Sulfur in Health and Disease

A Hypothesis on Sulfur Intoxication

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Since antiquity, sulfur has been used as a homeopathic medicine in various conditions. Its use has been empirical in nature, it being given in accordance with its various homeopathic effects when administered to sick patients. Advances in the study of basic sciences now enable us to understand many of these empirical applications, giving them new-found scientific validity. Sulfur plays an active role in numerous metabolic processes in the healthy human body.

Sulfur is a non-metal, lemon yellow in color, with atomic number 16 in the periodic table of the chemical elements. Its symbol is S and it is situated next to phosphorus (P, atomic number 15) to its left and chlorine (Cl, atomic number 17) to its right. The element immediately above it is oxygen (O, atomic number 8) and the element immediately below it is selenium (Se, atomic number 34).

It is characterized by high electronegativity and consequently gains electrons more easily than it loses them. Its oxides are acidic and tend to form anions and oxyanions in aqueous solution. Solutions in water are acidic (pK_{a1} = 7.00).

The essential amino acid methionine, which is apolar and hydrophobic, contains a sulfur atom in its side chain. It is converted to homocysteine and combines with the nonessential hydrophilic amino acid serine to form cysteine, a special nonessential amino acid. The side chain of cysteine contains a sulfhydryl (-SH) group, also known as a thiol group, which can undergo oxidation to form a covalent disulfide bond (-S-S-) with a second cysteine from the same or a different polypeptide chain.

The disulfide bonds form in the lumen of the rough endoplasmic reticulum (RER) of the cell in which oxidizing conditions predominate, unlike in the cytosol where the prevailing reducing conditions maintain cysteine residues in the reduced state (-SH). Disulfide bonds (S-S) are essentially found only in secretory proteins and in the exoplasmic domains of membrane proteins. The RER is also the site of synthesis of proteins that subsequently go on to form part of various cell membrane receptors.

The efficient formation of disulfide bonds in the lumen of the RER depends on the enzyme protein disulfide isomerase (PDI). This enzyme catalyzes the formation of disulfide bonds, which catalyze the protein folding of many proteins. In this process, PDI catalyzes the cleavage of some disulfide bonds and the formation of others, which implies an interchange between pairs of disulfide bonds in the polypeptide chain. PDI is found in all eukaryotic cells, particularly in organs such as the liver and pancreas.

Glutathione and the enzyme glutathione reductase are other enzymes involved in the formation of the appropriate disulfide bonds in many proteins and polypeptide hormones. Similarly, they have been shown to be involved in the metabolism of xenobiotics. Thus the disulfide bonds of cysteine contribute to the formation of the three-dimensional structure of the various protein chains.

The sulfate present in urine thus comes entirely from oxidation of L-cysteine.

The following list shows where sulfur is found in bodily metabolism:

- in the structure of the amino acids methionine, cysteine, homocysteine, and taurine
- in the structure of proteins

Sulfur, in its native form, is a yellow crystalline substance.

- in various roles in the immune system (immunoglobulins, cytokines)
- in adhesion molecules (cellular = CAM and intercellular = ICAM)
- in membrane receptors, such as insulin
- in leukotrienes, such as LTD_4 and LTE_4
- in the structure of growth hormone, calcitonin, dehydroepiandrosterone, insulin, prolactin, somatomedin, somatostatin, synthesis of T_3 and T_4
- in the peptides activin, inhibins, atrial natriuretic peptide, brain natriuretic peptide, C peptide, relaxin, arginine-vasopressin, oxytocin
- epidermal growth factor, nerve growth factor, platelet-derived growth factor, erythropoietin
- leptin, cholecystokinin
- in the structure of collagen fibers, desmosine, elastin, fibrillin, fibronectin, integrin, laminin, osteonectin, keratin
- in the structure of articular cartilage and glycosaminoglycans, chondroitin 4-sulfate and 6-sulfate, keratan sulfate I and II, heparin, heparan sulfate, dermatan sulfate
- constituent of the structure of the vascular wall, endothelins
- in the coagulation cascade, structure of fibrinogen
- as a catalyst in the respiratory chain of the citric acid cycle
- in cellular apoptosis (caspase enzymes)
- S-adenosylmethionine, synthesis of epinephrine, creatinine, melatonin
- hepatic metabolism of cytochromes and action on xenobiotics
- in gastric fluid and pancreatic fluid
- vitamins, such as thiamine, biotin
- Shigella toxin, diphtheria toxin, immunotoxin
- in the pharmaceutical and food industry and in agriculture

The sources of the sulfur entering the body are diverse, and the absorption occurs via a number of carriers, including food and the environment. Indirectly, we ingest sulfur in the form of toxic by-products of fuels derived from coal and petroleum, which on combustion produce sulfur dioxide. Direct ingestion of sulfur occurs primarily in our daily diet with the consumption of foods rich in the sulfites used in the food industry as preservatives and coloring agents to improve shelf life and color fixation, or with the ingestion of refined sugar, which is found in a high percentage of the food and drink that we consume each day, or with foods contaminated with pesticides.

The principles of Rudolf Arndt and Hugo Schulz, which demonstrate the linear pharmacological relation between dose and effect, give rise to the basic biological rule which states that the physiological action of a cell increases or decreases in relation to the intensity of the stimulus: Weak stimuli stimulate the life functions, moderately strong stimuli accelerate them, strong stimuli act as inhibitors, and the strongest stimuli suspend the life functions.

The high consumption of sulfur entering the body is probably transformed into an intense stimulus that displaces the equilibrium of the matrix and the membrane receptors, a phenomenon leading to modifications in the network of information received and transported through the matrix in the intranuclear, intracytoplasmic, and extracellular spaces.

A cascade effect then ensues that leads to a change in biochemical, immunological, and hormonal responses. This also destabilizes the three-dimensional structure of proteins, which, as we have already seen, need the presence of the disulfide bonds to maintain their stereochemical presentation and recognition at the cell membrane.

Similarly, changes are produced in the assembly of collagen and elastin fibers. Destabilization of the proteo- and aminoglycans that form the hydrated fibrous framework for the extracellular matrix results in competition between the H^+ ions of the weak acid of H_2O and the hydrogen ions of the strong acids SO_4^{2-} of sulfuric acid H_2SO_4 and HPO_4^{2-} of

phosphoric acid H_3PO_4. Proteoglycans and aminoglycans are substances that readily undergo electrolytic exchange. Their alteration destroys their capacity to retain water in the cartilage and extracellular matrix, changing their state of fluidity to a state of desiccation or gel formation; the end result of this alteration is a loss of the ability of the body to exchange information between different compartments, leading to loss of the state of systemic equilibrium. These alterations predispose the patient to chronic conditions such as diabetes, rheumatic disease, osteoporosis, and arthritis.

What happens in this information exchange? We do not know exactly, but can postulate one of the following:

- A change in body pH alters the behavior of the disulfide bonds, making them more rigid, the result being that the protein chain loses its capacity to adjust to the membrane receptor.
- An increase in these bonds causes changes in the three-dimensional structure of the protein chain.
- A loss of the capacity to form disulfide bonds causes the protein chains to break.
- A loss of cohesive strength of the disulfide bonds makes them cleave easily.

We do not know exactly how this destructive process occurs, but we are familiar with the catastrophic effect of sulfur consumption on the body. Within a few years, research will surely reveal to us in detail how the destructive effect of excessive intake of sulfur on bodily metabolism occurs.

Contrast this with the pharmacological viewpoint and therapeutic indication of allopathic medicine, in which the damage caused by an excess of sulfur is treated with sulfur-based drugs that the patient takes in high doses, causing a high degree of intoxication and consequent worsening of the disease. Although there may be a relative improvement due to an initial mechanism, what is seen long-term is a worsening of symptoms and a chronification of the initial disease process, each time necessitating more combinations of medicines. We can take as an example the profile and timescale of a chronic condition such as diabetes. For chronic diabetic illness, treatment is commenced with sulfonylureas, which are briefly effective. However, in time the body ceases to respond to these drugs, making it necessary to add another oral antidiabetic such as metformin or rosiglitazone, with the patient ultimately becoming dependent on insulin in order to manage symptoms and without this curing the disease. We return then to the patient as a chronic consumer of pharmacological substances that provide no cure but continually exacerbate the disease course and the permanent sulfur intoxication.

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