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REVIEW ARTICLE

Xanthine Oxidoreductase in Drug Metabolism: Beyond a Role as a Detoxifying Enzyme

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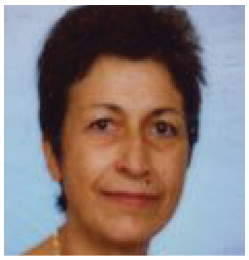
Abstract: The enzyme xanthine oxidoreductase (XOR) catalyzes the last two steps of purine catabolism in the highest uricotelic primates. XOR is an enzyme with dehydrogenase activity that, in mammals, may be converted into oxidase activity under a variety of pathophysiologic conditions. XOR activity is highly regulated at the transcriptional and post-translational levels and may generate reactive oxygen and nitrogen species, which trigger different consequences, ranging from cytotoxicity to inflammation. The low specificity for substrates allows XOR to metabolize a number of endogenous metabolites and a variety of exogenous compounds, including drugs.



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The present review focuses on the role of XOR as a drug-metabolizing enzyme, specifically for drugs with anticancer, antimicrobial, antiviral, immunosuppressive or vasodilator activities, as well as drugs acting on metabolism or inducing XOR expression.

XOR has an activating role that is essential to the pharmacological action of quinone drugs, cyadox, antiviral nucleoside analogues, allopurinol, nitrate and nitrite. XOR activity has a degradation function toward thiopurine nucleotides, pyrazinoic acid, methylxanthines and tolbutamide, whose half-life may be prolonged by the use of XOR inhibitors.

In conclusion, to avoid potential drug interaction risks, such as a toxic excess of drug bioavailability or a loss of drug efficacy, caution is suggested in the use of XOR inhibitors, as in the case of hyperuricemic patients affected by gout or tumor lysis syndrome, when it is necessary to simultaneously administer therapeutic substances that are activated or degraded by the drug-metabolizing activity of XOR.

Keywords: Anticancer drugs, Antimicrobial drugs, Immunosuppressive drugs, Nitrovasodilators, Purine analogues, Xanthine oxidoreductase.

1. INTRODUCTION

The enzyme xanthine oxidoreductase (XOR) converts hypoxanthine to xanthine and the latter to uric acid, which are the last two steps of purine catabolism in the highest uricotelic primates. This activity has a rate-limiting effect on the recovery of nucleotides because it interferes with the purine salvage pathway by producing the irreversible products xanthine and uric acid (Fig. **1**). Although the activity of XOR has been known for over a century, its function is not fully understood and appears wider than merely a housekeeping role in nucleic acid metabolism.

Depending on the circumstances, XOR has different enzymatic activities; it can act as (i) an oxidized nicotinamide adenine dinucleotide (NAD^+)-dependent dehydrogenase, (ii) a molecular oxygen (O_2)-dependent oxidase, (iii) a reduced nicotinamide adenine dinucleotide (NADH) oxidase, or (iv) a reductase for N-oxide, nitrite and nitrate. The products of XOR activity have both oxidant and antioxidant properties and are involved

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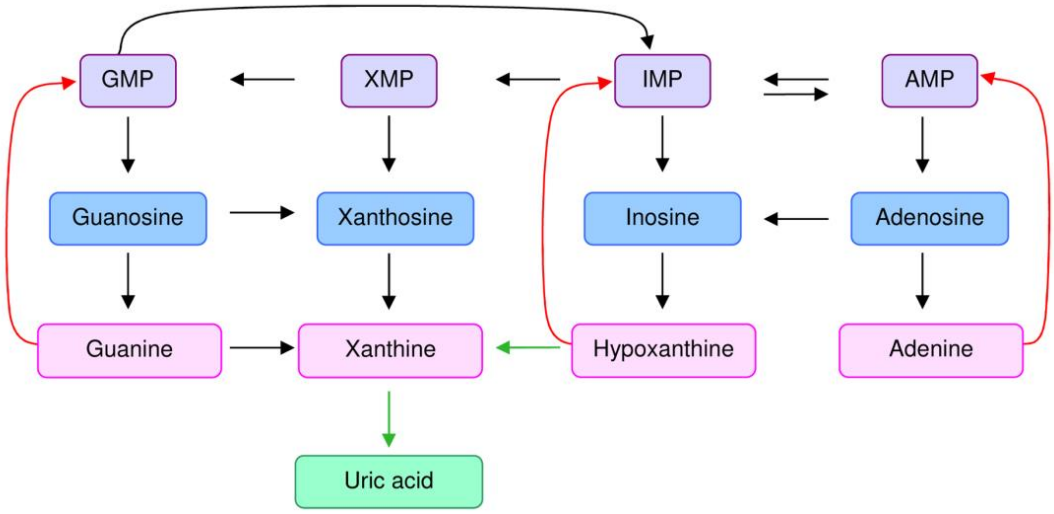

Fig. (1). Purine catabolism and the purine salvage pathway. AMP, GMP, IMP and XMP are the monophosphate nucleotides of adenine, guanine, hypoxanthine and xanthine, respectively. The purine salvage pathways are indicated with red arrows, and the green arrows refer to the reactions catalyzed by XOR activity (reviewed in [1]).

in the regulation of vascular tone and blood pressure as well as in the induction of inflammation and the reparative response (reviewed in [2]).

XOR has a low specificity for substrates and is able to metabolize a number of endogenous metabolites and a variety of exogenous compounds, including drugs, thus playing a significant role not only as a xenobiotic-detoxifier but also as a drug-metabolizing enzyme. The present review focuses on the function of XOR in the metabolism of pharmacological substances that are used for therapeutic purposes.

2. BIOLOGY OF XANTHINE OXIDOREDUCTASE

XOR belongs to a family of very ancient and highly conserved molybdo-flavoenzymes. This family includes aldehyde oxidase in plants and animals and some prokaryotic enzymes, which all possibly originated from a common ancestral XOR-coding gene system. Bacterial XOR is a heterotrimeric protein that involves the expression of three structural genes that code for three subunits corresponding to the N-terminal, central and C-terminal domains of the monomeric eukaryotic enzyme (see below). The phylogenetic distribution of molybdo-flavoenzymes has been previously reported (reviewed in [3,4]).

Eukaryotic XOR is a homodimeric protein that, in mammals, consists of two equal subunits of approximately 145 kDa, each including three domains of approximately 85, 40 and 20 kDa (Fig. **2**). The C-terminal domain, which is the largest domain, contains one atom of molybdenum (Mo) linked to a molybdopterin cofactor (Moco), the intermediate domain includes one flavin adenine dinucleotide (FAD) cofactor, and the N-terminal domain, which is the smallest domain, has two unequal ferredoxin iron-sulfur clusters [2Fe-2S]. During the reaction, electrons are transferred from the purine substrate to Moco, then to FAD via Fe/S I and Fe/S II, and ultimately released to the final electron acceptor, which is reduced (reviewed in [5]).

Constitutively, XOR is a NAD^+-dependent dehydrogenase (XDH, EC 1.17.1.4) that catalyzes the hydroxylation of hypoxanthine to xanthine and the hydroxylation of xanthine to uric acid with the production of NADH. Uric acid has a protective antioxidant action at physiological concentrations in plasma, whereas in excess, it has been associated with pathological conditions such as hypertension and nephrolithiasis. Additionally, uric acid may induce an inflammatory response and oxidative stress when released from injured cells in damaged tissue (reviewed in [6]).

In mammals, XOR may be converted into an oxidase (XO, EC 1.17.3.2), not only as a consequence of the catabolic process of XOR protein, but also as a post-translational regulation of XOR activity. This conversion occurs under a variety of pathophysiological conditions, such as the respiratory burst in phagocytic cells during inflammation, and during hypoxia/reoxygenation and ischemia/reperfusion injury or liver damage by viral infection or toxic substances. While XDH prevails intracellularly, XO is the prevalent form of the enzyme in body fluids, such as milk and plasma, where XOR may be secreted or released

from dead cells and transformed into XO (reviewed in [7]).

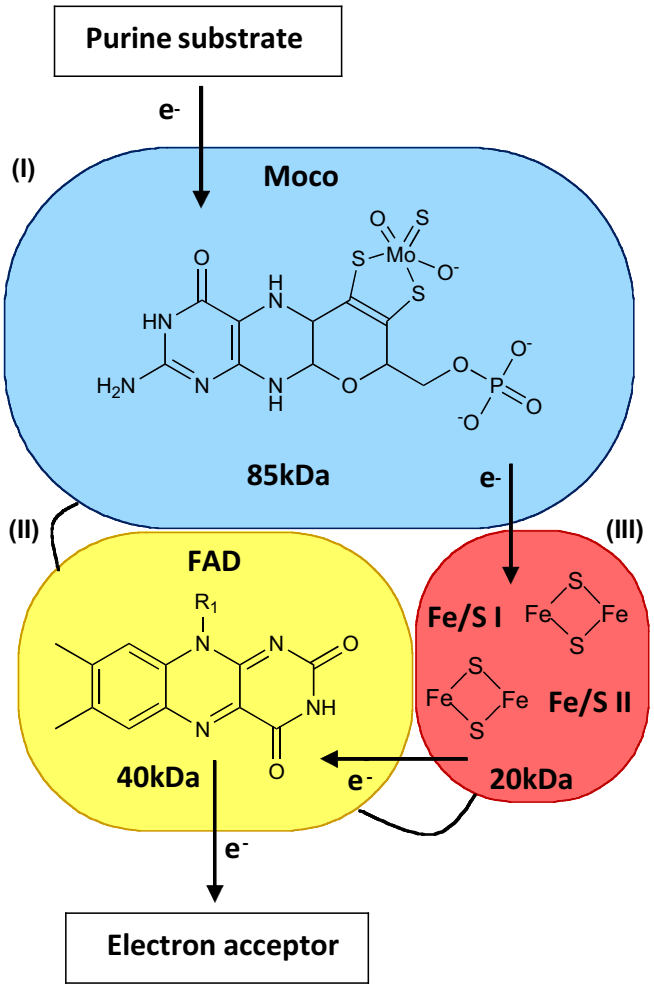

Fig. (2). Molecular structure and catalytic electron flow of xanthine oxidoreductase (XOR). Each XOR monomer consists of **(I)** a C-terminal domain of approximately 85 kDa (blue) that includes a molybdenum-containing molybdopterin cofactor (Moco) and a binding site for purine and nitrate/nitrite substrates; **(II)** an intermediate domain of approximately 40 kDa (yellow) that contains the flavin adenine dinucleotide (FAD) cofactor, which delivers the electrons to the final acceptor, either oxidized nicotinamide adenine dinucleotide or molecular oxygen, generating reactive molecular species; and **(III)** an N-terminal domain of approximately 20 kDa (red) that contains the iron-sulfur clusters Fe/S I and Fe/S II, which convey the electrons from Moco to FAD (reviewed in [3-5]).

The transition between XDH and XO may take place either irreversibly, by partial proteolysis, or reversibly, by the chemical or enzymatic oxidation of thiol groups. Both processes involve four Cys residues located in a linker peptide that connects the Mo- and FAD-containing domains. The reversible XDH to XO conversion occurs in two steps, which correspond to the formation of an initial disulfide bond in a rapid phase and the much slower formation of a second disulfide bond. Thus, the conversion includes an intermediate XOR form, having only the rapidly formed disulfide bond. This intermediate form can deliver electrons to both NAD^+ and O_2 [8].

Both XO and XDH may generate the reactive oxygen species (ROS) superoxide anion ($O_2^{\bullet-}$) and hydrogen peroxide (H_2O_2) during the oxidation of substrates. ROS production by XO occurs as a consequence of substrate oxidation. XDH produces ROS by the oxidation of NADH occurring at FAD-containing domain. This reaction is inversely dependent on the pH and the O_2 tension and is thus favored under hypoxic conditions. However, only the production of ROS via XO activity may be inhibited with allopurinol, which competes with substrates at the Moco site, but allopurinol is ineffective on the ROS production by NADH oxidase activity of XDH. At least in part, this consideration may justify the variable and disappointing results obtained with allopurinol in the attempt to reduce the tissue damage that results from ischemia/reperfusion (reviewed in [9]).

XOR-derived ROS in the presence of transition metals may create the highly cytotoxic hydroxyl radical ($HO^{\bullet}$) through the Haber-Weiss and Fenton reactions. Moreover, XOR can produce reactive nitrogen species (RNS) by reducing nitrate and nitrite to nitric oxide (NO) and converting the latter to peroxynitrite ($ONOO^-$) in the presence of $O_2^{\bullet-}$. As a physiological source of $O_2^{\bullet-}$, H_2O_2 and NO, XOR may deliver second messengers that can activate various pathways leading to phlogistic response, apoptosis, or cell differentiation. On the other hand, these reactive molecular species may mediate cytotoxicity and tissue damage or may induce mutagenesis, cell proliferation and tumor progression. The positive and negative biological effects of ROS and RNS derived from XOR activities have been recently reviewed [2].

Endothelial XOR is an enzyme that regulates inflammatory signaling and vascular tone. This pathophysiological role depends on the ability of XOR to produce ROS and NO, specifically after being released into circulation, converted to the oxidase form and bound to endothelial cells. XOR activity has been implicated not only in the activation of endothelial cells to induce an inflammatory response and/or to regulate the local vascular tone but also in the endothelial dysfunction that is crucial in atherosclerosis pathogenesis, car-

diovascular diseases and metabolic syndrome (reviewed in [10]).

XOR is mainly produced by epithelial cells, and it is localized primarily in the cytoplasm, with the exception of endothelial cells in which circulating XOR may bind to the cell membrane's outer surface. Although traces of the enzyme have been detected in almost all human tissues, high amounts of XOR have been found in only the lactating mammary gland, intestine, liver, kidney and vascular endothelium. The transcription of the human gene for XOR (*hXOR*) is normally down-regulated in most cells, with the exception of breast, kidney and digestive apparatus cells. However, an increase in XOR expression may be induced by hormones, growth factors, cytokines and low oxygen tension (reviewed in [7]).

XOR post-translational expression is also tightly modulated, leading to quantitative and qualitative changes in enzyme activity. XOR protein modifications may originate (i) the demolybdo- and/or desulfo-forms of the XOR protein, which can oxidize NADH, thus producing ROS, but are inactive in xanthine catalysis, and (ii) the interconvertible XOR dehydrogenase intermediate and oxidase forms (reviewed in [7]). The fine tuning of XOR expression and activity may be functional to keep the balance between the oxidant and anti-oxidant effects of its products in equilibrium (reviewed in [11]).

3. ANTICANCER AND IMMUNOSUPPRESSIVE DRUGS

Various antineoplastic drugs work by blocking cellular replication, thus acting on tumor blastic cells and on lymphoblasts, resulting in an immunosuppressive action. Some of these drugs are metabolized by XOR, which may cause an activating effect through a reductive process or may lead to drug degradation through an oxidizing activity (Fig. **3**).

Quinone antibiotics, such as doxorubicin, menadione, mitomycin C and streptonigrin, have anticancer activity against solid tumors. They may intercalate DNA base pairs, producing single-strand breaks and DNA cross-links. To exert their antineoplastic action, these drugs must be reductively activated by a one-electron reductase activity, and the role of XOR in this process has been investigated. Bovine milk XO reductively activated mitomycin C under anaerobic conditions [12]. The bioreductive activation process of doxorubicin, menadione and streptonigrin was performed *in vitro* by both purified XO and XDH; however, the latter was more efficient [13]. By reducing the anticancer quinone drugs, XOR generates ROS, which are responsible for the drug antineoplastic activity through the consequent formation of hydroquinone and semiquinone in aerobic and hypoxic conditions, respectively (reviewed in [14]).

Purine nucleotide analogues belong to another category of anticancer and immunosuppressive drugs that act on the basis of their similarity to endogenous compounds, allowing them to be metabolized like their regular analogues. All the steps of the development of these drugs were thoroughly discussed together with the problems regarding their metabolism by G.B. Elion in the lecture delivered when she earned the Nobel Prize for Phisiology or Medicine in 1988 (condensed in [15]). The XOR oxidative catabolism of these antimetabolite agents has a detoxifying role by granting their degradation.

6-Mercaptopurine (6-MP) is an anticancer agent that must be metabolized into active compounds. Through the purine salvage pathway, 6-MP-derivative thiopurine nucleotides can be incorporated into nucleic acids with cytotoxic consequences. 6-MP has been used for the treatment of acute lymphoblastic leukemia and as an immunosuppressive agent for the treatment of inflammatory bowel disease. In some therapeutic protocols, 6-MP is coadministered with its prodrug azathioprine, which is mostly used in organ transplantation and the treatment of autoimmune diseases as an immunosuppressant. 6-MP may undergo degradative oxidation by XOR from bovine milk and guinea pig liver [16]. It has also been reported that human liver XOR may metabolize 6-MP to 6-thiouric acid via 6-thioxanthine, and both the XO and XDH forms of the enzyme participate in this catabolic route [17].

An additional purine analogue that shows anticancer and immunosuppressive activities is 6-thioguanine (6-TG), whose action differs from that of 6-MP; however, in both cases, the mechanism is mediated by purine salvage pathways and causes the arrest of replication. 6-MP may generate the thioinosine monophosphate, which, in turn, can prevalently give rise to a methyl-derivative, thus inhibiting the de novo purine biosynthesis, or, to a lesser extent, be incorporated into thioguanine nucleotides for the synthesis of erroneous nucleic acids. 6-TG, on the other hand, is addressed to form thioguanosine monophosphate, thus generating fraudulent RNA and DNA bases. As for the catabolism, 6-TG is converted first to thioxanthine by guanine deaminase, then XOR generates thiouric acid. Alternatively, aldehyde oxidase can produce 8-hydroxy-thioguanine, which is then deaminated to the final

product thiouric acid [18]. XOR activity competes for 6-MP and 6-TG incorporation into nucleotides by degrading them to the inactive metabolites thioxanthine and thiouric acid (reviewed in [19,20]).

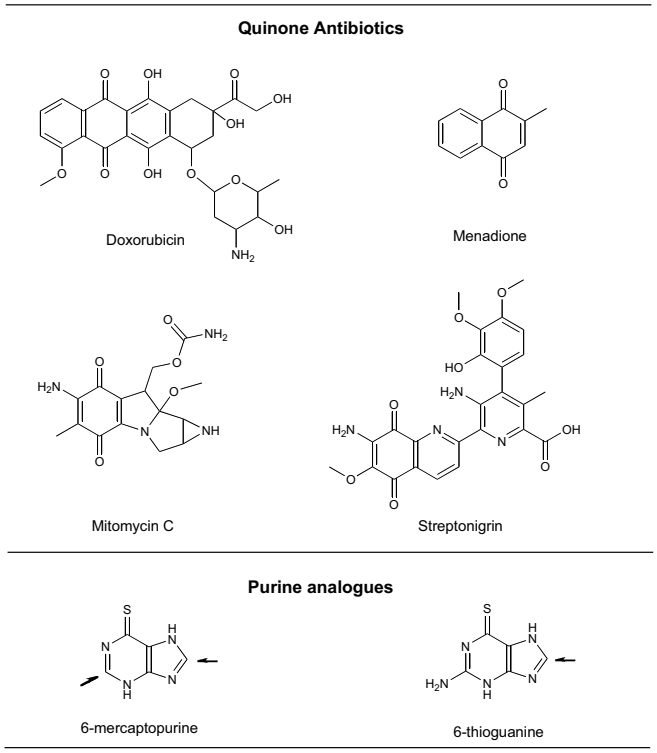

Fig. (3). Antiblastic drugs. Structural formulas of the quinone antibiotics doxorubicin, menadione, mitomycin C and streptonigrin and the purine analogues 6-mercaptopurine and 6-thioguanine. The positions of catalytic oxidation by xanthine oxidoreductase are indicated by arrows.

Methotrexate is a different antimetabolite drug that acts as a folate analogue compound and is also used in anticancer and immunosuppressive therapies, sometimes in combination with other antimetabolite drugs. XOR activity is inhibited by folate compounds such as methotrexate, resulting in increased plasmatic concentrations of thiopurine nucleotides (reviewed in [21]).

In low-responsive patients with inflammatory bowel diseases, the efficacy of thiopurinic drugs as immunosuppressive agents may be improved by inhibiting XOR activity with allopurinol, which allows reducing the dose and thereby the liver toxicity of the drug (reviewed in [22]). However, the interaction between allopurinol and thiopurinic drugs could enhance the risk of myelotoxicity as a result of the antiblastic effect. Thus, caution is needed in determining the pharmacological dosage, especially when treating patients with a genetically low level of thiopurine methyltransferase, which has a rate-limiting effect on the bioavailability of the active medicament (reviewed in [23]). Moreover, marked polymorphisms marked polymorphisms in *hXOR* have been reported, leading not only to classical xanthinuria but also to interethnic, gender-dependent and interindividual differences in the hepatic XOR activity in humans. Therefore, *hXOR* variant-bearing patients with low XOR expression could experience significantly increased hematopoietic toxicity and anti-leukemic effects when treated with thiopurinic drugs [24].

4. ANTIMICROBIAL DRUGS

Because of its ability to act as an *N*-oxide reductase, XOR may activate drugs containing this functional group that are used for their antimicrobial action. In the case of pyrazinoic acid, another bactericidal drug, XOR has a degradative role consequent to its oxidase activity (Fig. **4**).

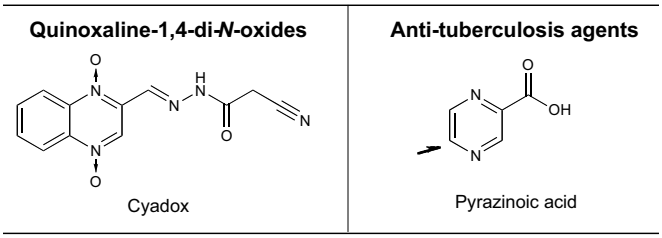

Fig. (4). Bactericidal drugs. Structural formulas of the quinoxaline-1,4-di-*N*-oxide cyadox and of the anti-tuberculosis agent pyrazinoic acid. The position of catalytic oxidation by xanthine oxidoreductase is indicated by arrow.

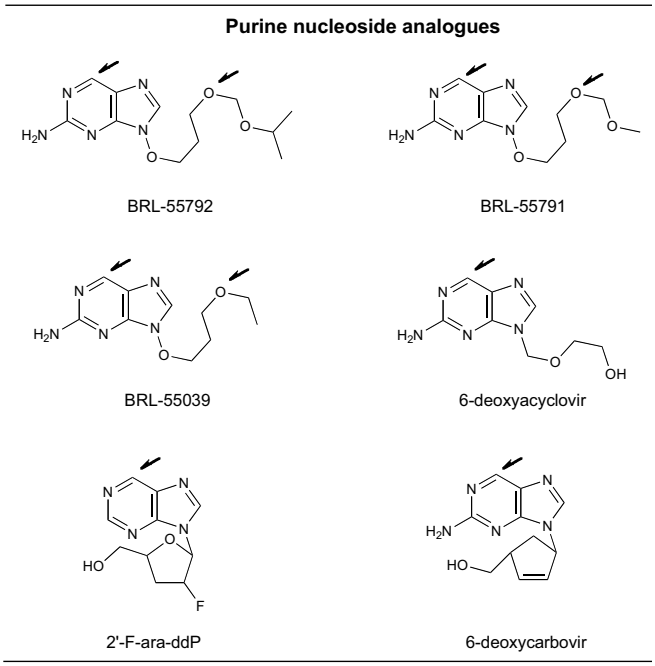

Fig. (5). Antiviral drugs. Structural formulas of purine nucleoside analogues, which are prodrugs of antiviral compounds. The positions of catalytic oxidation by xanthine oxidoreductase are indicated by arrows.

Quinoxaline-1,4-di-*N*-oxides have been widely used in veterinary practice for the prevention of bacterial infections in livestock and poultry. Cyadox is a safe member of this family of compounds that is added to feed for its antimicrobial and growth-promoting activity. To elucidate the metabolism of cyadox, a possible activating role of hepatic XOR was considered. Functionally active XOR was obtained by expression in *Spodoptera frugiperda* insect cells after XOR cDNA from porcine liver was constructed according to known DNA sequences of mammalian XOR. During xanthine oxidation under anaerobic conditions, recombinant porcine XOR has been shown to activate cyadox through reduction [25].

The results of a study conducted using *Escherichia coli* showed that the exposure to cyadox induced oxidative stress, suggesting that the bacteria were mainly killed by the induction of oxidative DNA damage. The DNA degradation induced by cyadox was attenuated by free radical scavengers. Additionally, both the free radical production and the bactericidal effect were lowered by the XOR inhibitor oxypurinol. Moreover, XOR activity may generate radicals in the presence of cyadox, suggesting that XOR is a cyadox-activating reductase [26].

Pyrazinamide is a prodrug used in the treatment of tuberculosis in combination with isoniazid and rifampicin to reduce the duration of the therapy. The prodrug may undergo biotransformation to the active form, pyrazinoic acid, through the activity of a bacterial deamidase; however, in patients and in animal models, a host-mediated conversion occurs that accounts for most of the active drug in the plasma. XOR is active in the catabolism of pyrazinoic acid, whose plasma concentration and half-life can be increased by inhibiting XOR with allopurinol [27].

5. ANTIVIRAL DRUGS

A series of purine nucleoside analogues and certain prodrugs of these compounds are used to inhibit viral replication in viral infection therapy. Prodrugs need to be activated *in vivo* through oxidation, and XOR is one of the activating enzymes (Fig. **5**).

Deoxyguanine analogues, such as BRL 55792, BRL 55791, and BRL 55039, that are prodrugs of the antiviral agent 9-(3-hydroxypropoxy)guanine can be activated by XOR. This activation, involving a 6-oxidation step in the cytosol followed by dealkylation, is mediated by cytochrome P450 (CYP). It has been demonstrated that XOR contributes to catalyze this reaction in human hepatocytes, whereas it is the only enzyme responsible for prodrug activation in the rat [28].

6-deoxyacyclovir is a prodrug of acyclovir, which is an acyclic guanine nucleoside analogue used for the therapy of the herpes virus infection. Unlike acyclovir, this prodrug is suitable for oral administration and is oxidized to the active form by XOR, which competes with the non-activating oxidation by aldehyde oxidase [29].

Acyclovir has also been used as an antiviral drug in the treatment of chronic type B hepatitis. To achieve the high serum concentrations of the drug that are required to inhibit viral replication, the oral administration of 6-deoxyacyclovir has been proposed because the prodrug is easily absorbed in the gastroenteric tract. In a perfused rat liver system, XOR inhibition with allopurinol resulted in the impaired hepatic metabolism of the prodrug, as demonstrated by the strong reduction in the appearance of acyclovir in the perfusate [30].

The dideoxy-fluoro-inosine nucleoside 2'-F-ara-ddI is an antiviral drug that is active against human immunodeficiency virus (HIV) and has been proposed for the treatment of neurological complications of acquired immune deficiency syndrome (AIDS). 2'-F-ara-ddI can be formed *in vivo* by the XOR-mediated biotransformation of the prodrug 2'-F-ara-ddP, which, differently from the active drug, has a low toxicity and can readily penetrate the blood-brain barrier [31].

Carbovir is a carbocyclic guanosine derivative with inhibitory activity on both HIV-1 replication and cytopathic effects in many human T-cell lines [32]. To improve its bioavailability, several carbovir prodrugs have been synthesized, specifically 6-deoxycarbovir, which is activated *in vivo* by both aldehyde oxidase and XOR (reviewed in [33]).

6. METABOLIC DRUGS

XOR can oxidize different drugs used to modify some aspect of metabolism. The result of XOR activity may be either the degradation or activation of the drug (Fig. **6**).

Methylxanthines are widely consumed; they are present in a variety of soft drinks and in different drugs for their diuretic and respiratory stimulant action. The transient alteration of glucose homeostasis and insulin resistance is induced by caffeine administration in both diabetic and healthy nondiabetic men and women (reviewed in [34]). Caffeine is used as a metabolic probe for the activity of CYP and other drug-metabolizing enzymes that are responsible for caffeine catabolism

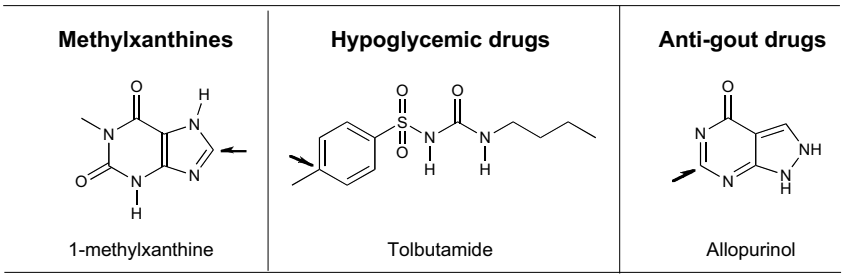

Fig. (6). Metabolic drugs. Structural formulas of 1-methylxanthine, tolbutamide and allopurinol. The arrows indicate the position of xanthine oxidoreductase catalysis.

(reviewed in [35]). This process requires XOR participation for the conversion of the caffeine-derived 1-methylxanthine to 1-methyluric acid [36].

Tolbutamide is a first-generation sulfonylurea used in type 2 diabetes treatment as an oral hypoglycemic drug for its activity in stimulating insulin release from the pancreas. The catabolism of tolbutamide to carboxytolbutamide involves the activity of CYP, which converts it to hydroxytolbutamide, alcohol dehydrogenase that generates tolbutamide aldeyde, and XOR or aldehyde oxidase that catalyzes the reaction from this intermediate metabolite to the final product [37], (reviewed in [38]).

Allopurinol has been widely used to lower uric acid levels in the serum of patients with gout or tumor lysis syndrome. Allopurinol needs to be activated to oxypurinol by XOR or aldehyde oxidase to inhibit XOR and exert its hypouricaemic action (reviewed in [39]).

7. VASODILATOR DRUGS

Nitrates used for vasodilatation are prodrugs that release NO by chemical reduction, which is, in part, mediated by enzymes. XOR can catalyze the reduction of nitrate and nitrite. The nitrite reductase activity of human XOR was evaluated *in vivo* by using the HepG2 and HMEC cell lines. The cell contribution to NO formation was proportional to the nitrite availability and was dependent on an acidic pH and hypoxia. The nitrite reductase activity of XOR purified from human liver was also ascertained. The results demonstrated that nitrite reduction and NO formation occur at the Mo center with either xanthine, which binds at the Mo domain, or NADH, which binds at the FAD domain, as the reducing substrate [40].

8. XOR-EXPRESSION INDUCING DRUGS

XOR products may interfere with the physiological activity of other drug-metabolizing enzymes in the liver. For this reason, the administration of drugs that induce XOR expression may alter the detoxifying function of the liver.

Interferon is used in the therapy of autoimmune diseases, cancer and viral infections. The deficit in the detoxifying activity of the liver induced by interferon is related to the inactivation of CYP. Because interferon stimulates XOR expression, it has been suggested that XOR-derived ROS could be, at least in part, responsible for the loss of CYP activity [41,42].

Phenytoin is an anti-epileptic drug that is used to control seizures because it can slow down impulses in the brain by blocking sodium channels in their inactive form. Phenytoin increases the expression of XOR and other drug-metabolizing enzymes in the liver and is metabolized to its inactive form by enzymes of the CYP family. By lowering the CYP activity, XOR-derived ROS are able to extend the half-life of phenytoin, thus contributing to its hepatotoxic effects, which are dependent on the oxidative stress induced by the drug [43].

CONCLUSION

The metabolism of xenobiotic substances, including drugs, is mostly mediated by members of the CYP family. However, it can also be performed by a variety of non-P450 enzymes, amongst which a significant role must be attributed to metallo-flavoenzymes.

The role of XOR as a drug-metabolizing enzyme is due to the poor specificity of its enzyme action that allows the utilization of a variety of substrates, including a wide range of xenobiotics. Specifically, the XOR activity is directly involved in the metabolism of a number of antiblastic and antimetabolic drugs used against neoplasia, autoimmune disease and viral infection.

We must therefore add the high catalytic versatility of XOR, which is able to carry out different enzymatic activities. Thus, XOR is able to act as an oxidase for purine analogues as well as a reductase for quinone

drugs, cyadox and nitrite. The indirect effects of XOR through the production of reactive species must also be taken into consideration when evaluating the influence of the XOR activity on the drug metabolism, as in the case of the antineoplastic activity of quinone, the antibacterial activity of cyadox and drugs inducing XOR expression.

Sometimes XOR activity has a degradative function toward a drug, as in the case of thiopurine nucleotides, pyrazinoic acid, methylxanthines and tolbutamide. The half-life of these drugs may be prolonged by the use of XOR inhibitors. For other drugs, XOR has an activating role, as in the case of quinone drugs, cyadox, antiviral nucleoside analogues, allopurinol, nitrate and nitrite, and is thus essential for their pharmacological action.

In conclusion, caution is suggested in the use of XOR inhibitors, as in the case of hyperuricemic patients affected by gout or tumor lysis syndrome, when it is necessary to simultaneously administer therapeutic substances that are activated or degraded by the drug-metabolizing activity of XOR. It is essential to avoid potential drug interaction risks, consisting either of a toxic excess of drug bioavailability due to a lack of XOR catabolic action or a loss of drug efficacy, when XOR activity is needed for the activation of a prodrug.

LIST OF ABBREVIATIONS

6-MP	=	6-mercaptopurine
6-TG	=	6-thioguanine
CYP	=	cytochrome P450
FAD	=	flavin adenine dinucleotide
[2Fe-2S]	=	iron-sulfur cluster
$HO^{\bullet}$	=	hydroxyl radical
H_2O_2	=	hydrogen peroxide
hXOR	=	human gene for xanthine oxidoreductase
MP	=	mercaptopurine
Mo	=	molybdenum
Moco	=	molybdenum-containing molybdopterin cofactor
NAD^+	=	oxidized nicotinamide adenine dinucleotide
NADH	=	reduced nicotinamide adenine dinucleotide
NO	=	nitric oxide
$ONOO^-$	=	peroxynitrite
RNS	=	reactive nitrogen species
ROS	=	reactive oxygen species
O_2	=	molecular oxygen
$O_2^{\bullet-}$	=	superoxide anion
XDH	=	xanthine dehydrogenase
XO	=	xanthine oxidase
XOR	=	xanthine oxidoreductase.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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