Production of the Neuromodulator H_2S by Cystathionine Beta Synthase via the Condensation of Cysteine and Homocysteine

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Abstract

Hydrogen sulfide (H_2S) has been observed in relatively high concentrations in the mammalian brain and has been shown to act as a neuromodulator[1]. However, there is confusion in the literature regarding the actual source of H_2S production. Reactions catalyzed by the cystathionine beta-synthase enzyme (CBS) are one possible source for the production of H_2S. Here we show that the CBS enzyme can efficiently produce H_2S via a beta-replacement reaction in which cysteine is condensed with homocysteine to form cystathionine and H_2S. The production of H_2S by this reaction is at least 50 times more efficient than that produced by hydrolysis of cysteine alone via beta-elimination. Kinetic studies demonstrate that the K_m and K_{cat} for cysteine is 3-fold higher and 2-fold lower, respectively, than that for serine. Consistent with these data, in vitro reconstitution studies show that at physiologically relevant concentrations of serine, homocysteine, and cysteine, about 5% of the cystathionine formed is from cysteine. We also show that AdoMet stimulates this H_2S producing reaction but that there is no evidence for stimulation by calcium and calmodulin as reported previously. In summary, these results confirm the ability of CBS to produce H_2S, but show in contrast to prior reports that the major mechanism is via beta-replacement and not cysteine hydrolysis. In addition, these studies provide a biochemical explanation for the previously inexplicable homocysteine-lowering effects of N-acetylcysteine treatments in humans.

Reference

1. Kimura. H. Hydrogen sulfide as a neuromodulator. (2002) Mol. Neurobio., 26(1), 13-19.