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Molybdenum and Tungsten in Biology

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ABSTRACT

The year of 2019 was declared by UNESCO as the "International Year of the Periodic Table of Chemical Elements", commemorating the 150th anniversary of its creation by the Russian scientist Dmitry Mendeleev. This communication celebrates two chemical elements, whose involvement in biological systems is poorly recognised and largely disregarded: molybdenum and tungsten. To bring to light the biological relevance, biotechnological potential and human health implications of these two metallic elements, this communication will present an overview on the molybdenum- and tungsten-containing enzymes. First, the enzymes catalytic features will be described (section 2), followed by an outline of selected biotechnological applications, related to environmental -nitrogen and carbon footprints- and energy issues (section 3), and an account on human health implications, several of which related with cardiovascular diseases and metabolic syndromes, which are main concerns of our western society (section 4).

SUMÁRIO

O ano de 2019 foi declarado pela UNESCO como o "Ano Internacional da Tabela Periódica dos Elementos Químicos", celebrando os 150 anos da sua criação pelo cientista russo Dmitry Mendeleev. Esta comunicação celebra dois elementos químicos cujo envolvimento em sistemas biológicos é pouco conhecido e, por isso, pouco valorizado: molibdénio e tungsténio. De modo a reconhecer o potencial biotecnológico e as implicações para a saúde humana destes dois elementos metálicos, esta comunicação apresentará uma visão geral sobre os enzimas contendo molibdénio e tungsténio. Primeiramente, serão apresentadas as propriedades catalíticas dos enzimas (secção 2), seguidas da descrição de algumas aplicações biotecnológicas relacionadas com problemas ambientais -pegada de azoto e de carbono- e de energia (secção 3) e implicações para a saúde humana, muitas das quais relacionadas com problemas cardiovasculares e síndromes metabólicos (secção 4).

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ABBREVIATIONS

AO, aldehyde oxidase; DMSOR, dimethylsulfoxide reductase; FDH, formate dehydrogenases; mARC, mitochondrial amidoxime reducing component; NaR, nitrate reductase; SO, sulfite oxidase; ROS, reactive oxygen species; XO, xanthine oxidase.

1. INTRODUCTION

Molybdenum and tungsten are heavy metallic elements, with atomic numbers 42 and 74 (Figure 1). They are present in the Universe and in Earth crustal rocks and oceans in very small amounts (Table 1). Yet, regardless of the environmental scarcity, molybdenum is essential to most organisms [1-3] from archaea and bacteria to higher plants and mammals, being found in the active site of enzymes that catalyse oxidation-reduction reactions involving carbon, nitrogen and sulfur atoms of key metabolites [4-11]. Presently, more than 50 molybdenum-containing enzymes are known, the great majority of which

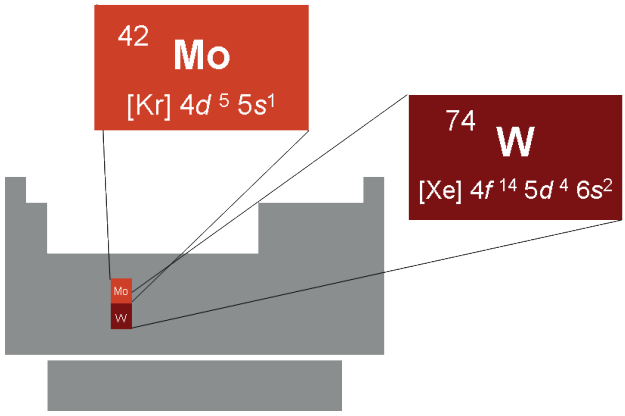


Figure 1. Molybdenum and tungsten in the Periodic Table of the Chemical Elements.

are prokaryotic, with eukaryotes holding only a restricted number of molybdoenzymes (mammals, for example, have only four). Tungsten, probably because of its limited bioavailability (Table 1), is far less used, being present only in prokaryotic organisms, most of which are thermopilic anaerobes [4,12-15]. As molybdenum, tungsten is involved in oxidation-reduction reactions, several of which constitute key steps in the global biogeochemical cycles of carbon, nitrogen and sulfur.

Table 1. Abundances of molybdenum, tungsten and some other elements with biological relevance in different environments [16]

Location	Abundance (ppb by atoms)						
	Mo	W	Fe	H	C	N	O
Universe	0.1	0.003	$20x10^3$	$930x10^6$	$500x10^3$	$90x10^3$	$800x10^3$
Crustal rocks	230	120	$23x10^6$	$31x10^6$	$3.1x10^3$	$29x10^3$	$600x10^6$
Oceans	0.64	0.004	0.33	$662x10^6$	$14.4x10^3$	220	$331x10^6$
Human body	7	—	$6.7x10^3$	$620x10^6$	$120x10^6$	$12x10^6$	$240x10^6$

In biological systems, molybdenum and tungsten are mainly found associated with pyranopterin molecules (Figure 2), moieties that act as a metal scaffold in the same way as the haem ring coordinates the iron in haem proteins [4,5,9-11,15]. Noteworthy, molybdenum can also be found in a heteronuclear molybdenum/iron centre, present only in the nitrogenase enzyme (Figure 2) [17-26]. Keeping on with the comparison with haem proteins, in which different modifications of the basic haem ring (haem *b*, *c* and several other) and of the substrate binding pocket are combined to achieve different metabolic purposes using a single metal (iron), also in molybdo- and tungstoenzymes, different active site structures have evolved to create diverse chemical reactivities using the same metal. These different active site architectures are the basis for the classification of these metalloenzymes into five large families (parallel to haem types), denominated after one benchmark enzyme (Figure 2) [5,10]: sulfite oxidase (SO), xanthine oxidase (XO), dimethylsulfoxide reductase (DMSOR), nitrogenase (these four containing molybdenum) and tungstoenzymes families.

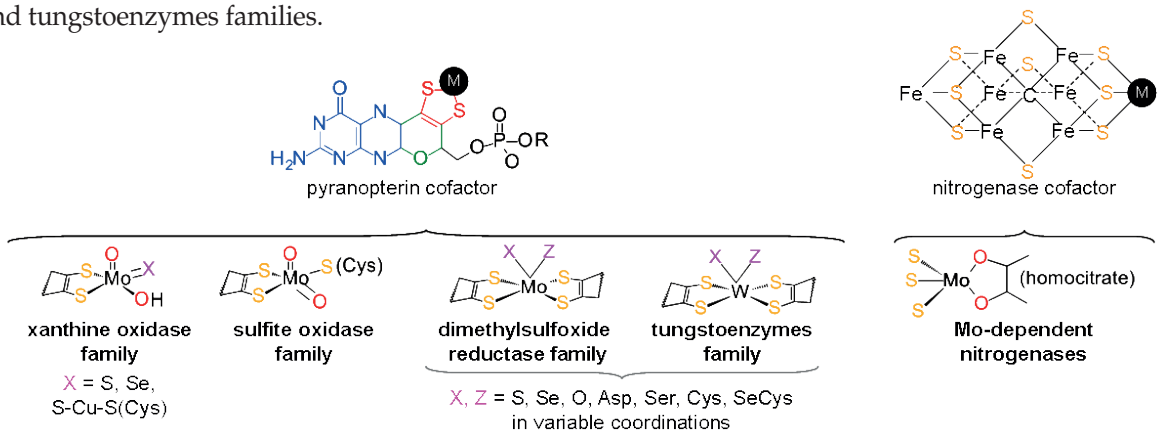


Figure 2. Schematic representation of the structures of the active site of the molybdenum- and tungsten-containing enzymes. On top, structure of pyranopterin and nitrogen cofactors (M, stands for metal, molybdenum or tungsten). The pyranopterin cofactor molecule is formed by pyrano(green)-pterin(blue)-dithiolene(red)-methylphosphate(black) moieties. The dithiolene (–S–C=C–S–) group forms a five--membered ene-1,2-dithiolate chelate ring with the molybdenum/tungsten atom. On bottom, structures of the molybdenum and tungsten centres of the five families of molybdo- and tungstoenzymes in the oxidized form. For simplicity, only the cis-dithiolene group of the pyranopterin cofactor is represented in the xanthine oxidase, sulfite oxidase, dimethylsulfoxide reductase and tungstoenzymes families; likewise, only the coordinating sulfur atoms of the nitrogenase cofactor are represented in the molybdenum-dependent nitrogenases.

2. MOLYBDENUM AND TUNGSTEN-CONTAINING ENZYMES FAMILIES

2.1. Sulfite Oxidase Family

The SO family enzymes are characterised by having an active site that holds a molybdenum ion coordinated, in a distorted square-pyramidal geometry, by an apical oxo group (Mo=O) and, in the equatorial plane, by the two sulfur atoms of the *cis*-dithiolene group (–S–C=C–S–) of one pyranopterin cofactor molecule, one oxo group (Mo=O) and one cysteine sulfur atom (Mo-S(Cys)) (Figure 2) [9-11,27,28]. This family comprises the prototype vertebrate liver SO (eq. 1) [29-33], diverse prokaryotic sulfite dehydrogenases [34-39], the eukaryotic assimilatory nitrate reductase (NaR; an enzyme involved in nitrate assimilation in plants, algae and fungi; eq. 2) [40-49], among several other enzymes [50-62].

vertebrate sulfite oxidase (sulfite oxidation to sulfate):

$$SO_2^{2-} + H_2O + 2\ \text{cytochrome}\ c\,(Fe^{3+}) \longrightarrow OSO_2^{2-} + 2\ \text{cytochrome}\ c\,(Fe^{2+}) + 2H^+ \quad (1)$$

plant nitrate reductase (nitrate reduction to nitrite):

$$ONO_2^- + NAD(P)H + H^+ \longrightarrow NO_2^- + H_2O.. + NAD(P)^+ \quad (2)$$

The enzymes from this family typically catalyse oxo-transfer reactions, both the insertion and the abstraction of an oxygen atom, as is clearly exemplified by the SO-catalysed sulfite oxidation to sulfate (eq. 1) and by the NaR-catalysed nitrate reduction to nitrite (eq. 2), respectively. During the oxygen atom insertion catalysis -as exemplified by the SO catalysis [30,52,59,63-72]- is the oxidised $Mo^{6+}{=}O_{equatorial}$ centre that acts as the direct oxygen donor and oxidant (Figure 3-a). Conversely, during the oxygen atom abstraction catalysis -NaR catalysis [43,45,46,73-77]- is the reduced Mo^{4+} centre, whose equatorial oxo group was eliminated in the form of a water molecule, that acts as the direct oxygen acceptor and reducer (Figure 3-b). In both cases, the ultimate oxygen atom donor or acceptor is a water molecule (follow the red oxygen atoms in eq. 1 and 2 and in Figure 3-a,b) and the molybdenum ion is re-oxidised or re--reduced (respectively) via electron transfer from the physiological partner.

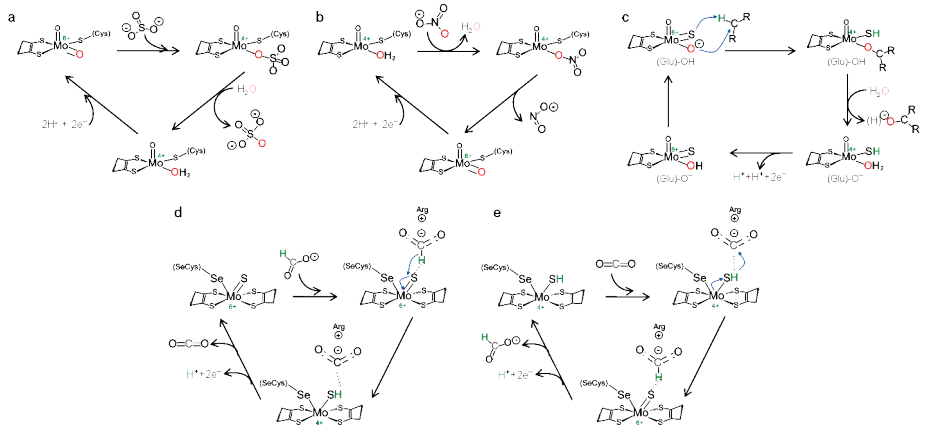
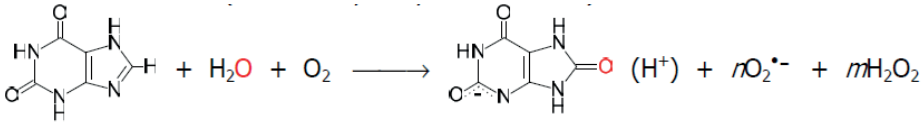


Figure 3. Simplified mechanistic proposals for the reactions catalysed by selected enzymes. Reactions were chosen to highlight the key mechanistic features of these enzymes. (a) Reaction of sulfite oxidase-catalysed sulfite oxidation to sulfate (sulfite oxidase family – oxygen atom insertion). (b) Reaction of eukaryotic nitrate reductase-catalysed nitrate reduction to nitrite (sulfite oxidase family – oxygen atom abstraction). (c) Reaction of xanthine oxidase-catalysed xanthine hydroxylation to urate (xanthine oxidase family – oxygen atom insertion with hydrogen atom abstraction). (d) and (e) Reaction of formate dehydrogenase-catalysed formate oxidation and carbon dioxide reduction, respectively (dimethylsulfoxide reductase oxidase family – hydrogen atom abstraction and insertion respectively; note: the active site of these enzymes can harbour a selenocysteine or a cysteine residue – for simplicity, only the former case is represented). See text for details.

2.2. Xanthine Oxidase Family

The XO family enzymes hold a molybdenum-containing active site that is closely related with the one of the SO family, but with the distinctive feature of not having the molybdenum directly coordinated to the protein (Figure 2) [9-11,78]. These enzymes, instead, harbour one equatorial, catalytically labile, -OH group plus one terminal sulfo (Mo=S) or seleno (Mo=Se) group. This family comprises the prototype mammalian XO (eq. 3) [47,78-94], mammalian aldehyde oxidase (AO) (eq. 4) [94-117], bacterial aldehyde oxidoreductase (eq. 5) [118-124] or hydroxybenzoyl-CoA reductase (eq. 6) [125-128].

mammalian xanthine oxidase (xanthine hydroxylation to urate):



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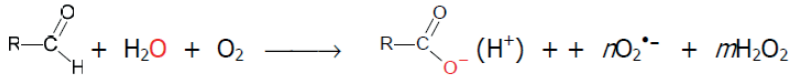
mammalian aldehyde oxidase (aldehyde hydroxylation to carboxylate):



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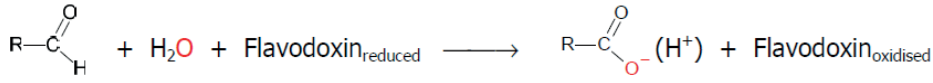
bacterial aldehyde oxidoreductase (aldehyde hydroxylation to carboxylate):



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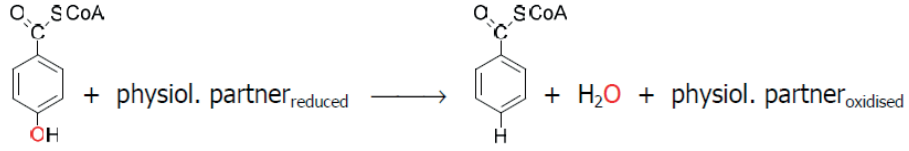
bacterial hydroxybenzoyl-CoA reductase (hydroxybenzoyl-CoA dehydroxylation to benzoyl-CoA):



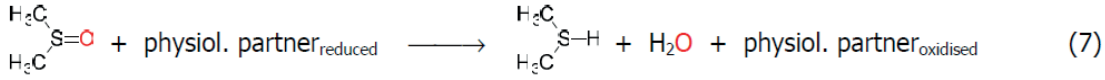
(6)

The enzymes from this family typically catalyse the hydroxylation of a C-H bond in aromatic heterocyclic compounds (eq. 3) and aldehydes (eq. 4, 5), as well as, the reverse reaction of dehydroxylation (eq. 6). During the hydroxylation catalysis -as exemplified by the XO catalysis [47,79,80,82,83,86,88,91,129--136]- the terminal sulfo (or seleno) group of the oxidised molybdenum centre, $Mo^{6+}=S_{equatorial}$ (or $Mo^{6+}=Se_{equatorial}$) is key to activate the C-H bond to be cleaved, acting as a hydride acceptor, while the equatorial labile oxygen acts as the direct oxygen donor (Figure 3-c). In the reverse dehydroxylation reaction (eq. 6), it is the reduced Mo^{4+}-$SH_{equatorial}$ that acts as the direct hydride donor [127,128]. As described for the SO family, water is the ultimate source of the oxygen atom incorporated into the hydroxylated product (follow the red oxygen atoms in eq. 3 to 6 and in Figure 3-c) and the molybdenum ion is re-oxidised via electron transfer from the physiological partner.

2.3. Dimethylsulfoxide Reductase Family

The DMSOR family enzymes are characterised by having an active site that holds a molybdenum ion coordinated by four sulfur atoms of two pyranopterin cofactor molecules; the molybdenum coordination sphere is completed by oxygen and/or sulfur and/or selenium atoms in a diversity of combinations, in a trigonal prismatic geometry (Figure 2) [9-11,137]. Most often, the molybdenum ion is directly coordinated to the polypeptide chain, as the SO family enzymes. Yet, the DMSOR family enzymes display a remarkable diversity of coordinating residue side chains, including not only cysteine, but also selenocysteine, aspartate and serine residues. In addition, and similar to the enzymes of the XO and SO families, the active site of these enzymes can also have terminal sulfo and oxo groups. This family is the most diverse one of the molybdoenzymes, comprising only prokaryotic enzymes, such as the prototype DMSOR (eq. 7) [137-147], three different types of NaR enzymes (dissimilatory membrane-bound enzymes, dissimilatory periplasmatic enzymes and assimilatory cytoplasmatic enzymes) [148-160], arsenite oxidase (eq. 8) [161-164], formate dehydrogenases (FDH; eq. 9)) [165-192], polysulfide reductase (eq. 10) [193-197] and many other diverse enzymes [137,182,198-201].

bacterial dimethylsulfoxide reductase (dimethylsulfoxide reduction to dimethylsulfide):



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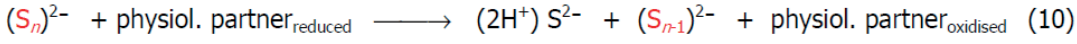
bacterial arsenite oxidase (arsenite oxidation to arsenate):

(8)

bacterial formate dehydrogenase (reversible formate oxidation to carbon dioxide):

(9)

bacterial polysulfide reductase (polysulfide reduction to sulfide):



(10)

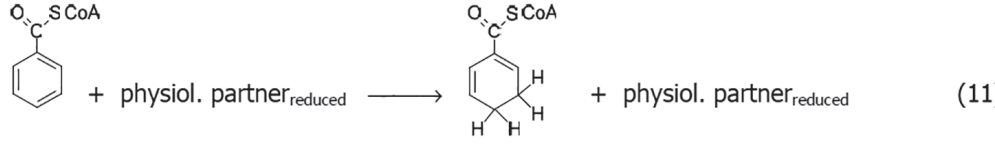
The enzymes from this family catalyse remarkably different reactions, including oxygen atom transfer, hydrogen atom transfer and sulfur atom transfer, as can be exemplified by the DMSOR-catalysed dimethylsulfoxide reduction to dimethylsulfide (eq. 7) or the NaR-catalysed nitrate reduction to nitrite and the arsenite oxidase (eq. 8) (for oxygen transfer), the FDH-catalysed reversible formate oxidation to carbon dioxide (eq. 9) (for hydrogen transfer) and the polysulfide reductase-catalysed polysulfide reduction to sulfide (eq. 10) (for sulfur transfer). This extraordinary diverse chemical reactivity is, as can be anticipated, matched by the diverse active site architecture displayed by these enzymes. Hence, both arsenite oxidase and DMSOR reductase, enzymes that catalyse oxygen atom insertion (eq. 8) and abstraction (eq. 7), respectively, hold one terminal oxo group. During arsenite oxidase-catalysed oxygen insertion, it is the labile oxo group of the oxidised centre, Mo^{6+}=O, that acts as the direct oxygen donor [161-164] -similarly to the SO catalysis (Figure 3-a). Conversely, during DMSOR-catalysed oxygen

abstraction, it is the reduced Mo^{4+} centre, whose catalytically labile oxo group was eliminated in the form of a water molecule, that acts as the direct oxygen acceptor [202-205] -in parallel to the NaR catalysis (Figure 3-b). As in SO and XO family enzymes, the ultimate oxygen atom donor or acceptor in these two DMSOR family enzymes is a water molecule and the molybdenum ion is re-oxidised or re-reduced (respectively) via electron transfer from the physiological partner. The mechanistic strategy proposed for the sulfur atom abstraction catalysed by the polysulfide reductase, an enzyme holding also a terminal oxo group, is comparable to the DMSOR one, with the reduced Mo^{4+} centre, whose catalytically labile oxo group was eliminated in the form of a water molecule, acting as the sulfur atom acceptor [193,194,197]. In contrast, FDH, that catalyses the reversible hydrogen atom transfer (eq. 9), holds one terminal sulfo group. During catalysis, it is the terminal sulfo group of the FDH oxidised molybdenum centre, Mo^{6+}=S, that acts as hydride acceptor, while the reduced centre, Mo^{4+}-SH, acts as hydride donor (Figures 3-d and 3-e) [185-192] -comparable to the XO family enzymes catalysis (Figure 3-c).

2.4. Tungstoenzymes Family

The active site of this enzymes family is similar to the one of the DMSOR family of molybdoenzymes. The tungstoenzymes harbour one tungsten ion, in the place of the molybdenum, coordinated by four sulfur atoms of two pyranopterin cofactor molecules, plus oxygen and/or sulfur and/or selenium atoms, in a diversity of arrangements, in a trigonal prismatic geometry or in a distorted octahedral coordination geometry (Figure 2) [4,10,206]. This family comprises prokaryotic enzymes of diverse functions, including benzoyl-CoA reductase (eq. 11) [207-211], aldehyde oxidoreductase (enzyme homologous to the one from the XO family (eq. 5)) [212-216], FDH (enzyme homologous to the one from the DMSOR family (eq. 9)) [14,217-233], among several other enzymes. Matching the active site structural similarity with the DMSOR family enzymes, the reaction mechanism of tungstoenzymes is, in general, believed to be similar to the ones of DMSOR family enzymes [207,210,234-239].

bacterial benzoyl-CoA reductase (benzoyl-CoA reduction to cyclohexa-1,5-diene-1-carboxyl-CoA)



(11)

2.5. Nitrogenase Family

This family only comprises the molybdenum/iron-dependent nitrogenase. (*It should be noted that, besides the molybdenum/iron-dependent enzyme, there are also other similar nitrogenases that depend on vanadium/iron and only on iron; those enzymes, however, exhibit lower catalytic efficiencies and products stoichiometry [240--257]. The molybdenum-independent nitrogenases will not be herein discussed and the term "nitrogenase" will be used to refer only to the molybdenum/iron-dependent enzyme.*)The nitrogenase active site holds a complex, high-nuclearity centre, comprising one molybdenum and seven iron ions (Figure 2) [10,17-26,258-269]. This unique centre, present only in the nitrogenase, can be viewed as two cubes, with a common corner made of a carbide ion (C^{4-}) ([$Fe_4S_3C_{common}$] and [$MoFe_3S_3C_{common}$]) and bridged by three additional sulfur

ions; besides the three sulfur ions from the "cube", the molybdenum ion is further coordinated by one homocitrate ion (Figure 2).The nitrogenase enzymes are known for long, with the first mention to the biological dinitrogen fixation occurring in the middle of the nineteenth century [270]. These bacterial enzymes catalyse the remarkable reaction of dinitrogen reduction (fixation) to ammonium, with the cleavage of the exceptionally stable N≡N triple bond (eq. 12), a key step in the global biogeochemical cycle of nitrogen (Figure 4).

bacterial nitrogenase (dinitrogen reduction to ammonium):

$$N{\equiv}N + 8H^+ + 8e^- + 16MgATP \longrightarrow 2NH_3 + H_2 + 16MgADP + 16P_i \qquad (12)$$

Unravelling the mechanism by which the triple bond of dinitrogen is cleaved by nitrogenase has been a highly challenging task. While the structure of the nitrogenase proteins and of their metal centres is presently well known, there are still many uncertainties regarding the reaction mechanism. The most recent mechanistic proposals suggest that the activation and reduction of dinitrogen depends on the prior reductive elimination of iron-based hydrides, in the form of dihydrogen [256,271-275]. This proposal is based on the fact that the formation of dihydrogen is obligatory for the dinitrogen reduction to occur (eq. 12) and this mechanistic strategy would allow the enzyme to store the necessary high reducing power to cleave the dinitrogen bond. The molybdenum ion, suggested to be present in an unprecedented 3+ oxidation state (Mo^{3+}) [276,277], is thought to be essential to tune the centre electronic structure to modulate its reduction potential and/or to facilitate the substrate binding or protonation [278-280].

3. BIOTECHNOLOGICAL APPLICATIONS AND HUMAN HEALTH IMPLICATIONS

3.1. Carbon Footprint and Atmospheric Carbon Dioxide Utilization – Formate dehydrogenases

The global energy demand and the present high dependence on fossil fuels have caused the increase in the atmospheric carbon dioxide concentration for the highest values since records began [281]. Due to its significant green-house effect, carbon dioxide rise is responsible for large and unpredictable impacts on the world climate, besides being responsible for ocean warming and acidification (its major sink) [282,283]. While some authors defend that these alterations are no longer reversible, the carbon dioxide emissions must be greatly decelerate. Future energy sources should be carbon-neutral and based on solar, wind and geothermal energy and new methods to store, transport and use "on demand" the energy from these sources must be developed.

One solution to control the actual "carbon dioxide crisis" (alongside all other efforts to reduce emissions) would be the use of a renewable, low (or zero) carbon-dependent energy, to scavenge the atmospheric carbon dioxide and convert it back into fuels [284]. Certainly, the carbon dioxide abundance makes it an attractive source for the production of fuels and other synthetic added-value chemicals and there is a huge interest in the development of strategies to efficiently scavenge and activate the atmospheric carbon dioxide [281,285-288]. One of the major challenges is the thermodynamic and kinetic stability of the carbon dioxide molecule that makes its laboratory/industrial activation a very difficult task. Living organisms, on the contrary, have found several different strategies to activate and use carbon dioxide [289-292], applying different chemical approaches, with specific enzymes, to cleave the C-O bond

(reduction to carbon monoxide) and form C-C (*e.g.*, addition to ribulose 1,5-bisphosphate) and C-H bonds (reduction to formate) [288-294].

Understanding the chemical strategies already tested and proved by Nature would certainly contribute to the development of new efficient biocatalysts for the atmospheric carbon dioxide utilization [281,288,295-301]. In this respect, the utilization of molybdenum- and tungsten-containing FDH enzymes (eq. 9; sections 2.3. and 2.4.) is most promising. FDH confers to the future biocatalyst specificity, selectivity and efficiency: only carbon dioxide is consumed, only one product, formate, is formed (no need for further purification procedures) and the reaction proceeds at actually mild conditions of temperature, pressure and pH (ambient temperature and pressure and neutral pH). The carbon dioxide reaction product, formate, is an interesting compound for several reasons: it is the first (and stable) intermediate in the reduction of carbon dioxide to methanol or methane; it is used as a chemical building block in industry; it is a viable energy source, easier to store and transport than dihydrogen (formate and dihydrogen are oxidised at similar potentials) and fuel cells that use formate are already being developed. All these positive outcomes make worthwhile the actual investigation aiming to develop more efficient (bio) catalysts to convert carbon dioxide into formate using FDH enzymes.

3.2. Environment and Food: A World Wide Problem

3.2.1. Nitrate Bioremediation – Nitrate Reductases

The exponential rise of the human population and the consequent demand of food have lead to a global increase in intensive agricultural practices, with the use of massive amounts of nitrogen-based fertilisers [302]. The overload of soils with nitrate and ammonium contaminates not only the land, but also the fresh surface, ground waters and marine waters, causing a cascade of environmental and human health problems. The highly soluble nitrate, *e.g.*, can pollute the aquifers that supply drinking water and contaminate fish and shellfish cultures; together with phosphorous-containing fertilisers, can lead to the eutrophication of aquatic ecosystems, with its concomitant destruction [303,304]. Moreover, the long--range transport of these highly soluble nitrogen-based fertilisers expands the environmental and human health problems far from the original local borders.

One solution to mitigate the actual nitrate contamination would be the introduction of key removal steps in waste water treatment plants. Regarding the nitrate removal, the utilisation of molybdenum--dependent NaR enzymes (eq. 2), with their inherent specificity, selectivity and efficiency, would be ideal. The subsequent reduction of nitrite, that is toxic as nitrate, would be achieved by other specific enzymes.

3.2.2. Nitrogen Fixation – Nitrogenase

As highlighted above, the ever growing demand of food have lead to a global increase in intensive agricultural practices, with the use of massive amounts of nitrogen-based fertilisers. In our modern society, the factor that most frequently limits agricultural production is the nitrogen availability and nearly half of the existing human population could not be fed without the use of industrially produced nitrogen fertilisers [305].

The ammonium production is achieved by the well known Haber-Bosch process, a heterogeneous catalytic process that operates at high temperatures and pressures to reduce dinitrogen to ammonium

[306-308]. This industrial process, with its harsh conditions, is neither energetically efficient nor environmentally responsible. Understanding the biological dinitrogen reduction to ammonium (Figure 4, eq. 12, section 2.5) [48,309-312] could, thus, help us in the development of improved, "greener", environmentally friend, synthetic catalysts or of genetically modified organisms with the capacity to fix their own nitrogen. Undoubtedly, the dinitrogen abundance in the atmosphere (where it accounts for 78.1% of the entire volume) makes it an attractive source for the production of ammonium. In fact, prior to the invention of the Haber–Bosch process, the organisms that fixate dinitrogen (some free-living archea and bacteria, *e.g.*, *Azotobacter*, and symbiotic bacteria, *e.g.*, *Rhizobium*) were responsible for 95% of fixed bioavailable nitrogen [17,267,268,313-322].

The nitrogenase enzymes are known for long, with the first mention to the biological dinitrogen fixation occurring in the middle of the nineteenth century [270]. Presently, due to the increasing awareness of the environmental issues behind the need to "feed the world", there is an intense research around nitrogenases and new developments are foreseen -and much needed- for the near future.

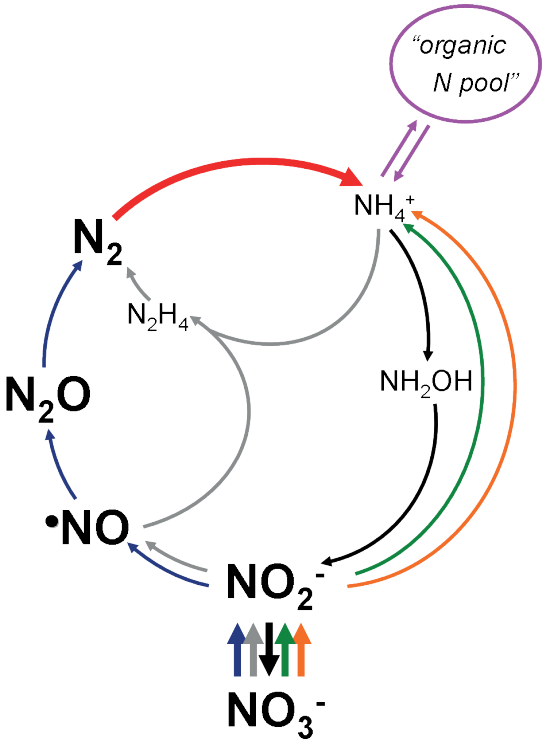


Figure 4. Biogeochemical cycle of nitrogen. Dinitrogen fixation, red arrow; dissimilatory nitrate reduction to ammonium, green arrows; assimilatory ammonification, orange arrows; denitrification, blue arrows; nitrification, black arrows; anaerobic ammonium oxidation, grey arrows; "organic nitrogen pool", pink arrows. The molybdenum-dependent steps are highlighted with thicker lines.

4. HUMAN HEALTH IMPLICATIONS

Molybdenum plays several key roles in humans, even though we only hold four molybdenum-containing enzymes, XO, AO (XO family), SO and the newly identified mitochondrial amidoxime reducing component (mARC) (SO family).

One striking molybdenum role occurs in the purine metabolism, whose dependence on molybdenum is common to almost all forms of life, with only a very small number of organisms use other mechanisms to oxidise xanthine, *e.g.*, some yeasts [1-3,323-326]). In humans, XO is involved in the sequential hydroxylation of hypoxanthine and xanthine into urate (section 2.2.) and due to this activity, XO is one of the targets for therapy of hyperuricaemia and gout [327,328]. In humans, urate is the end-product of purine catabolism (*in some other animals, urate is further oxidised to allantoin, by uricase [329-331]*) and a high blood urate concentration is a risk factor for gout [332], kidney diseases [333], endothelial dysfunction [334-337] and other diseases related to metabolic syndromes [338]. To control the urate concentration, clinicians use XO inhibitors (and/or drugs to increase urate secretion) [339]. The efficacy of XO inhibition as a strategy for prevention of gout attack is well established and the XO inhibitor allopurinol (an isomer of hypoxanthine) has been used to treat gout for more than 40 years.

The human AO is key to handle aldehydes/carboxylates and heterocyclic compounds and has been suggested to participate in the metabolism of neurotransmitters and in the formation of retinoic acid, a metabolite of retinol (vitamin A) that is involved in growth and development [96-99,106,108-110,114].

Furthermore, due to the XO and AO ability to generate reactive oxygen species (ROS) under normoxia (eq. 3 and 4), these enzymes have been implicated in signalling pathways and, most significantly, in some ROS-mediated diseases, when their ROS production becomes imbalanced; these include the well known ischaemia-reperfusion injury [340-345] and other cardiovascular and related diseases [84,87,112,113,116,117, 346-363], which are major health concerns of our western society. The recently identified ability to generate signalling nitric oxide under hypoxia, from nitrite (eq. 13), establishes further links between the XO and AO and human diseases, such as hypertension, endothelial dysfunction and other conditions associated with a reduced nitric oxide bioactivity [92,94,364-375].

$$NO_2^- + \text{physiol. partner}_{\text{reduced}} \longrightarrow 2\,{}^{\bullet}NO + \text{physiol. partner}_{\text{oxidised}} \qquad (13)$$

In addition, both XO and AO, together with mARC, are key players in the metabolism of xenobiotic compounds. Besides the mentioned "classic" substrates (above and section 2.2), XO and AO catalyse the oxidation (mostly hydroxylation) of a wide variety of carbon centres of heterocyclic aromatic compounds, namely substituted pyrimidines, purines, pteridines, and related compounds, and of compounds containing aldehyde groups; XO and AO have also a broad range of reducing substrates, being able to catalyze the reduction of several *S*-oxides, *N*-oxides and other unrelated compounds [84,87,91,96-99,100,102,104,106-111,114,113,117,351,376-386]. The mARC enzyme, in its turn, is also able to catalyse the reduction of a wide variety of *N*-hydroxylated compounds [375,387-404]. This unusual substrate promiscuity makes these three enzymes relevant players in the metabolism of xenobiotic compounds, in parallel with the well known cytochrome P_{450}-containing isoenzymes system [405-410]. Some examples of their toxicological and pharmacological importance can be found in the deleterious activation of azo

dyes (used as colorants in food and cosmetics [411,412]), the beneficial activation of anti-neoplasic [413,414] and anti-hypertensive drugs [415] or the redundant drug deactivation [99,116,416-422]. The XO, AO and mARC promiscuity has, in fact, been a serious problem for drug development, since many drugs designed to resist other liver metabolising enzymes (namely the cytochrome P_{450}-containing isoenzymes system) are often oxidised/reduced by one of these enzymes. The resulting reduced active drug bioavailability (consequence of the drug metabolism/inactivation by these enzymes) and consequent decreased/abolished therapeutic efficacy is, actually, causing many clinical trials to fail.

The high impact of molybdoenzymes in human metabolism and in a wide range of human pathological conditions is clearly evident from the above discussion on the XO, AO and mARC roles. Yet, the most striking role of molybdenum in humans is certainly provided by SO, whose deficiency is an actual life threat [423-430]. Sulfite (derived not only from the catabolism of sulfur-containing amino acids, but also from sulfur-containing xenobiotic compounds) is toxic and its controlled oxidation to sulfate, by SO (eq. 1), is critical for survival. Confirming this vital role are the severe neonatal neurological problems, including attenuated brain growth, mental retardation, seizures and early death, caused by human SO deficiency. The SO deficiency, when caused by the inability to synthesise the pyranopterin cofactor that holds the molybdenum ion (Figure 2; and not by protein mutation (*e.g.* [431])), can be treated with the continuous administration of the cofactor produced synthetically [429,430].

5. CONCLUDING REMARKS

In living organisms, molybdenum and tungsten are found in the active site of enzymes that catalyse redox reactions. Some of these reactions constitute key steps of the global biogeochemical cycles of nitrogen, carbon and sulfur. The molybdenum participation in the nitrogen cycle is of particular relevance: nitrogen fixation and photosynthesis are two of the most important processes for Life on Earth and the dinitrogen reduction is highly dependent on molybdenum. Remarkably, molybdenum has also a high impact in human metabolism, being involved in a wide range of human pathological conditions. Moreover, the utilisation of molybdenum- and tungsten-containing enzymes is highly promising for solving some of the present humankind's problems in the fields of environment, agriculture and energy.

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