Sulfite Sensitivity
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Sulfite sensitivity is caused by a relative deficiency of the enzyme sulfite oxidase. According to FDA estimates, only 1% of our population suffers from sulfite sensitivity and those suffering from true sulfur sensitivity is even less than this. (Vally, Misso et al. 2009)

As a consequence of these reported adverse reactions, the US Food and Drug Administration (FDA) acted in 1986 to prohibit the use of sulphites on fruits and vegetables that were to be served raw or presented as fresh to the public. For foods and drinks in which the use of sulphite was permitted, sulphite concentrations 410 p.p.m. had to be declared on the label. Despite the introduction of these regulations, there continued to be sporadic reports of serious adverse effects following unintended ingestion of sulphites. (Vally, Misso et al. 2009)

Symptoms
Sulfite sensitivity is a condition characterized by asthma-like symptoms, including wheezing, chest tightness, coughing, extreme shortness of breath, and even loss of consciousness. Other symptoms include flushing, angioedema, itching, hives, contact dermatitis, swelling of eyes, hands and feet, nausea and diarrhea, and anaphylactic shock.

In addition to episodic and acute symptoms, sulphites may also contribute to chronic skin and respiratory symptoms. (Tutuncu, Kucukatay et al. 2012)

Patients with sulfite oxidase deficiency may present with seizures (epilepsy). (Lee 2011)

Since glutamate metabolism appears to be inhibited by sulfite, amyotrophic lateral sclerosis (ALS) of non-mutant superoxide dismutase (SOD) type may be caused by sulfite toxicity. (Woolsey 2008)

Elevated levels of serum sulfite were found in patients with chronic renal failure. (Kajiyama, Nojima et al. 2000)

Wine
Sulfites occur naturally in all wines. Sulfites are commonly introduced to arrest fermentation at a desired time, and may also be added to wine as preservatives to prevent spoilage and oxidation at several stages of winemaking.

Many people, although not severely sulfite sensitive, will exhibit the “red-wine stuffy nose” after drinking just a single glass of red wine. Others get a characteristic alcohol flush on the face and neck when drinking red wine, beer, or hard liquor. (2006)

Bisulfite
Bisulfite is one of the few sulfating agents approved by the Food and Drug Administration (FDA) as a food preservative and antioxidant to prevent or reduce spoilage. It also appears as an
ingredient of many medications, such as antibiotics, analgesics, anesthetics, etc. Sulfites in foods or drinks can be present as sulfur dioxide, sodium sulfite, sodium or potassium metabisulfite, and sodium or potassium bisulfite. (Tarlo and Sussman 1993)

**Sulfur Dioxide**

Sulfur dioxide, formed during the combustion of fossil fuels, is a major air pollutant near large cities. Sulfur dioxide can be hydrated to bisulfite in the lung and upon contact with fluids lining the air passages as follows. (Ranguelova, Bonini et al. 2010)

\[
\begin{align*}
SO_2 + H_2O & \rightarrow HSO_3^- + H^+ \\
HSO_3^- + H_2O & \rightarrow SO_3^{2-} + H_3O^+
\end{align*}
\]

**Nitrates**

Sulfite and nitrate metabolism are linked. If the sulfite concentration is higher than that of nitrite, almost all of the nitrite is consumed by sulfite, suppressing the production of NO. Ingestion of wine results in the enhancement of NO production in the stomach, which is postulated to be due to the reduction of salivary nitrite by polyphenols in wine. Sulfite in wine suppresses NO production induced by polyphenols by enhancing the consumption of salivary nitrite via reaction a-1 in the stomach. If the concentration of sulfite in wine is decreased, more NO can be produced in the stomach after wine is consumed. (Takahama and Hirota 2012)
**Sulphite Oxidase**

Sulphite oxidase is a mitochondrial enzyme that catalyses the oxidation-reduction reaction of sulfite and water, yielding sulfate. The electrons produced are transferred to the electron transport chain, allowing generation of ATP in oxidative phosphorylation.

Sulfite oxidase is required to metabolize the sulfur-containing amino acids cysteine and methionine in foods. Lack of functional sulfite oxidase causes a disease known as sulfite oxidase deficiency. This rare but fatal disease causes neurological disorders, mental retardation, physical deformities, the degradation of the brain, and death.

Sulfite is detoxified in the liver and lung to sulfate by sulfite oxidase, a molybdenum-dependent mitochondrial enzyme. Sulfite oxidase deficiency is one of the most accepted causes of sulfite hypersensitivity and toxicity. (Rangelova, Bonini et al. 2010)

\[
\text{SO}_3^{2-} + \text{H}_2\text{O} \rightarrow \text{SO}_4^{2-} + 2\text{H}^+ + 2\text{e}^-
\]

There are three enzymes: sulfur dioxygenase, sulfite oxidase and sulfur transferase. (Kabil and Banerjee 2010)
**Lab Tests**

In conventional medicine, the diagnosis of sulfite sensitivity can only be made by appropriately conducted provocative challenge.

Sulfite test strips can be used on urine samples. A positive sulfite dipstick finding of very fresh urine is highly suggestive of sulfite oxidase deficiency; however, a negative dipstick finding does not eliminate suspicion.

Urine organic acids may reveal lactate (a nonspecific finding) but can rule out common organic acidemias. Urinary urothion (a degradation product of molybdopterin) can be measured by a few laboratories. A low level is virtually diagnostic for molybdenum cofactor deficiency (except in cases of profound molybdenum deficiency). Urinary thiosulfate (a metabolite of cysteine) can also be measured by a few laboratories.

An elevated urinary thiosulfate level is essentially diagnostic of sulfite oxidase deficiency or molybdenum cofactor deficiency. The plasma uric acid level is typically low or low-normal in individuals with molybdenum cofactor deficiency; however, it is normal in those with isolated sulfite oxidase deficiency. Plasma lactate and pyruvate levels may be highly elevated, although this finding is nonspecific. Urinary xanthine and hypoxanthine levels can be measured in selected laboratories. These levels are elevated in individuals with molybdenum cofactor deficiency but are normal in those with sulfite oxidase deficiency. (Arnold 2012)

Analysis of alpha-aminoadipic semialdehyde is an important tool in the diagnosis of antiquitin deficiency (pyridoxine-dependent epilepsy). However continuing use of this test has revealed that elevated urinary excretion of alpha-aminoadipic semialdehyde is not only found in patients with pyridoxine-dependent epilepsy but is also seen in patients with molybdenum cofactor deficiency and isolated sulphite oxidase deficiency. Sulphite was shown to inhibit alpha-aminoadipic semialdehyde dehydrogenase in vitro. (Mills, Footitt et al. 2012)

Assessment of total homocysteine levels in plasma may be an additional tool for selective screening for isolated sulphite oxidase deficiency. Strongly decreased/undetectable values of total homocysteine in plasma are typical findings in isolated sulphite oxidase deficiency (and in molybdenum cofactor deficiency with combined deficiencies of sulphite oxidase, xanthine dehydrogenase and aldehyde oxidase) and should always result in careful diagnostic work-up, especially if the clinical presentation is compatible with sulphite oxidase deficiency. (Sass 2006)

Elevated levels of sulfur on hair analysis may suggest sulfite oxidase deficiency.

**Molybdenum**

Sulfite oxidase is an oxidoreductase class enzyme that catalyzes the reaction from sulfite to sulfate. This is a mitochondrial molybdohemoprotein meaning molybdenum is a necessary cofactor in the synthesis of this enzyme. Not enough molybdenum, not enough sulfite oxidase is produced possibly resulting in sulfite sensitivity. (2006)

In order to gain biological activity and fulfill its function in enzymes, molybdenum has to be complexed by a pterin compound thus forming the molybdenum cofactor.
Nitrate reductase and sulphite oxidase are sister enzymes. They belong to the enzyme super-family of molybdenum oxotransferases that also includes DMSO reductase, xanthine oxidase, and nitrite reductase. (Mendel 2007)

Human Moco deficiency (MoCD) results in the complete loss of sulphite oxidase, xanthine oxidase and aldehyde oxidase activity. MoCD are classified into three groups according to the affected steps within the biosynthetic pathway. Symptoms are characterized by progressive neurological damage. They are mainly caused by the deficiency of sulphite oxidase protecting the organs (in particular the brain) from elevated concentrations of toxic sulphite. (Schwarz, Mendel et al. 2009)
The electrons are transferred to the electron transport chain. (Garrett, Johnson et al. 1998)
**SAM and ATP**

Molybdenum cofactor synthesis involves four steps that require S-adenosylmethionine (SAM) and adenosine triphosphate (ATP). (Veldman, Santamaria-Araujo et al. 2010)

S-adenosylmethionine (AdoMet) is a cofactor for the conversion of GTP into Precursor Z, which forms the molybdenum cofactor. (Zhang and Liu 2011)
**Pyridoxal 5′-Phosphate (P5P)**

Molybdenum cofactor deficiency that leads to the accumulation of sulfite, a nucleophile capable of reacting with pyridoxal 5′-phosphate. Low pyridoxal 5′-phosphate levels were also seen in a group of children with transiently elevated urinary excretion of sulfite and/or sulfcysteine, suggesting that there may be other situations in which sulfite accumulates and inactivates pyridoxal 5′-phosphate. (Footitt, Heales et al. 2011)

**Iron and Copper**

Clearly, the formation of active Mo-enzymes depends not only on the availability of Mo but also on the presence of the two metals iron and copper. (Mendel 2007)

**Heavy Metals**

Heavy metal ions inhibit molybdoenzyme activity by binding to the dithiolene moiety of molybdopterin in Escherichia coli. (Neumann and Leimkuhler 2008)

It has been shown that a combined exposure of tungsten and arsenic causes leukemia, which may be related to impaired SO activity and overproduction of reactive oxygen species. (Steinberg, Relling et al. 2007)

High levels of tungsten can cause sulfite oxidase deficiency by antagonizing molybdenum. (Johnson and Rajagopalan 1976)

**Garlic**

Garlic is rich in organosulfur compounds considered responsible for most of its pharmacological activities. Allicin (diallyl thiosulfinate), the main organosulfur compound, is produced from the amino acid alliin by action of the enzyme alliinase when garlic is crushed. Allicin, unstable in aqueous solution, rapidly decomposes mainly to diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), and ajoene. After consumption, neither allicin nor its metabolites have been found in blood or urine, indicating that these compounds are rapidly metabolized. (Benavides, Squadrito et al. 2007)

Cardioprotective effects of dietary garlic are mediated in large part via the generation of hydrogen sulfide (H2S). Garlic-derived organic polysulfides are converted by erythrocytes into hydrogen sulfide, which relaxes vascular smooth muscle, induces vasodilation of blood vessels, and significantly reduces blood pressure. (Ginter and Simko 2010)
**Sulfur-Containing Amino Acids**

Methionine, cysteine, homocysteine, and taurine are the 4 common sulfur-containing amino acids. Only two are normally present in proteins, namely methionine and cysteine. Methionine cannot be synthesized by the human body and must be supplied by the diet, whereas cysteine requirements can, in principle, be met by an excess of dietary methionine. However, cysteine is known as a semi-essential amino acid because humans can synthesize it from methionine to a limited extent. (Predmore, Lefer et al. 2012) (Brosnan and Brosnan 2006)
Figure 2 Hydrogen sulfide—biosynthesis and metabolism. $\text{SO}_3^{2-}$ and $\text{SO}_2^{3-}$ cannot be used to measure hydrogen sulfide production as they can also be formed from direct oxidation of L-cysteine with cysteine deoxygogenase. Compiled and adapted from references [5,6,17–18].
References


