lived species remains unknown. A measure of longevity employed in this study is maximum longevity residual, which represents the relationship of the observed maximum lifespan of the species to its expected, body size-based lifespan calculated with the mammalian allometric equation [8]. Human and naked mole-rat belong to species with the highest maximum longevity residual. The naked mole-rat (*Heterocephalus glaber*) is a eusocial subterranean rodent native to East Africa. It has become the focus of increased attention in the field of aging and cancer research due to its extremely long life- and healthspan [9] as well as its resistance to cancer [10]. Here, we determine blood sulfide concentrations in six mammals (naked mole-rat, human, mouse, guinea pig, *Fukomys mechowii*, *Fukomys micklemi*) differing in their maximum longevity residual. In addition, since CBS activity in the liver significantly contributes to the circulating H_2S levels [11], we comparatively analyse the naked mole-rat *CBS* gene.

2. Material and methods

2.1. Animals

Naked mole-rat colonies are maintained at Leibniz Institute for Zoo and Wildlife Research, Berlin, Germany in an artificial burrow system with tunnels and plexiglass boxes. The system is heated to 26–29 °C with a constant high relative humidity of 60%–80%. The chambers contain wood bedding, twigs and unbleached paper tissue. Fresh food is given daily *ad libitum* and includes sweet potatoes, carrots, fennel, apples, a cereal supplement containing vitamins and minerals, and oat flakes. Sampling was approved by the local ethics committee of the "Landesamt für Gesundheit und Soziales", Berlin, Germany (#ZH 156).

F. micklemi and *F. mechowii* are maintained at the animal facilities of the Department of General Zoology, University of Duisburg-Essen, Germany. They are housed as family groups in glass terraria on horticultural peat and fed *ad libitum* with carrots and potatoes every day, apples every second day, and grain and lettuce once a week. Room temperature and humidity is kept constant at 24 ± 1 °C and 40 ± 3%, respectively. Sampling was approved by Landesamt für Natur-, Umwelt- und Verbraucherschutz Nordrhein-Westfalen (Az. 84-02.04.2013.A164).

Guinea pigs (*Cavia porcellus*, Dunkin Hartley HsdDhl:DH) were purchased from Harlan Laboratories, AN Venray, Netherlands. Animals are maintained at Leibniz Institute for Zoo and Wildlife Research, Berlin, Germany under room conditions in plastic cages with litter and hay as bedding. The range of the room temperature is 18–20 °C and of the humidity 40–50%. Fresh food is given daily and includes carrot, cucumber, salad, apples, and dry feed. Sampling was approved by the local ethics committee of the "Landesamt für Gesundheit und Soziales", Berlin, Germany (G02217/12).

Mice (*Mus musculus*, C57BL/6) were maintained at the Center of Sepsis Control and Care (Jena University Hospital, Jena, Germany). They were maintained under artificial day-night conditions at room temperature, and received a standard diet and water *ad libitum*. Animals were randomly selected for each experiment. Sampling was approved by Thüringer Landesamt für Verbraucherschutz (02-035/12).

2.2. Human samples

Blood samples were obtained from healthy volunteers of European origin after written informed consent and approval by the Jena University Ethics Committee (3624-11/12).

2.3. Quantification of sulfide in whole blood

Sulfide was measured by GC/MS after extractive alkylation using a bis-pentafluorobenzyl derivative. The method and its calibration were described in detail in [12]. 25 μl blood was used and the volume of the reaction mixture was adjusted accordingly. Species and sampling information is listed in Table 1.

Blood sulfide level was correlated with maximum longevity residual obtained from the AnAge database (http://genomics.senescence.info/species accessed on 14.09.2015). Of note, there are

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