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A diet rich in taurine, cysteine, folate, B_{12} and betaine may lessen risk for Alzheimer's disease by boosting brain synthesis of hydrogen sulfide

Mark F. McCarty[a,*], James H. O'Keefe[b], James J. DiNicolantonio[b]

[a] Catalytic Longevity, San Diego, CA, United States
[b] Saint Luke's Mid America Heart Institute, Kansas City, MO, United States

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ABSTRACT

The gaseous physiological modulator hydrogen sulfide (H_2S) has recently been shown to exert a variety of neuroprotective effects. In particular, the treatment of transgenic mouse models of Alzheimer's disease (AD) with agents that release H_2S aids preservation of cognitive function, suppresses brain production of amyloid beta, and decreases tau phosphorylation. The possible physiological relevance of these findings is suggested by the finding that brain and plasma levels of H_2S are markedly lower in AD patients than matched controls. Hence, nutraceutical strategies which boost brain synthesis or levels of H_2S may have potential for prevention of AD. The chief enzyme which synthesizes H_2S in brain parenchyma, cystathionine beta-synthase (CBS), employs cysteine as its rate-limiting substrate, and is allosterically activated by S-adenosylmethionine (SAM). Supplemental taurine has been shown to boost expression of this enzyme, as well as that of another H_2S source, cystathionine gamma-lyase, in vascular tissue, and to enhance plasma H_2S levels; in rats subjected to hemorrhagic stroke, co-administration of taurine has been shown to blunt a marked reduction in brain CBS expression. Brain levels of SAM are about half as high in AD patients as in controls, and this is thought to explain the reduction of brain H_2S in these patients. These considerations suggest that supplementation with cysteine, taurine, and agents which promote methyl group availability – such as SAM, folate, vitamin B_{12}, and betaine – may have potential for boosting brain synthesis of H_2S and thereby aiding AD prevention. Indeed, most of these agents have already demonstrated utility in mouse AD models – albeit the extent to which increased H_2S synthesis contributes to this protection remains unclear. Moreover, prospective epidemiology has associated low dietary or plasma levels of folate, B12, and taurine with increased dementia risk. Rodent studies suggest that effective nutraceutical strategies for boosting brain H_2S synthesis may in fact have broad neuroprotective utility, possibly aiding prevention and/or control not only of AD but also Parkinson's disease and glaucoma, while diminishing the neuronal damage associated with brain trauma or stroke.

Biological gases may aid prevention of Alzheimer's disease

In mouse models of Alzheimer's disease (AD), nitric oxide (NO) of vascular origin – synthesized by the endothelial nitric oxide synthase (eNOS) – has been shown to slow onset of cognitive dysfunction by suppressing the production of amyloid beta peptides [1–3]. This effect of NO is mediated by cGMP, and reflects decreased transcription of amyloid precursor protein (APP) and of the beta-secretase (BACE1) which catalyzes the initial cleavage required for amyloid beta production. NO of vascular origin can also decrease brain microglial activation and suppress tau phosphorylation [4]. Hence, it has been proposed that practical measures which optimize cerebrovascular eNOS activity may have value for preventing or slowing the onset of AD, and that this phenomenon may help to explain the fact that vascular risk factors associated with endothelial dysfunction have emerged as risk factors for AD [5,6].

Another biological gas produced by the vasculature, hydrogen sulfide (H_2S), has recently been shown to have a range of neuroprotective properties in high physiological concentrations, presumably reflecting the modulatory effects of reversible conversion of protein cysteine groups to persulfides [7,8]. In particular, H_2S is protective in rodent models of AD. Treatment of AD model mice, such as the 3xTg-AD strain, with H_2S releasing chemicals or H_2S-rich spa water, administered peritoneally, has been shown to promote conservation of cognitive function, decrease brain levels of amyloid beta, and lessen tau phosphorylation [9–13]. The reduction in amyloid beta appears to reflect decreased production stemming from down-regulation of the proteases required for its production – BACE1 and gamma-secretase (presenilin-1)

* Corresponding author at: Catalytic Longevity, 811 B Nahant Ct., San Diego, CA 92019, USA.
E-mail address: markfmccarty@gmail.com (M.F. McCarty).

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– and up-regulation of the alpha-secretase (ADAM17) which diverts APP metabolism to a harmless pathway [10]. Additionally, decreased brain levels of APP have been reported in H_2S-treated 3xTg-AD mice [12]. Hence, H_2S appears to exert effects on APP processing that are similar and complementary to those of NO. Indeed, the benefit of H_2S in this regard may reflect, at least in part, the ability of H_2S to promote efficient NO signaling by a range of actions [14].

However, H_2S may achieve neuroprotection in AD by additional mechanisms. Rodent studies have found that H_2S opposes microglial polarization toward a pro-inflammatory M1 phenotype, and stems inflammasome activation (responsible for production of interleukin-1β, thought to play a pathogenic role in AD [15,16]) by decreasing expression of the P2X7 receptor [17,18]. Activation of neuronal ATP-sensitive channels in neurons may also contribute to H_2S-mediated neuroprotection [19].

The protective effects of endogenous or exogenous H2S in rodent models of AD are particularly intriguing in light of a report that brain levels of H_2S are markedly lower (by over 50%) in the brains of AD victims than in those of matched controls [20]. Moreover, plasma levels of H_2S are lower in AD patients than in controls [21]. Expression of the enzyme primarily responsible for H_2S synthesis in the brain, cystathionine beta-synthase (CBS), is no lower than it is in control brains, and brain cysteine levels are also comparable. However, brain levels of S-adenosylmethionine (SAM), a compound that allosterically activates CBS by 2–3 fold, are markedly lower in AD brains, which likely explains why H_2S levels are decreased [20,22,23]. Additionally, levels of SAM and the ratio of SAM to S-adenosylhomocysteine (an index of methylation capacity) have been found to be decreased in the cerebrospinal fluid of AD patients – albeit an earlier study failed to observe this [24,25]. Why brain SAM levels are depressed in AD remains unclear. In any case, measures that boost brain SAM levels likely would ameliorate the deficit of H_2S in AD brains.

Dietary/nutraceutical support for brain hydrogen sulfide synthesis

In light of evidence that H_2S favorably influences AD pathogenesis in rodent models, and that H_2S levels are depressed in the brain and plasma of AD patients, it is reasonable to speculate that this deficit of H_2S activity contributes to the pathogenesis of AD. If this is the case, then practical measures which boost brain levels of H_2S – either by increasing brain synthesis of this compound, or boosting its plasma levels – may have some utility for preventing or slowing AD onset.

The K_m of CBS for cysteine is high – about 6.8 mM – in comparison to tissue levels of this amino acid (around 100 μM) [26]. Hence, a diet relatively rich in cysteine – or supplementation with adequate amounts of N-acetylcysteine – would be expected to increase brain synthesis of H_2S by mass action. The enzyme chiefly responsible for H_2S synthesis in vascular tissue, cystathionine gamma-lyase (CSE), likewise has a K_m for cysteine far higher than ambient cysteine levels, so increased cysteine intake would likely boost vascular production of H_2S as well [26,27]. N-acetylcysteine is subjected to esterase activity soon after absorption, giving rise to cysteine; it is commonly employed as an oral supplement for boosting tissue cysteine levels since, as compared to cysteine itself, it is more stable (less prone to disulfide formation), better tolerated, and more efficiently absorbed [28].

There is recent evidence that supplemental taurine can enhance vascular production of H_2S. In normotensive and hypertensive mice treated with oral taurine, vascular expression of both CSE and CBS was enhanced; in human mesenteric arteries exposed ex vivo to taurine, taurine dose-dependently increased expression of both of these enzymes [29]. In pre-hypertensive subjects treated with oral taurine 1.6 g daily), plasma H_2S approximately doubled, and both clinic and ambulatory blood pressures were decreased significantly [29]. Since H_2S is known to exert a range of vascular-protective effects, these new findings might finally rationalize, at least in part, the well-documented protective impact of taurine on rodent models of atherosclerosis, hypertension, and heart failure [30,31]. It is therefore important to determine if taurine can up-regulate expression of CBS in the brain, as it does in the vasculature. Intriguingly, a very recent report indicates that induction of intracerebral hemorrhage in rats markedly reduces expression of CBS and H_2S in peri-hematomal brain regions, but that i.p. administration of 50 mg/kg taurine immediately after hemorrhage induction largely prevented this reduction in CBS and H_2S [32]. Taurine treatment also reduced brain edema, neuronal damage, and inflammatory response; this benefit might be at least in part owing to maintenance of H_2S synthesis, as administration of sodium hydrosulfide has previously been shown to be protective in the same model [18]. Unfortunately, the researchers did not report whether taurine administration could boost brain expression of CBS in control mice; hence, it is not yet clear whether taurine can directly stimulate CBS expression, or whether it just offsets the negative impact of certain pathogenic signals on its expression; in any case, it appears that taurine can support CBS activity in certain types of neuropathology. An increase in plasma levels of H_2S stemming from increased vascular production might also be expected to confer a measure of neuroprotection.

A deficit of brain SAM appears to be largely responsible for the decrease in H_2S levels observed in AD brains. Hence, measures which enhance brain SAM levels may have potential for prevention of AD. While it is possible to administer SAM directly as a nutraceutical, its relatively high cost make it less than ideal as a tool for primary prevention. However, less expensive measures for promoting re-methylation of homocysteine – thereby re-synthesizing methionine and boosting SAM synthesis – are available. Insuring optimal dietary intakes of folate and vitamin B12 can promote homocysteine re-methylation via the one-carbon folate pool. Additionally, dietary or supplemental betaine can promote re-methylation of homocysteine via the enzyme betaine homocysteine methyltransferase [33]. Impressively, a standard serving of steamed leaf spinach (100 g) provides about 580 mg of betaine and about 200 mcg folic acid; hence, daily ingestion of spinach may represent a practical strategy for supporting methylation reactions in the brain and other tissues.

CBS can employ a range of different reactions to liberate H_2S from cysteine. Under physiological conditions, the reaction in which cysteine interacts with homocysteine to generate cystathionine and H_2S is by far the most significant [34]. Since re-methylation of homocysteine to generate methionine and SAM could be expected to decrease the availability of a key substrate for CBS, it might be argued that the increased activation of CBS promoted by SAM would be offset by a reduction in substrate for this enzyme, such that the impact on flux through CBS would be equivocal. However, kinetic studies have shown that varying homocysteine within physiological levels has minimal impact on flux through CBS, whereas cysteine levels markedly influence this flux [26]. In this regard, homocysteine levels in AD brains were found to be about double those found in control brains – yet H_2S synthesis was markedly diminished [20]. Hence, nutritional measures which promote homocysteine re-methylation would indeed be expected to enhance H_2S synthesis via allosteric activation of CBS by SAM.

Fig. 1 summarizes mechanisms whereby nutraceuticals may support cerebral synthesis of H_2S via CBS.

Evidence pertaining to impact of cysteine, taurine, and methylation catalysts on AD risk

Studies in animal models of AD and in neuronal cell cultures, as well as epidemiological findings, are reasonably supportive of the possibility that cysteine, taurine, SAM, folate, and betaine can favorably influence the development of AD, albeit none of these provide evidence bearing on the role of H_2S in mediating this protection. In particular, many studies point to low methylation status as a risk factor for AD [35]. While diminished brain H_2S production may play a role in this effect, up-regulated transcription of certain AD-promoting genes, stemming from decreased promoter methylation, also appears to play a role in this

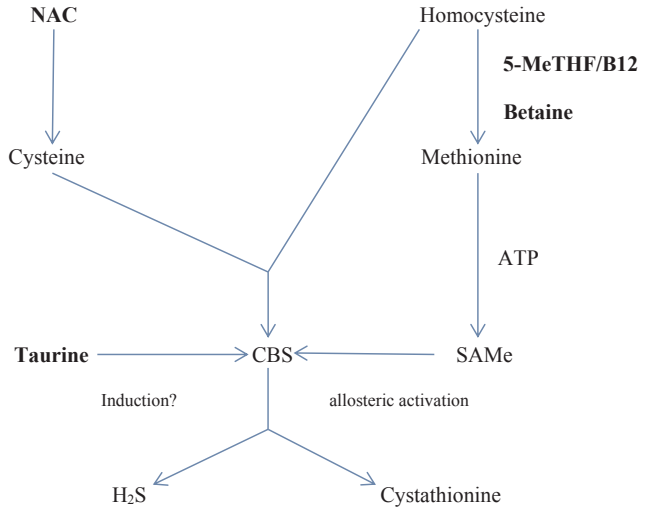

Fig. 1. Nutraceutical support of cerebral synthesis of H_2S via Cystathionine β-Synthase. 5-MeTHF = 5-methyltetrahydrofolate.

regard. Indeed, AD is characterized by a global reduction in DNA methylation in the frontal cortex and hippocampus, and by decreased promoter methylation of the APP, BACE-1, and PS1 genes [36–40]. In AD model mice, folate deficiency accelerates the onset of brain amyloidosis, whereas concurrent SAM supplementation alleviates this effect [41–45]. Addition of SAM to a normal diet also slows development of brain amyloid deposition in 3xTg-AD mice [46]. In APP-transgenic mice, SAM administration prevents hypomethylation of the BACE1 promoter as well as global hypomethylation, and diminishes amyloid pathology [36]. In neuroblastoma cell cultures, SAM exposure down-regulates amyloid beta expression and PS1 expression [47]. With respect to betaine, few if any studies have evaluated its utility in AD model mice – albeit this agent counteracts memory impairment in rats subjected to chronic cerebral hypoperfusion [48]. However, in N2a cells transfected with the Swedish mutant of APP, betaine exposure decreases production of amyloid beta – an effect associated with down-regulation of BACE1 and up-regulation of alpha-secretase activity [49].

With respect to epidemiology, some, though not all [50,51], prospective studies observe a higher risk for AD associated with low folate status or elevated homocysteine [52–56]. In AD patients, plasma folate tends to be low and homocysteine high compared to matched controls [56]. Moreover, the MTHFR C667T polymorphism, which lessens the efficiency of folate-catalyzed methylation, is linked to increased AD risk [57]. The association of dietary betaine with subsequent AD risk has not been assessed. However, in light of the high levels of betaine and folate provided by spinach and other green leafy vegetables, it is intriguing that the Rush Memory and Aging project observed that elderly people who consumed 1–2 servings of green leafy vegetables daily, as compared to those who rarely consumed these vegetables, were about 11 years younger in “mental age” [58,59].

The utility of folate for methyl group transfer is also dependent on adequate vitamin B12 status. Not surprisingly, prospective studies find that sensitive markers for B12 status, such as serum holotranscobalamin, correlate inversely with risk for AD and dementia [56,60–62]. AD is also associated cross-sectionally with lower B12 status. An increase in risk for cognitive impairment among diabetics using metformin might be traceable to impairment of B12 absorption induced by this drug [63,64].

Evidence regarding the impact of cysteine intake – as modulated by supplementation with N-acetylcysteine (NAC) – is somewhat equivocal. NAC administration can aid retention of learning and memory in mice injected with amyloid beta intra-cerebroventricularly, and, in vitro, protects neurons from the toxicity of amyloid beta [65,66]. NAC exposure down-regulates APP transcription in neuroblastoma cells [67]. In APP/PS1 transgenic AD model mice subjected to isolation stress, NAC administration prevents an elevation of amyloid beta and of PS1 levels in the brain, while aiding maintenance of hippocampal long-term potentiation and preservation of contextual-fear memory [68]. Chronic administration of antioxidant cocktails containing NAC, lipoic acid, and sometimes other agents have improved cognition in SAMP8 aging-accelerated mice, and in aging rats, decreased brain levels of BACE1 and amyloid beta-42, while improving spatial learning and memory [69,70]. In Tg2576 AD model mice, such an antioxidant cocktail prevented the decline in cortical- and hippocampal-dependent memory relative to non-transgenic mice, while decreasing brain levels of soluble amyloid beta [71]. On the other hand, a regimen of daily exercise and NAC administration in APP/PS1 transgenic mice was found to have no impact on decline on learning and memory or on brain amyloid deposition and synaptic loss [72]. Furthermore, in stroke-prone spontaneously hypertensive rats, NAC administration was associated with an increase in blood-brain barrier permeability, an increase in cortical amyloid beta plaques, and no change in plaque level elsewhere in the brain [73]. It should be noted that NAC administration could influence brain antioxidant function by enhancing glutathione synthesis, an effect likely enhanced by co-administration of lipoic acid [74]. Hence, many of the effects of supplemental NAC may be independent of H_2S synthesis.

In regard to taurine, administration of taurine in drinking water to APP/PS1 transgenic mice prevented a decline in their performance on Y-maze and passive avoidance tests, while decreasing hippocampal levels of insoluble amyloid beta [75]. It is conceivable that a protective effect of taurine on excitotoxic cell death contributed to this benefit [76,77]. In addition, taurine *in vitro* is reported to act as an agonist for the LXR receptor in macrophages, without however promoting lipid synthesis in hepatocytes [78]. Pharmaceutical liver X receptor (LXR) agonists are suspected to have potential for prevention of AD, as they boost astrocyte secretion of lipidated apoE particles; these in turn act on microglia to promote intra- and extracellular proteolysis of amyloid beta [79–81]. Whether supplementation with taurine can increase LXR activity in the brain has not been studied. A recent analysis of the Framingham cohort has found that higher plasma taurine levels correlate with decreased risk for incident dementia [82].

Summary

Available data do not allow us to conclude that an increase in endogenous H_2S production achieved with increased intakes of cysteine, taurine, and methylation catalysts would be of sufficient magnitude to influence the pathogenesis of AD – though rodent studies indicate that a sufficiently high exposure to H_2S would be protective in this regard. However, there is strong reason to suspect that a diet and/or nutraceutical supplements supporting brain methylation capacity would favorably influence AD risk, in part by altering promoter methylation of genes that play a key role in AD pathogenesis. Taurine has received little study in regard to AD risk, but the few data that are pertinent are promising; an anti-excitotoxic effect may contribute to its utility. Supplemental NAC, at least when accompanied by lipoic acid, is protective in rodent AD models, possibly reflecting, in part, increased glutathione synthesis. The impact of NAC alone has been more equivocal in rodent studies. Rodent studies are needed to define the impact of supplementation with NAC, taurine, and methylation catalysts on H_2S synthesis in the brain, and to assess the influence of such supplementation in AD models.

It may be noted that a nutraceutical strategy that supports effective brain production of H_2S may have more general neuroprotective activity. Indeed, endogenous and exogenous H_2S has been shown to provide protection in rodent models of Parkinson’s disease; skewing of microglial function to an anti-inflammatory M2 phenotype may play an important role in this regard [17,19,83–86]. Favorable effects of H_2S in rodent models of traumatic brain injury, chronic cerebral

underperfusion, intracerebral hemorrhage, and glaucoma have also been reported [18,32,87-89].

Declaration of Competing Interest

JJD is author of The Salt Fix and Superfuel. MFM and JHO are owners of nutraceutical companies.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.109356.

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