Review

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Review

Ergothioneine as a Protective Agent against Age-Related Diseases: Issues Needing More Research

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Abstract

Ergothioneine (ET) is a diet-derived compound that is avidly absorbed and retained by the human body using a specialised transporter, OCTN1. A substantial and growing body of evidence implicates ET in maintaining human health and protecting against age-related diseases, especially neurodegenerative diseases, and multiple studies indicate that low blood ET levels increase the risk of developing age-related diseases. Despite the growing interest in ET, much fundamental work remains to be done on its metabolism, intracellular and intercellular transport (especially in the brain), precise mechanisms of cytoprotection, interactions with the microbiome, mycobiome and human pathogens, and identifying the factors that control body ET levels. This narrative review explores these issues and suggests what research needs to be done to improve our understanding of ET biology.

Keywords: Ergothioneine; OCTN1; antioxidant; mitochondria; mycobiome; microbiome; *M. tuberculosis*

1. Introduction

Ergothioneine (ET; structure shown in Figure 1) is a compound first discovered in 1909; it can only be made by fungi and some bacteria, including cyanobacteria, and a few yeasts [1–11]. Several researchers investigated its properties in the 1940s and 1950s, mostly studying its antioxidant abilities. It was then largely ignored for decades, as reflected by the low number of published papers (Figure 2). Melville [8] provided an excellent review of this early work. When humans consume ET, it is rapidly absorbed by a selective transporter (OCTN1) present in the small intestine (and in many other organs; Figure 3), distributed to all body tissues, avidly retained (half life in the body estimated at several weeks) and renally reabsorbed [1–4,9,10] and there is evidence that ET is passed from mother to child through breast milk and the placenta, since OCTN1 is expressed there [2,3,9,12–14]. These facts strongly suggest that ET is important to the human body: selective transporters are usually only seen for essential vitamins (e.g. vitamin C [15]) and minerals; many other dietary compounds with antioxidant properties (e.g. most polyphenols) are poorly absorbed and rapidly metabolised, so that their concentrations in human tissues and body fluids are very low (reviewed in [2,16]). By contrast, blood and tissue levels of ET in humans and other animals are usually much higher [1–4]. Indeed, this potential importance of ET was recognised as long ago as 1959, by Melville [8], who wrote "*the avidity with which dietary ET is incorporated into tissues of all animals, the tenacity with which it is held there, and its characteristic non-uniform pattern of distribution in these tissues* (see Figure 3) *are all facts which hint that there is a purpose in its presence*". The major dietary source of ET in most populations is mushrooms [6,7,9,11,17]), although smaller amounts are found in other foods such as asparagus, other plants, *spirulina,* meat, fish and even beluga whales [6,7,9,17–19].

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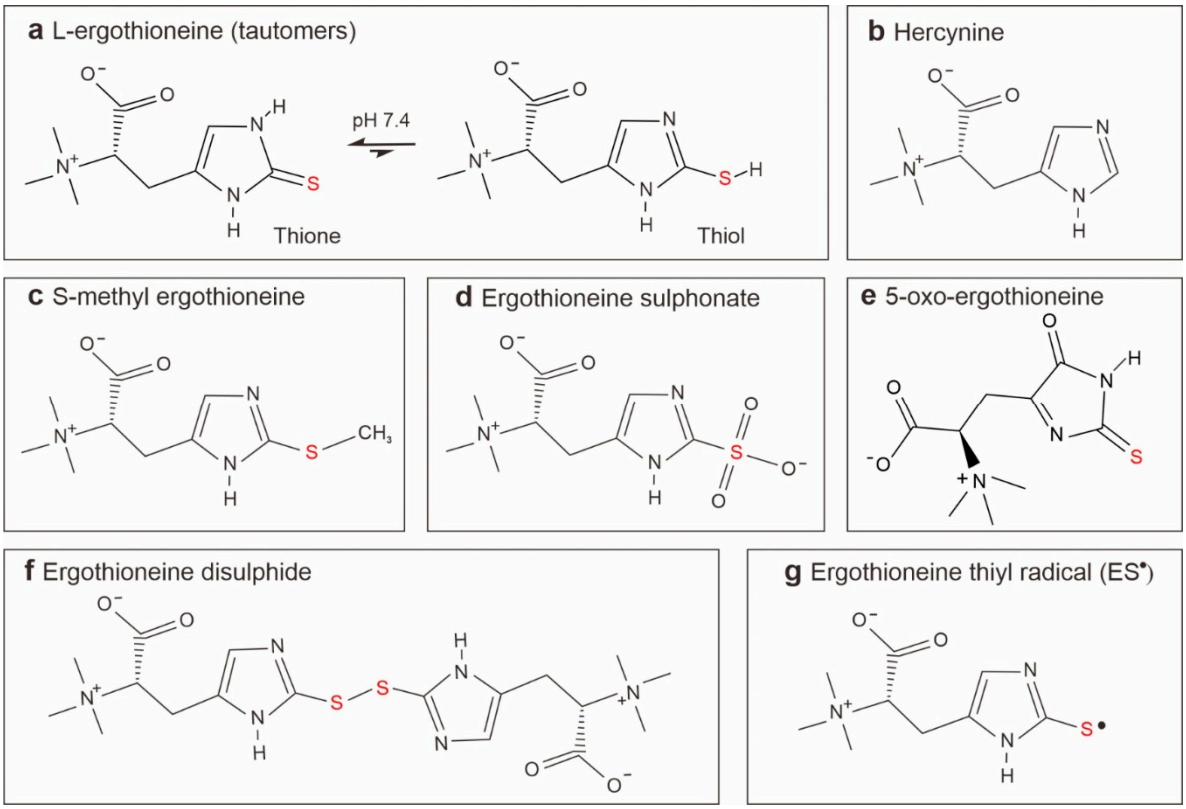

Figure 1. Chemical structures of the (*a*) L-ergothioneine thione-thiol tautomers (the thione form is heavily favoured) and its metabolites (*b*) hercynine, (*c*) *S*-methyl ergothioneine, (*d*) ergothioneine sulphonate. Oxidation products of ET include (*e*) 5-oxoET, (*f*) ET disulphide, and (*g*) a sulphur radical

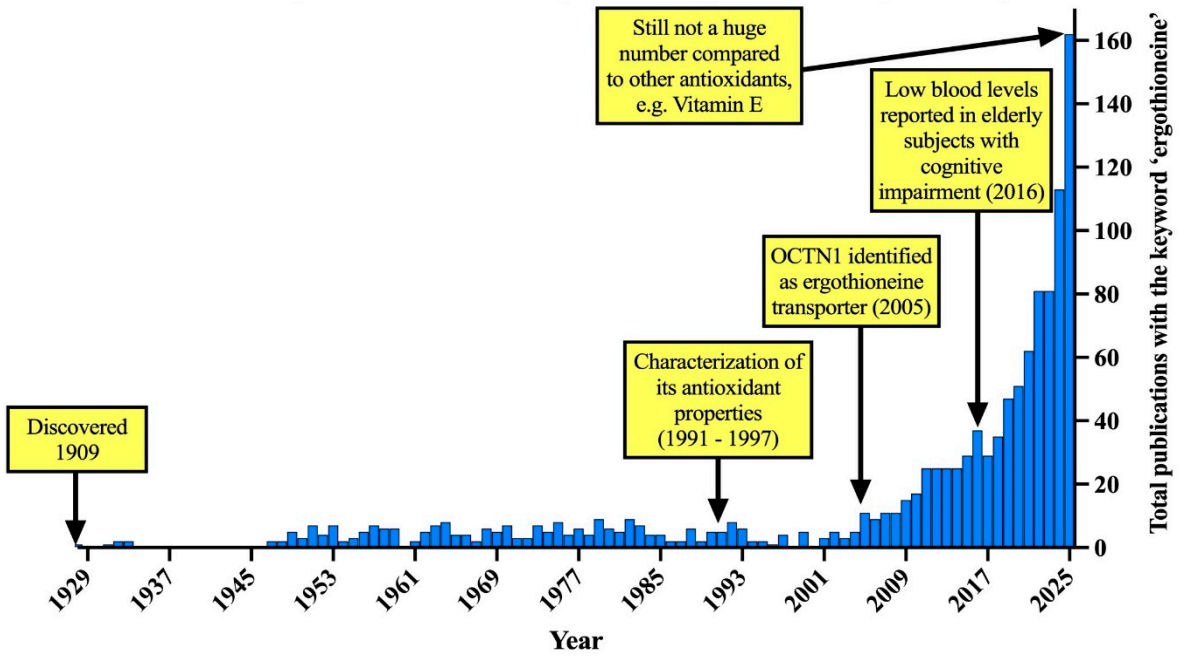

Figure 2. Number of publications with keyword "ergothioneine" (Pubmed).

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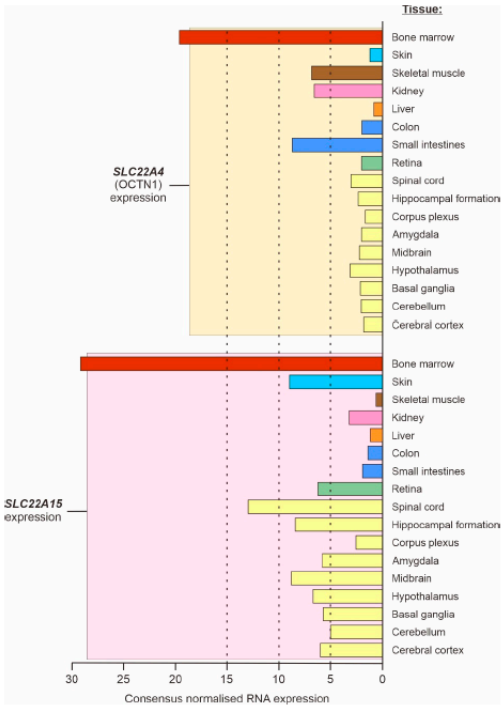

Legend:

Comparison of normalised mRNA expression of *SLC22A4* (OCTN1) and *SLC22A15* across a range of human tissues (data adapted from the Human Protein Atlas; https://www.proteinatlas.org/).

SLC22A4 expression is highest in the small intestine, kidney and skeletal muscles, whereas *SLC22A15* expression is markedly higher in the brain, retina, and skin. Both transporters are expressed abundantly in the bone marrow, and are present in the adult human liver albeit at lower levels.

Figure 3. Expression of transporters in the human brain and other tissues.

The recent increasing interest in ET, as revealed by more publications (Figure 2), was sparked by two factors. One was the identification of OCTN1, encoded by the gene *slc22a4*, as the ET transporter [20–22]. OCTN1 can transport a few other substrates *in vitro* [23] but studies of its transport kinetics reveal that ET is likely to be the major significant substrate *in vivo* [20–22,24,25]. A second factor was the growing realisation, first pointed out in 2016 [26,27], that low blood ET levels in humans are associated with, and can sometimes predict (e.g. [28,29]), increased risk of developing age-related conditions such as cognitive impairment, cardiovascular disease, dementia, frailty, Parkinson's disease and macular degeneration [2–4,26–41], as well as chronic renal disease [42] and pre-eclampsia [43]. Indeed, ET has been suggested to be a compound critical to implantation and pregnancy maintenance [44]. The association of low human ET levels with increased risk of disease appears not to be just correlational: a cause-consequence relationship between low ET levels and the above age-related diseases is strongly suggested by a large number of studies on laboratory animals, cells and other systems showing that ET is highly neuroprotective in models of dementia, stroke, eye disease, hearing loss, neuropathy, sleep disorders and Parkinson's Disease (reviewed in [1–3,31], also see [45–67]). Several pilot human clinical trials have indicated significant neuroprotective effects of ET [68–70] and many others are underway, including a planned trial on kidney dialysis patients, who have very low ET levels because washout of ET during dialysis is combined with its impaired renal reabsorption [71,72].

As a result of the above discoveries, ET is becoming increasingly popularised on social media, podcasts, and talk shows such as You Tube, as a "healthy longevity" agent. The number of published papers on it, although still small (e.g. as compared to papers on the possible health benefits of flavonoids, carotenoids or vitamins C and E), is gradually increasing (Figure 2), although overall awareness of ET among the public and medical professionals is still low. ET is now being sold by itself, or as a constituent of several "longevity supplements", through online platforms such as Amazon. Pure ET appears safe for human consumption and has been approved for human usage by the European and USA Food and Supplement Safety Regulatory Agencies (reviewed in [2,3]). Of course, a major problem revealed by analyses of multiple commercial supplements is poor quality control (QC); a recent example reports that many of the formulations of the popular supplement nicotinamide mononucleotide being sold do not match the contents claimed on the labels [73]. Hence,

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ET for human use should be obtained from a reputable source that has established and validated (ideally externally validated) QC protocols.

Although the number of papers reporting studies with ET is increasing (Figure 2), many of them are reviews or meta-analyses (for some 2025 examples see [74–80]). Very few of these publications, and indeed few research groups globally, are digging down into the basic biochemistry and molecular biology underlying the actions of ET. This lack of fundamental research into ET is unfortunate and needs to be addressed. Let us discuss the areas that the author believes need attention.

2. Ergothioneine Chemistry and Metabolism Have Scarcely Been Explored, Especially in the Brain

The chemistry of ET (and of thiones generally: Figure 1) in relation to biological systems has only been explored to a very limited extent [81–83]. For example, several studies report that ET's unique chemical properties can improve the efficiency of solar cells [84–86] – but the mechanism(s) by which this occurs and their possible relevance to biological systems have not been elucidated. Three metabolites of ET have been identified [2,3], namely hercynine, ET sulphonate and S-methyl ET (Figure 1) but there has been no systematic search for others. S-methyl ET presumably arises by the action of a methyltransferase, but it has not been identified. None of these three compounds is present in mice lacking OCTN1, who have no ET in their tissues [2], suggesting that all three derive from ET. A role for ET in drug metabolism has been suggested: incubation of liver microsomes from several animals with ET and NADPH led to production of ET conjugates with paracetamol, raloxifene, diclofenac, clozapine, carbamazepine, and tamoxifen, among other drugs [87,88]. The significance of this in vivo remains to be discovered, although a raloxifene – ET conjugate has been detected in vivo in rats [87].

It has been suggested that when ET acts as an antioxidant by scavenging various oxygen radicals and other reactive oxygen species (ROS) the sulphonate and hercynine are produced, and thus could be biomarkers of ROS generation [89–91], their levels possibly providing evidence that ET has antioxidant properties *in vivo* (discussed further in section 3 below). However, this needs to be validated *in vivo* in humans by comparison with established biomarkers of ROS generation and oxidative damage (e.g. [10,16,92,93]. Oxidation products of ET exposed to various ROS also include a thiyl radical ($ES^{\bullet}$), ET disulphide and 5-oxoET (Figure 1)[82,83]. The enzymes that act upon ET in humans and other animals and how ET influences the cell and tissue lipidomes, metabolomes and transcriptomes have not been elucidated, although some preliminary proteomic studies have been published in mice [94]. Some of the oxidized forms of ET can be reduced by the enzyme glutathione reductase plus reduced glutathione (GSH) and by thioredoxin reductase [83] but the importance of this *in vivo* needs more investigation. ET has also been reported to inhibit γ-glutamyl transpeptidase, an enzyme on cell surfaces that catalyses the hydrolysis of GSH, although fairly high concentrations of ET are required (K_i ~170 μM) [95]. Nor have the potential biological roles of the three known ET metabolites (and any other metabolites yet to be identified) been investigated. Do they contribute to ET's cytoprotective effects? When ET enters cells, some of it is taken up by mitochondria [5,96], but where the rest of it goes is unknown, nor has the subcellular distribution of OCTN1 been accurately mapped, apart from its presence on plasma membranes [22].

This lack of knowledge of ET distribution, metabolism and any biological effects of its metabolites is especially true for the brain. ET has been reported to be present in human and other animal brains (and in human cerebrospinal fluid) in multiple studies [2,3,9,10,34,97–105], and supplementing with ET increases brain levels in laboratory animal studies [100]. However, no one has yet identified OCTN1 in intact human blood-brain barrier [2,22] although it is present in human brain microvascular endothelial cells and several other regions of the human brain (Figure 3) (reviewed in [2,22]. It thus remains to be discovered how ET enters the human brain, as it clearly does.

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OCTN1 is not the only molecule capable of transporting ET. Another human transporter, SLC22A15, encoded by the *slc22a15* gene, which is not involved in the intestinal absorption of ET but is widespread in the brain (Figure 3), can also transport ET, albeit with much lower affinity (K_m ~ 400 μM) and lower V_{max} compared with OCTN1, K_m ~ 21 μM [9,22,106,107]; the major substrate of SLC22A15 seems to be creatine [108]. Mitochondria from OCTN1-knockout mice can still take up ET, albeit at a slower rate than mitochondria from wild-type mice, and the transport mechanism has not yet been identified [96].

3. The Mechanism(s) of Action of Ergothioneine Is(Are) Unclear and Are Likely to Be Multifactorial

ET is frequently described as an antioxidant, and indeed it can scavenge several important ROS, including hydroxyl radical ($^{\bullet}OH$), hypochlorous acid (HOCl), hypobromous acid (HOBr), ozone (O_3), peroxynitrite ($ONOO^-$/ONOOH) and singlet oxygen, as well as perhaps being able to inhibit the HOCl-generating enzyme myeloperoxidase. It can also render pro-oxidant transition metal ions (Fe^{2+}, Cu^+) less redox active by chelating them. It can scavenge methylglyoxal, acrolein, and possibly other cytotoxic aldehydes that result from lipid peroxidation [2,3,9,89–91,109–116]. Several published papers have presented evidence that ET can activate the "master regulator" of endogenous antioxidant defences, Nrf2, and so raise their levels *in vivo* [50,117–123]. But how ET does this is unclear: does it modify the phosphorylation of keap1 by activating various kinase enzymes [118,121,123–126], or does ET interact directly with the thiol groups on keap1; these are the two usual mechanisms by which Nrf2 is activated [125,126]? These mechanisms need to be elucidated, although *in silico* studies have suggested that ET might bind to the active site of Nrf2 to prevent its proteasomal degradation [120].

Despite its powerful antioxidant activities *in vitro*, evidence that ET exerts significant antioxidant effects *in vivo* remains scarce, as reviewed in [2,10], although if ET only acts as an antioxidant at specific sites where it accumulates in the human body, this would be hard to detect by measuring systemic biomarkers of oxidative stress (reviewed in [16,93,127]. Indeed, tissue injury, which usually leads to increased oxidative damage for a variety of reasons, as reviewed in [16], can promote upregulation of OCTN1 levels, resulting in increased accumulation of ET in the injured tissue. This accumulation has been proposed to be an adaptive cytoprotective mechanism [128], although the protection need not necessarily be by antioxidant action, of course.

Several other lines of evidence also suggest that the antioxidant properties of ET may not be its only mode of action *in vivo*. First, antioxidants have generally shown only limited effectiveness in the treatment or prevention of human diseases [16,127,129–134] whereas ET seems more promising (as reviewed above), although this remains to be fully validated by large-scale double blind placebo controlled clinical trials. Second, ET biosynthesis has been identified in anaerobes, suggesting that ET production may have evolved for reasons other than antioxidant properties, although no metabolic roles of ET specific to anaerobes have yet been discovered [135–137]. However, it remains possible that anaerobes evolved antioxidants (including ET perhaps) to protect against free radicals generated by radiation damage (a major problem in the "pre-oxygen" world because of the lack of Earth's ozone layer [16,136,137]); these antioxidants might have later allowed anaerobes to survive transient exposures to O_2 as O_2 levels rose in the atmosphere due to the evolution of photosynthesis [16,138–140]. Several papers have described radioprotective effects of ET [141–143].

Indeed, multiple mechanisms of ET action other than antioxidant ones have been suggested (Figure 4) and there is an urgent need to establish their relative importance, which may, of course, vary depending on the organism, organ, tissue, cell, organelle and the injurious agent . The anti-inflammatory and anti-fibrotic properties of ET described in multiple animal studies [42,43,124,126,144–154] may be of especial importance in prevention and treatment of age-related diseases, including neurodegenerative diseases, in which inflammation is intimately involved, as it is in ageing generally ("inflammaging") [155,156]. The proposed abilities of ET to promote neurogenesis and neuronal differentiation and enhance the actions of neurotrophic factors [157–160]

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may also be very important in protection against neurodegeneration. To date, these studies are mostly based on work with cell cultures, although human studies are beginning to appear [161] – more studies are needed to establish the importance of ET *in vivo* in enhancing neurogenesis, synaptogenesis, neuronal differentiation and the beneficial effects of neurotrophic factors, and the mechanisms by which ET is acting. **It cannot be over-emphasised that a non-toxic brain-penetrant agent safe for human consumption, that not only slows neurodegeneration but also promotes the genesis and function of new neurons would be of immense value in the slowing and prevention of age-related diseases of the nervous system, especially for dementia [31]**, in the world's rapidly-ageing populations; time will tell if ET can deliver on this potential.

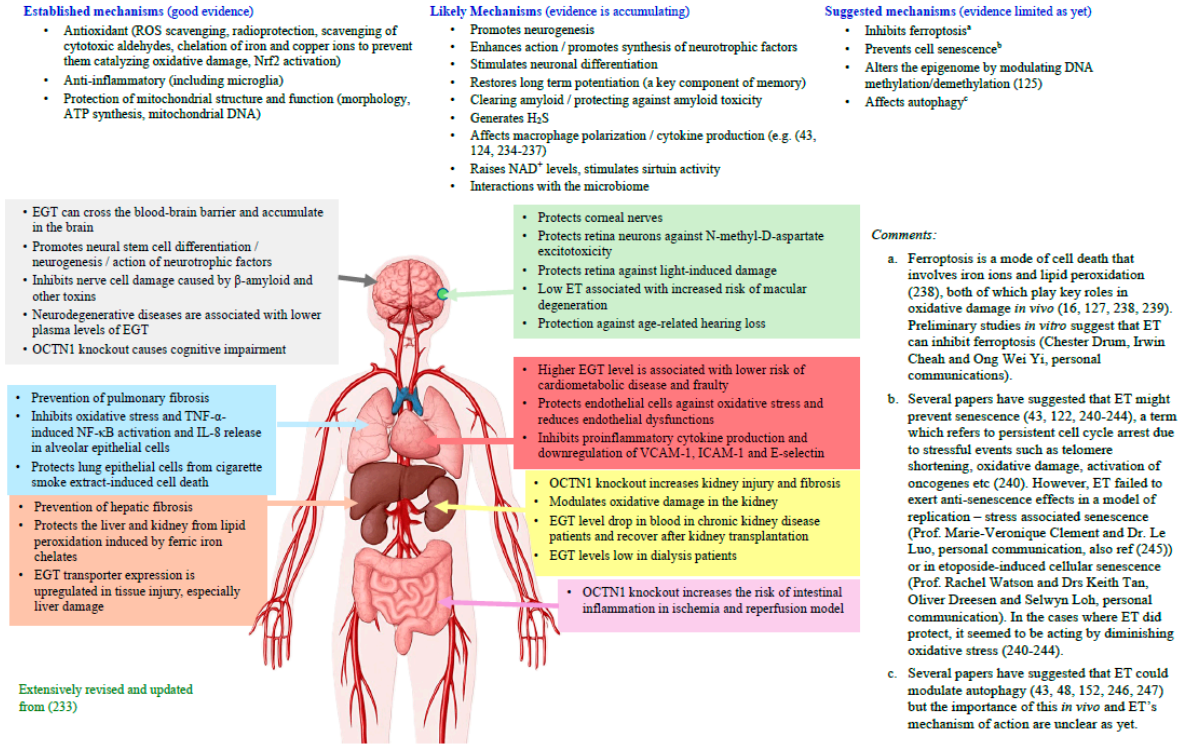

Figure 4. What are the mechanisms of action of ergothioneine? [233].

Returning to the mechanism of ET's action, two recent papers in *Cell Metabolism* proposed that the actions of ET in mitochondria are its major cytoprotective role, suggesting that the generation of hydrogen sulphide (H_2S) from ET is a key mechanism [162,163]. However, they reached different conclusions as to how this is achieved. One [162] reported that ET binds to and activates the enzyme 3-mercaptopyruvate sulphotransferase, but the other [163] that ET acts as a substrate for cystathionine gamma-lyase, leading to increases in NAD^+ levels. Indeed, there is a voluminous literature claiming that raising tissue NAD^+ levels promotes healthy longevity [164] although there are some conflicting data (reviewed in [164,165]). These discrepancies between [162] and [163] need to be resolved. In any case, is H_2S likely to explain all the biological actions of ET? The author is sceptical. Low levels of H_2S can indeed be neuroprotective [166–172], but higher H_2S levels can cause tissue damage [171,173–176], as illustrated by studies on breast cancer [176], human stroke and animal models of stroke [173,174]. Indeed, to quote a recent paper [175] on the mechanisms used by *C. elegans* to avoid exposure to H_2S: "H_2S is an energy source, a toxin and a gasotransmitter". The biological effects of N-acetylcysteine (NAc) have also been suggested, at least in part, to be due to H_2S generation [177,178], yet NAc has both protective and damaging effects in vivo, including promoting cancer development under some circumstances (reviewed in [127]). By contrast, no one has yet found pro-neurodegenerative or other toxic effects of ET, even at high doses, in any animal model or in the clinical trials conducted to date.

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4. Interaction of ET with the Human Microbiome Has Scarcely Been Studied

It is not only humans and other animals that avidly take up ET; several (and possibly all, most have not been studied) plants do, obtaining ET by interaction of their roots with fungi and bacteria in the soil [6,179,180]. Many bacteria can also take up and accumulate ET [181–185]. ET is efficiently absorbed in the small intestine, but some passes through to the colon and can be measured in human faeces [2]. Presumably if subjects consume ET-rich diets or supplements containing ET, more will end up in the colon. Since the body will have absorbed the ET it requires in the small intestine, uptake and metabolism of ET by the colonic microbiome would not be expected to deprive the human body of ET, but there are other potential concerns. Research into interactions of ET with the microbiome is just beginning [186–189], but one concern that has been raised is that some colonic bacteria can degrade ET using the enzyme ergothionase to eventually produce trimethylamine, which is absorbed from the gut and converted by the liver to trimethylamine oxide (TMAO) [190–192]. TMAO is epidemiologically the exact opposite of ET: in most (but not all) studies high levels of TMAO are associated with increased risk of several diseases, including cognitive impairment and cardiovascular disease [190–192]. Hence could too much dietary ET be deleterious by raising TMAO levels? Preliminary evidence (reviewed in [2]) suggests that ET is not a significant source of TMAO in humans, which is consistent with the literature on the safety and health-promoting aspects of ET reviewed above. Indeed, a recent study [70] showed that administration of 10 or 25mg per day of ET for 16 weeks to human subjects did not raise plasma TMAO levels and another study suggested that trimethylamine (the precursor of TMAO) is actually beneficial to human health [193]. Although increased levels of ergothionase genes have been reported to be present in the colonic microbiome of patients with colorectal cancer [188], ET actually appears to be toxic to colorectal cancer cells, based on *in vitro* studies [194]. However, other pathways of ET metabolism by the colonic microbiome are rapidly being discovered [188,195,196] and the potential health effects of the products of these pathways is an area ripe for further investigation.

The stomach and small intestine also have a microbiome [197,198]. The duodenal/small intestinal microbiome is poorly characterised and how it might take up or metabolise ET and thus affect its uptake into the human body is largely unknown. However, one constituent of the small intestine microbiome is *Lactobacillus reuteri* (*Limosilactobacillus reuteri*); strains of this organism have been widely promoted as probiotics to promote human gut health [199,200]. Some strains of *L. reuteri* avidly take up ET [181] – whether or not these bacteria could absorb enough ET to compete with its human intestinal update is unknown. It presumably would depend on their abundance; something to think about when selecting probiotics, perhaps – should we even preload them with ET to prevent them taking it from our diet and possibly to keep them alive for longer in the GI tract?

However, an important component of the gastric microbiome is *Helicobacter pylori*. *H. pylori* cannot synthesize ET, but takes it up avidly, and ET helps to protect this pathogen against the antimicrobial effects of ROS generated by human phagocytes as part of the defensive immune response [182,185]. Indeed, the high efficiency of ET uptake was illustrated in a recent paper [201] describing conjugation of an anti-microbial compound with ET as a vehicle to deliver that compound to *H. pylori* and eradicate this pathogen. Along similar lines, an ET-coated imaging agent has been used to image kidney disease: the agent bound to OCTN1 in the kidney [202]. Unfortunately, *H. pylori* can trigger chronic gastritis, in the worst-case scenario leading to gastric cancer [185]. Could uptake of dietary ET by *H. pylori* aggravate this? We do not know – it has not been studied. As discussed above, ET has anti-inflammatory effects, which should help to ameliorate risk. Epidemiological evidence suggests that consumption of mushrooms, a major dietary source of ET, is negatively associated with risk of gastritis and gastric cancer [203,204]. Of course, mushrooms contain multiple compounds that could be protective against cancer [203,204] and so these studies do not prove that ET is responsible for the protection.

5. ET and Other Human Pathogens

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Several bacteria can synthesise ET, and some are human pathogens, including *Burkholderia pseudomallei*, the causative agent of human melioidosis [205]. One of the most studied pathogens is *Mycobacterium tuberculosis*, the agent responsible for human tuberculosis (TB). This organism uses two sulphur-containing compounds, ET and mycothiol, to help protect itself against ROS generated by the human immune system, thereby hindering its eradication and facilitating its persistence in the human body [206,207]. Indeed, there has been some work on inhibitors of ET synthesis as potential therapeutic agents against *m. tuberculosis* [208]. Could consuming ET facilitate TB development in infected subjects? We do not know, but it may be unlikely since *M. tuberculosis* and other mycobacteria do not possess an uptake transporter for ET, so presumably they cannot accumulate it from their surroundings [183]. However, *B. pseudomallei* can (ref [205] and our unpublished results). In addition, *H. pylori, Streptococcus pneumoniae, Listeria monocytogenes, Clostridium difficile, Enterococcus faecalis* and *Staphyloccus aureus* are among the pathogenic bacteria that can take up ET and use it for cytoprotection [182–185]. Could dietary ET enhance their pathogenicity? Another gap in our knowledge.

6. Can ET Be Synthesized in the Human Body?

The consensus view is that ET cannot be made in animals [1–4,8,209,210], and our experiments with laboratory mice (reviewed in [2]) confirm that view. All known ET biosynthetic pathways begin with the amino acid histidine [211], so we simply fed animals with N^{15}-histidine and looked for N^{15}-labelled ET, which we never found. However, bioinformatic analyses of the gut microbiota in humans and other animals confirm that all the genes necessary to make ET are present [181] but of course they may not be being transcribed and translated to produce active enzymes, or present together in a single organism.

However, the human gut not only has a microbiome, it has a mycobiome, a collection of fungi [212]. Many fungi can make ET; could this ever happen *in vivo* and, if so, would the fungi retain ET or release it into the human body? We don't know, but a few studies suggest that ET might sometimes be made. For example, ET can be synthesized by several established human pathogenic fungi, including *Cryptococci* and *Candida* species and *Aspergillus fumigatus* [213–216]. Could they perhaps sometimes generate and release ET within the human body?

As mentioned earlier, cyanobacteria can synthesize ET [11] and have been reported as present in the human gut microbiome [217,218] although the species present have not been directly shown to synthesize ET. Perhaps they could under certain circumstances.

7. Why Some Humans Have Low ET Levels Is Unclear

Low ET levels in humans are strongly associated with higher risk of age-related diseases, as reviewed above. But why do some people have low levels? The obvious explanation is poor diet (hence the frequent suggestion to eat more mushrooms), but evidence suggests that there is more to it than that. For example, poor renal function (e.g. due to diabetes) could prevent ET reabsorption from the kidney ultrafiltrate [71,72,150]. The *slc22a4* gene that encodes OCTN1 has several polymorphisms [22,219–224], that could lead to amino acid substitutions affecting the transport of ET by OCTN1. Their population frequency and precise effects on the kinetics of ET transport *in vivo* remain to be studied in detail, one of the many aspects of ET biology that need to be explored in more depth. For example, a mutation in *slc22a4* has been linked to human hearing loss [222,225], and indeed ET has been shown to protect against age-related or *cis*-platin-induced hearing loss in animal studies [47,119]. This mutation was reported to severely decrease ET uptake by OCTN1 [222]. A mouse study reported that there are circadian changes in the intestinal expression of OCTN1 [226] and a rat study suggested that administration of 1α,25-dihydroxyvitamin D_3 can modulate OCTN1 levels [227]; the relevance of either to humans has not been studied. The interaction of ET with other dietary nutrients, and their potential effects on ET uptake in the gastrointestinal tract or by the body tissues, have also not been studied. Nor have possible interactions of ET with medications been examined in detail: an

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early suggestion that ET could influence the pharmacokinetics of the drug gabapentin does not seem to be a significant effect [228,229]. One possible drug interaction could be with the calcium channel blocker verapamil, which inhibits OCTN1 [20] and is often used in the laboratory to probe the role of this transporter in the actions of ET (e.g. [24,49,55]. Another issue worth further exploration is species differences. For example, OCTN1 expression is high in rat and mouse livers and human foetal liver [22], but lower in adult human liver (Figure 3). When mice consume ET, a lot enters the liver [100], but this may not be true in humans [22,230]. The distributions of OCTN1 in the various cell types of mouse and human brain are also different [22].

8. Conclusion

Evidence is growing that ET is a valuable component of the human diet and may even be essential for healthy longevity [1–4,8,28,31]; the late Professor Bruce Ames called it a "longevity vitamin" [231]. Indeed, increased OCTN1 activity has been proposed as an early evolutionary trait in Neolithic farmers to decrease the risk of ET deficiency, since many of the plants they first domesticated were low in ET [232]. There is a threshold blood level of ET, below which the risk of multiple age-related diseases increases [2], but is the optimal level of ET to maintain health greater than this? An analogy could perhaps be with vitamin C; only low intakes are needed to prevent overt symptoms of deficiency (scurvy), but larger amounts of vitamin C seem necessary for optimal health [15]. So should we all be consuming ET supplements, or just eating more mushrooms? Many aspects of ET biology need to be investigated before making firm recommendations. I hope that this narrative review will stimulate more research in the field. In studies of a very large number of human subjects, we have never found anyone completely lacking ET: does this mean that OCTN1 and ET are essential for early human development and human life?

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