GeroScience (2018) 40:359–360
https://doi.org/10.1007/s11357-018-0035-x

LETTER TO THE EDITOR

The high degree of cystathionine β-synthase (CBS) activation by S-adenosylmethionine (SAM) may explain naked mole-rat's distinct methionine metabolite profile compared to mouse

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Received: 31 May 2018 / Accepted: 2 July 2018 / Published online: 7 August 2018

We read with interest the recent paper by Lewis et al. (Lewis et al. 2018), in which the authors determined metabolic profile of the naked mole-rat (NMR). We would like to draw readers' attention to our article on a key enzyme of the methionine metabolism (Dziegelewska et al. 2016) which complements findings of Lewis et al.

Methionine is an essential amino acid. Its metabolism starts with conversion to S-adenosylmethionine (SAM), which acts as a methyl group donor. After methyl group transfer, it is converted to S-adenosylhomocysteine and then to homocysteine which (i) can be remethylated back to methionine, closing the methionine cycle or (ii) enters the transsulfuration pathway, in which cysteine is formed. The crucial regulatory enzyme at this point is cystathionine β-synthase (CBS), which catalyzes the first and rate-limiting step of the transsulfuration. CBS activity is increased by SAM and thus adjusts to methionine levels. As the reaction catalyzed by CBS is irreversible, it depletes methionine pool.

Lewis et al. show lower serum levels of methionine and some of its metabolites in NMRs compared to mice (Lewis et al. 2018). The possible reasons for this difference may be diet and distinct features of NMR CBS. NMRs feed on the underground parts of plants, such as roots and tubers, which are low in methionine. As pointed out by Lewis et al., an additional source of methionine may be coprophagia as well as supplementation with protein-rich cereal in captivity. Our work on NMR CBS may explain, at least in part, why methionine levels remain low despite these additional methionine sources. We showed that NMR CBS is activated to a higher degree by SAM compared to mouse and human (Dziegelewska et al. 2016). This suggests that when methionine is abundant, the flux into the transsulfuration, and hence depletion of methionine from methionine cycle, is higher in NMR. This goes in line with the fact that Lewis et al. observed no difference in the levels of cysteine. High activation of CBS by SAM could provide an evolutionary forced mechanism for "endogenous methionine restriction" in the NMR.

As methionine restriction prolongs lifespan (Lee et al. 2016) and the flux into the transsulfuration is increased in the long-lived Ames dwarf mice (Uthus and Brown-Borg 2006), it appears that high activation level of NMR CBS could contribute to the extraordinarily long lifespan of this species in support of evolutionary theories of aging.

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