Ergothioneine — an old vitamin coming of age

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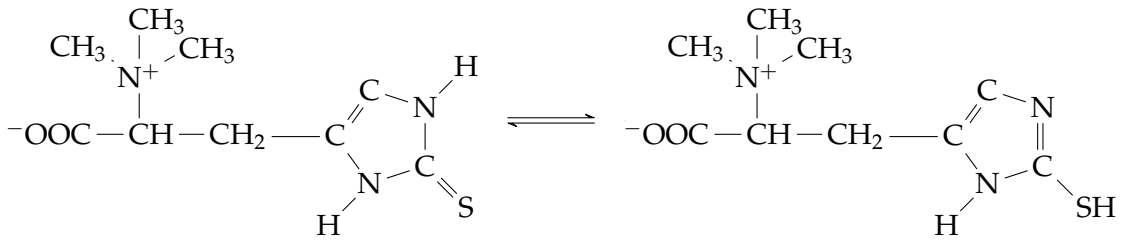
In 1909, the French chemist Tanret discovered ergothioneine in the fungus ergot, *Claviceps purpurea*, which grows on rye. Only a couple of years later Barger and Ewins determined the chemical structure, noting the presence of sulfur and an imidazole ring, but the thione form was not immediately recognised. This was a little before Mueller in the US carried out the first purification of methionine (from lysates of casein), which he believed at first might have the structure $C_2H_5SCH_2CH(NH_2)COOH$. Barger went on in 1928 to produce the correct structure of methionine as well, and probably every biochemistry textbook written since the 1960s has included some mention of this proteinogenic amino acid. Ergothioneine (2-mercapto-histidine trimethylbetaine, or EGT for short) was rather forgotten.‡ Over the last decade or so there has been a sustained surge of interest, reviewed, for example, by Cumming and others in 2018, and by Paul in 2022; here I will give just a flavour of the highlights. Although mycobacteria and fungi were found to produce EGT, it was only in this century that research showed not only that cyanobacteria and other microbes make it in large amounts, but EGT is the principal protective reducing agent within these cells, unlike eukaryotes and Gram-negative bacteria which use glutathione (GSH) instead. Melville and Eich showed in the 1950s that rats and chickens are unable to make EGT, but they could take up considerable amounts of it from oats, which they found contains far more EGT than corn. They commented that the EGT content of oats appears to vary from crop to crop, suggesting that at least part of the EGT content was of fungal origin, which chimes with the work of Tanret. It has even been suggested that ploughing may disrupt mycorrhizal fungi, and no-till farming methods may increase the EGT content of crops. Plants have yet to be shown to produce EGT independently.

EGT is highly soluble in water, and exists in equilibrium between its thiol and thione tautomeric forms. This equilibrium makes it more stable than ordinary thiols, and gives it a higher redox potential of -60 mV, instead of the normal -200 mV to -320 mV at equilibrium between free SH groups and disulfides. The thermostability means that EGT survives cooking, which is convenient since we obtain it solely from food. EGT accumulates in skin cells where it reduces oxidative damage by UV light, and facilitates DNA repair. It is used as an ingredient in several skin-care products. Interestingly, EGT shows exactly the same UV-protective properties in the mushroom *Cordyceps militaris* (used medicinally), which increases EGT production when subjected to UV light. Other mushrooms including porcini and especially golden oyster mushrooms (*tamogitake* in Japanese) are rich sources of EGT in the human diet.

Ergothioneine in its thione and thiol forms



Human cells take up EGT through a dedicated transporter (ETT), first discovered in 2005, formerly known as OCTN1 and now as SLC22A4. SLC stands for solute carrier family; humans have 458 genes from this superfamily which are divided into 65 separate families, and SLC22 contains 28 members. These SLC22 proteins are highly conserved and found in organisms such as flies and sea-urchins as well as humans. SLC22A14 turned out to be a mitochondrial riboflavin transporter, essential for male fertility. Another human SLC22 gene, *SLC22A15*, was "deorphaned" in 2020, and found to encode a second EGT transporter highly expressed in the brain. Knocking out the *OCTN1/SLC22A4* equivalent gene in zebrafish or mice confirms that this highly conserved transporter is responsible for uptake of EGT, which is found most concentrated in cells of the liver and the eye as well as the nervous system.

ETT is highly specific, implying EGT has at least some characteristic properties of a vitamin, and the review by Paul was partly motivated by the desire to have EGT recognised as such. Some studies have suggested that a mutation of the ETT gene may be associated with Crohn's disease, ulcerative colitis, and type I diabetes. The knockout zebrafish also showed a 4-fold increase in 8-oxoguanine, leading to the suggestion that EGT might have a universal role of eradicating singlet oxygen. Despite its apparently lower reductive power than GSH (from a simple comparison of redox potential) EGT turns out to be very good at capturing singlet oxygen, one of the most damaging reactive oxygen species that can arise inside a cell. It should not really be too surprising therefore if humans have at least two genes dedicated to EGT uptake.

Different but related synthetic pathways have been found in the organisms that produce EGT. Mycobacteria synthesise EGT from histidine and cysteine with the help of glutamate and five enzymes encoded by a single operon (*egtABCDE*). EgtA is responsible for producing γ-glutamyl-cysteine from glutamate and cysteine. Histidine is triply methylated by EgtD using S-adenosyl-methionine to give hercynine, which then reacts with γ-glutamyl-cysteine to give γ-glutamyl-hercynylcysteine sulfoxide. Loss of the glutamate yields hercynylcysteine sulfoxide, the immediate precursor of EGT. Cyanobacteria use a different pathway that depends on GSH. The pathway in the filamentous fungus *Neurospora crassa* is simpler, producing hercynylcysteine sulfoxide directly from hercynine and cysteine, while the yeast *Saccharomyces pombe* apparently uses only two enzymes to make EGT, also without using glutamate. *M. smegmatis* mutants unable to make EGT were found to have growth rates similar to wild-type, but to be highly susceptible to oxidative agents. Mycobacteria produce another protective agent called mycothiol (MSH), reported to be present at much higher levels than EGT in normal cells, and possibly even more important. EGT, however, appears to play a role in bioenergetic homeostasis, and *Mycobacterium tuberculosis* (*Mtb*) carrying *egtA* or *egtD* mutations shows much reduced survival rates when challenged with anti-TB drugs. These *Mtb* mutant cells also have strongly reduced survival inside macrophages, and animal studies with *Mtb*-infected mice showed that loss of EGT reduced the bacterial load in the lungs by about 75%.

In humans, SLC22A4 is highly expressed on the apical membranes of both the small intestine and the proximal tubular cells of the kidney, where it promotes absorption from the diet and renal re-absorption respectively. EGT supplementation received safety approval in 2016 (in Europe) and 2018 (in the US). Studies show EGT is rapidly absorbed and retained in the body, and supplementation can increase EGT levels. Mice given high doses of EGT showed the greatest accumulation in the liver, and there is the possibility that further EGT transporters may be discovered to explain fully its distribution. The connection between EGT and the brain however is generating the most interest in many recent reports, because EGT has been shown to protect neurons from damage by cisplatin or β-amyloid, and it reduces age-related learning difficulty and memory loss. Humans show decreased levels of EGT after the age of 60, and some small studies have indicated a correlation between EGT levels and cognitive impairment, dementia and Parkinson's disease. A Norwegian study published in 2010 found a correlation between mushroom intake and cognitive performance in the elderly. Higher plasma levels of EGT are associated with lower risk of coronary disease, cardiovascular diseases and overall mortality. Diabetic rats given EGT supplements for six weeks showed reduced indications of cardiac injury, lipid peroxidation and inflammation. Other studies with such rats showed a greatly improved condition of the liver, and there is great interest now in finding whether EGT can improve the condition of patients suffering from non-alcoholic fatty liver disease (NAFLD), a widely prevalent comorbidity of type 2 diabetes.

EGT is not accepted as a vitamin because it has not been shown to be essential. It has been proposed instead to be a "longevity vitamin" or a nutraceutical. Standard vitamins (and essential minerals or amino acids) are components of the diet required to maintain health. Other nutrients may be conditionally essential, but EGT so far has not yet made even that list. It does very much seem to be an important factor in healthy ageing however. In Japan, Alzheimer's disease and Parkinson's disease are relatively rare, despite the long life expectancy, and there is a growing interest in whether mushrooms and fermented foods might be the reason why. Americans and Europeans eat far fewer mushrooms than the Japanese, and often they eat button mushrooms which are very low in EGT. Perhaps with changes in agricultural practice and a changed attitude to mushrooms, the West can find a practical and simple means of alleviating cognitive decline in the elderly.

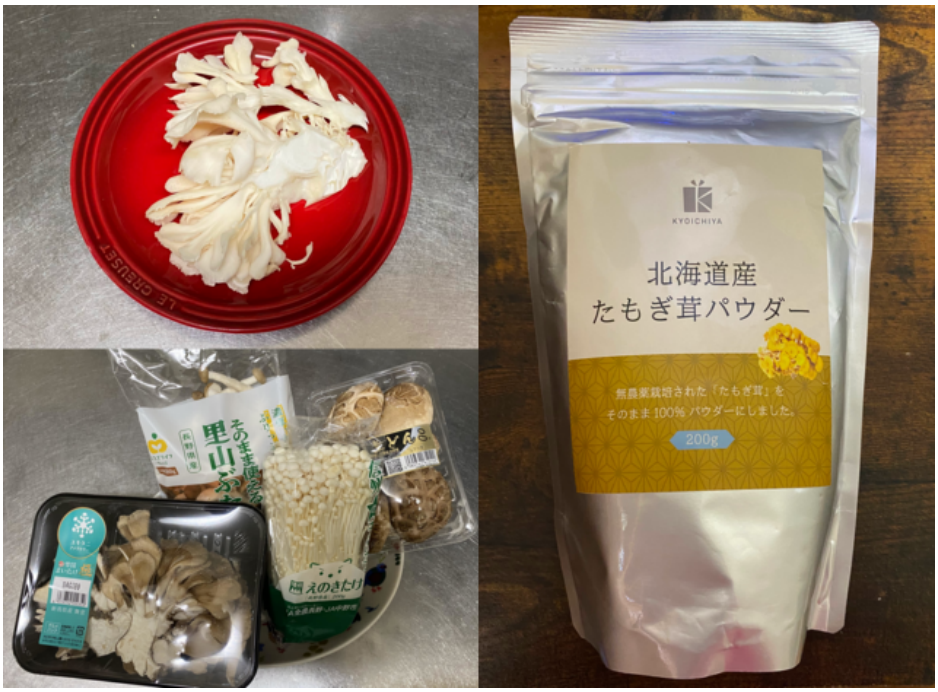


Figure 1: A variety of mushrooms available in Japanese supermarkets. Top left, *maitake*; bottom left, mushrooms from the supermarket including *shiitake*, *enokitake* and *maitake*. Right, powdered golden oyster mushroom *tamogitake* (タモギタケ also written たもぎ茸). This 200 gram bag contains over 2 grams of EGT.

‡Mercapto is one of those little Latin hangovers in biochemistry, and simply means a thiol group. It comes from *mercurium captans* and simply means *mercury grabbing*, which is one of the things thiol groups are good at. Thio, of course, just means sulfur, in Greek.

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