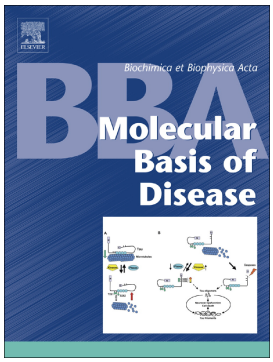

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THE ROLE OF XANTHINE OXIDOREDUCTASE AND URIC ACID IN METABOLIC SYNDROME

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Abbreviations: COX-2, cyclooxygenase-2; FAD, flavin adenine dinucleotide; HDL, high-density lipoprotein; Moco, molybdopterin cofactor; PCOS, polycystic ovary syndrome; RNS, reactive nitrogen species; ROS, reactive oxygen species; TGF-β, transforming growth factor-beta; XDH, xanthine dehydrogenase; XO, xanthine oxidase; XOR, Xanthine oxidoreductase

Abstract. Xanthine oxidoreductase (XOR) could contribute to the pathogenesis of metabolic syndrome through the oxidative stress and the inflammatory response induced by XOR-derived reactive oxygen species and uric acid. Hyperuricemia is strongly linked to hypertension, insulin resistance, obesity and hypertriglyceridemia. The serum level of XOR is correlated to triglyceride/high density lipoprotein cholesterol ratio, fasting glycemia, fasting insulinemia and insulin resistance index. Increased activity of endothelium-linked XOR may promote hypertension. In addition, XOR is implicated in pre-adipocyte differentiation and adipogenesis. XOR and uric acid play a role in cell transformation and proliferation as well as in the progression and metastatic process. Collected evidences confirm the contribution of XOR and uric acid in metabolic syndrome. However, in some circumstances XOR and uric acid may have anti-oxidant protective outcomes. The dual-face role of both XOR and uric acid explains the contradictory results obtained with XOR inhibitors and suggests caution in their therapeutic use.

Keywords: Cardiovascular diseases; Metabolic syndrome; Oncogenesis; Oxidative stress; Uric acid; Xanthine oxidoreductase.

1. Metabolic syndrome

Metabolic syndrome is a multifactorial pathological condition defined by the association of several metabolic disorders. The list includes obesity, especially visceral obesity, dyslipidemia with high triglycerides and/or low level of high-density lipoprotein (HDL) cholesterol, hypertension and fasting hyperglycemia. The presence of any three of these five alterations is diagnostic for the syndrome [1,2]. The risk factors characterizing this syndrome are predictive for both cardiovascular diseases and type 2 diabetes. Studies from various countries show a worldwide distribution of metabolic syndrome with a prevalence related to age, although it has also been observed in young people as long as they were obese subjects (reviewed in [3,4]).

The main mechanisms that attest the metabolic derangement and contribute to its development are insulin resistance and the abundance of circulating free fatty acids. The former may have a genetic origin or be caused by aging alterations and the latter is often associated with obesity or at least an enlarged waist circumference, due to a sedentary lifestyle. Adipose tissue produces pro-inflammatory cytokines that may be responsible for insulin resistance, lipolysis and liver production of pro-thrombotic factors. Thus, the inflammatory chronic state, elicited by obese adipose tissue through an abnormal adipokine production, results in endothelial dysfunction and a pro-thrombotic state (reviewed in [5]) (Fig. 1a).

Lipolysis occurs in expanded subcutaneous adipose tissue as well as in hypertrophied visceral fat, in both cases affecting the hepatic metabolism with glucose production and synthesis of very low-density lipoprotein. The consequent hypertriglyceridemia favors a change in the composition of HDL resulting in a decreased cholesterol content and increased clearance from the circulation. High levels of circulating free fatty acids and impaired insulin activity may both lead to hyperglycemia, because they contribute not only to increased glucose production by the liver but also to a reduced glucose uptake by muscle and adipose tissue (reviewed in [4,6]).

Insulin resistance-elicited hyperinsulinemia enhances renal sodium reabsorption that may induce hypertension. Hypertension also derives from the secretion of angiotensinogen, leptin and resistin by adipose tissue, which, in addition, may reduce nitric oxide (NO)-dependent vasodilation by releasing a high level of free fatty acids [7]. A low bioavailability of NO is closely associated with insulin resistance that impairs the endothelial function

(reviewed in [8]). Metabolic syndrome and hyperinsulinemia have been associated with oxidative stress and inflammation (reviewed in [9]), both leading to a high serum level of oxidized LDL that contributes to the development of atherosclerosis and its negative cardiovascular consequences [10]. Moreover, hyperinsulinemia increases urate reabsorption in the proximal tubule and causes hyperuricemia, so that elevation of the uric acid level in serum is often associated with metabolic syndrome (reviewed in [11,12]) (Fig. 1b).

2. The biology of xanthine oxidoreductase

The enzyme xanthine oxidoreductase (XOR) mainly has the function of catalyzing the conversion of hypoxanthine to xanthine and the latter to uric acid, and these are the last two steps of purine catabolism in the highest uricotelic primates. Since uric acid is an irreversible product, XOR activity precludes the purine salvage pathway, thus having a rate-limiting effect on the recovery of nucleotides (reviewed in [13]). Its low specificity for substrates together with the variety of its catalytic activities enables XOR to play a role as a detoxifying enzyme for endogenous metabolites as well as for xenobiotic compounds, including drugs (reviewed in [14]).

XOR is a metalloflavoprotein belonging to a family of enzymes with a wide phylogenetic distribution from prokaryotic organisms to humans and a possible common derivation from an ancestral XOR-coding gene system (reviewed in [15]). XOR evolved from a highly conserved enzyme with dehydrogenase activity, which is the only form present in lower organisms, to the inter-convertible mammalian oxidase form. This evolution conferred on XOR the role of producing various secondary messengers in inflammatory signaling (reviewed in [16]). The eukaryotic XOR protein has a homodimeric structure and each chain includes three domains: the C-terminal domain of approximately 85 kDa with a molybdenum-containing molybdopterin cofactor (Moco), the intermediate domain of approximately 40 kDa with one flavin adenine dinucleotide (FAD) cofactor, and the N-terminal domain of approximately 20 kDa with two unequal iron-sulfur redox centers. These ferredoxin clusters transfer the electrons from Moco to FAD during purine dehydrogenation (reviewed in [17]) (Fig. 2).

The human XOR protein is strictly controlled at both the transcriptional and post-translational levels to allow modulation of its catalytic activities. XOR expression is normally down-regulated in most tissues with the exception of the epithelial cells of lactating breast, gastrointestinal tract, kidney and liver. However, it can be up-regulated by

low oxygen tension, as well as by cytokines, growth factors and various hormones (reviewed in [18]). After translation, the Moco cofactor requires to be activated by sulfuration. XOR can exist in demolybdo-and/or desulfo-forms, which are inactive in xanthine catalysis at the Moco site, although they retain nicotinamide adenine dinucleotide (NADH) oxidase activity at the FAD site. In addition, XOR comes in two inter-convertible forms: xanthine dehydrogenase (XDH, EC 1.17.1.4), prevailing inside the cell, and xanthine oxidase (XO, EC 1.17.3.2), mostly present in biological fluids, such as milk and plasma (reviewed in [19]). The transition from XDH to XO occurs through limited proteolysis or oxidation of sulfhydryl groups, which includes an intermediate XOR form that has both the NAD^+-dependent dehydrogenase and the O_2-dependent oxidase activities [20].

In addition to uric acid, XDH generates NADH while XO produces superoxide anion and hydrogen peroxide, which give rise to the cytotoxic hydroxyl radical via the Haber-Weiss and Fenton reactions in the presence of transition metals. Conditions of low pH and hypoxia can promote the formation of superoxide anion and NO by the NADH oxidase and nitrate reductase activities of XOR, respectively (reviewed in [21]). XOR activities may produce a variety of reactive oxygen (ROS) and nitrogen (RNS) species, although other enzymes are implicated in the generation of these. XOR-derived ROS and RNS may have a cytotoxic action that is useful in the white blood cell defenses against bacterial illness (reviewed in [22]). On the other hand, these XOR products may contribute to tissue damage in different pathological conditions including the reperfusion injury that occurs after flow restoration in previously blood-deprived organs or in ischemic tissues (reviewed in [23]). Competitive XOR inhibitors, such as allopurinol, may block reactions at the Moco site, but not the production of oxidant species at the FAD site.

In physiological conditions, human plasma contains only traces of XOR, deriving from dead cells, in particular from hepatocytes, which release XOR into circulation, where the transition occurs from XDH to XO (reviewed in [19]). XOR has been localized in the endothelium, probably due to its capacity for adhering to the endothelial surface by competing for the binding sites of heparin [24]. The products of endothelium-linked XOR together with those of other oxidases have the physiological role of modulating the systemic redox equilibrium by producing ROS, NO and uric acid (reviewed in [16]). This XOR activity strongly increases in coronary heart disease and is inversely proportional to the vasodilation stimulated by endothelium, suggesting that XOR activity may contribute to endothelial dysfunction in cardiovascular diseases [25]. XOR products can promote a pro-

oxidant and pro-inflammatory state by regulating endothelial function, since ROS and RNS increase the permeability of the vascular lining. In addition, they modulate the arteriolar tone, thus explaining the XOR implication in the pathogenesis of hypertension, cardiovascular diseases and atherosclerosis (reviewed in [16,22]).

3. The pathophysiological role of uric acid

Uric acid is the catabolic product of exogenous dietetic compounds, as well as of endogenous purines, and its serum level results from the equilibrium between its generation, mainly in the liver, and its elimination, mostly through the kidney (reviewed in [26]). In addition, urate transporters are present on the surface of renal proximal tubule cells to reabsorb uric acid, thus ensuring the homoeostasis of uricemia in humans [27].

Uric acid has an anti-oxidant activity within the circulation that may be relevant in the prevention of cancer, so that a correlation has been hypothesized between the serum level of uric acid and the increased life expectancy of uricotelic primates, as compared to ureotelic animals [28]. On the other hand, uric acid may exert a pro-oxidant activity, mainly within the cell, possibly because of the free radicals derived from its reaction with ROS, NO and RNS, in particular in the presence of myeloperoxidase (reviewed in [29]). A dual-face role has been attributed to serum uric acid, as a protective anti-cancer factor as well as a tumor promoter, and this ambiguity is supported in both directions by population-based studies enrolling huge amounts of patients with a long term follow up (reviewed in [22]). As an answer to this apparent contradiction, a J-shaped correlation has been proposed between the effect of time-varying serum concentration of uric acid and the risk of cancer incidence in a cohort of 78,850 male patients followed up for 12 years [30]. In this study, a higher tumor frequency was observed with both low and elevated uricemia as compared with the normal range, which is close to 4.5 mg/dl. However, only the patients in the upper third of the distribution showed a statistically significant increased risk for malignancies, especially hematopoietic cancers.

Uricase gene loss during evolution and the consequent increase in uric acid serum level has been hypothesized as giving another survival advantage to uricotelic hominoids, because this mutation helped ensure adequate blood pressure, in spite of the low salt intake that was typical in a Paleolithic diet [31]. However, adverse effects have been associated with uric acid-derived free radicals, such as reduced availability of NO, cyclooxygenase-2 (COX-2) expression and up-regulation of the renin/angiotensin pathway, platelet activation, migration and proliferation of vascular myocytes, production of pro-

inflammatory cytokines by macrophages (reviewed in [11,29,32]). The pro-inflammatory activity of uric acid explains the clinical outcome of hyperuricemic gout patients. The other adverse effects listed above result in endothelial dysfunction that may represent a pathogenic mechanism for coronary disease, diabetes, hypertension and acute stroke (reviewed in [33]). Indeed, hyperuricemia is an independent risk factor for cardiovascular disease and has an unfavorable prognostic significance in the above reported pathological conditions [34].

Another hypothesis has been formulated about the biological meaning of the mutations in higher primates causing failure of uricase activity. The mutations occurred over a long period of cooling and meat shortage, during which the diet was based on fruits that are rich in fructose. The ability of fructose to elevate the serum level of uric acid was already known fifty years ago [35]. The metabolism of this sugar may cause ATP depletion, increased purine catabolism and uric acid production that is responsible for intracellular oxidative stress and favors fat storage, hepatic gluconeogenesis and insulin resistance (reviewed in [36,37]). The increased level of serum uric acid may lead not only to hypertension, kidney and cardiovascular diseases, but also to fatty liver, obesity, metabolic syndrome and diabetes. Thus, uricase knockout subjects could more easily overcome starvation periods, but are more exposed to fat accumulation and related pathological consequences when food is available in abundance [38,39].

The pathophysiological role of serum uric acid is still controversial and it is not fully clarified whether hyperuricemia represents only a marker, or rather an etiological agent of tissue damage. Most studies have been based on XOR inhibition by allopurinol, which has an anti-oxidant activity by itself, thus interfering with the results (reviewed in [33]).

In addition, uric acid is released from damaged cells, in particular following necrotic cell death, and acts as a danger signal for leukocytes and mesenchymal stromal cells, thus eliciting acute or chronic inflammation and a repair process [40] (Fig. 3).

4. Hyperuricemia and metabolic syndrome

A growing number of studies suggest that hyperuricemia could contribute to the pathogenesis of metabolic syndrome (reviewed in [16,41]) (Fig. 4).

An oral fructose load was shown to cause an elevation in uric acid serum level that was higher and more protracted in gouty subjects and in their healthy children than in normal people [35]. In rats, a high fructose diet induced not only hyperuricemia but also weight gain, hyperinsulinemia and hypertriglyceridemia, while the lowering of serum uric acid level

with either allopurinol or a uricosuric agent counteracted these metabolic alterations [42]. Similar results were obtained with the non-competitive XOR inhibitor febuxostat, which normalized the serum level of uric acid and alleviated hypertension, hyperinsulinemia and hypertriglyceridemia in rats with fructose-mediated metabolic syndrome. In addition, XOR inhibition significantly reduced the renal hemodynamic and morphologic alterations induced by hyperuricemia [43]. These results suggested a pathogenic role for hyperuricemia in fructose-induced metabolic syndrome, possibly because of the uric acid-mediated endothelial dysfunction. In agreement with this hypothesis, treatment with allopurinol reduced the malondialdehyde and myeloperoxidase levels, which are markers of oxidative stress, and improved endothelial function by increasing the flow-mediated dilation in patients with metabolic syndrome [44].

Another hypothesis suggests that increased fat accumulation in the liver could be induced by uric acid through endoplasmic reticulum stress and upregulation of lipogenesis (reviewed in [45]). These metabolic alterations are associated with reduced ATP level and impaired fat oxidation that may result in obesity and diabetes (reviewed in [46,47]). The association between hyperuricemia and dyslipidemia with hypertriglyceridemia and low HDL cholesterol was reported in cross-sectional studies involving a large number of subjects [48,49]. A recently published five-year cohort study, evaluating the data of 6476 Japanese, showed that hyperuricemia becomes an independent risk factor for developing high LDL cholesterol and hypertriglyceridemia, although not for low HDL cholesterol [50].

Meta-analysis studies gave a significantly positive association between the serum level of uric acid and the subsequent development of type 2 diabetes ([51]; reviewed in [52]). It has been known for a long time that, in conditions of low serum concentration of reductants, uric acid is toxic for pancreatic beta cells and may be diabetogenic in rabbits [53]. As determined by the available tests, insulin resistance showed a positive correlation with the serum level of uric acid, and the pharmacologic lowering of the latter consequently improved the sensitivity to insulin. There is a double correlation: i) insulin resistance may induce a decreased renal excretion of uric acid, as well as increased uric acid production through the hexose monophosphate shunt; ii) hyperuricemia may worsen the insulin resistance by limiting the bioavailability of NO, which is required for insulin-dependent glucose uptake (reviewed in [47,54]). Insulin resistance favors the uptake of glucose by non-insulin dependent tissues and the polyol pathway that induces the consumption of nicotinamide adenine dinucleotide phosphate (NADPH). The lack of NADPH results in a

decreased availability of reduced glutathione with consequent oxidative stress that, in turn, impairs NO production (reviewed in [55]).

Large epidemiologic studies showed a positive correlation between the elevation of serum uric acid and hypertension, increased waist circumference, fasting hyperglycemia, hyperinsulinemia, hypertriglyceridemia and high serum levels of C-reactive protein. The association between hyperuricemia and hypertension was reported in a study examining 8415 Chinese people, with an additive effect of triglycerides and uric acid levels on diastolic blood pressure [56]. A 5-year retrospective study examining 3584 Japanese subjects showed that, even when asymptomatic, hyperuricemia is a strong risk marker for developing hypertension from prehypertension, suggesting the need of further investigation to ascertain if the onset of hypertension could be avoid by lowering hyperuricemia in prehypertensive subjects [57].

Uric acid induced hypertension through different mechanisms including the activation of NADPH oxidase and consequent cellular oxidative stress (reviewed in [41]). Although high levels of serum uric acid are often associated with metabolic syndrome [58], hyperuricemia is not included amongst the diagnostic criteria that have been internationally proposed for the definition of this pathological condition. However, the pro-oxidant action of hyperuricemia may induce inflammation and endothelial dysfunction by lowering the NO availability, thus promoting hypertension, metabolic syndrome and cardiovascular and renal diseases (reviewed in [59,60]). Moreover, mice lacking the enterocyte urate transporter Glut9 showed not only hyperuricemia but also elevated body fat, hypercholesterolemia and hypertension. The early-onset of metabolic syndrome in Glut9-deficient mice was reversed by treatment with allopurinol [61].

Though numerous studies concerning both experimental animal models and epidemiological clinical data suggest that serum uric acid may cause or at least exacerbate hypertension and kidney disease, results are still inconclusive and do not support the usefulness of XOR inhibitors or uricosuric agents in the treatment of cardiovascular and kidney diseases (reviewed in [62]). However, chronic hyperuricemia appears to be involved in the pathogenesis of metabolic derangement leading to metabolic syndrome, and its control may improve the prevention of hyperglycemia and hypertension ([63]; reviewed in [47,64]). A 10-year cohort study was carried out in 1192 middle-aged Italian subjects to evaluate the long-term incidence of new metabolic syndrome onset in relation to the serum uric acid level. The results of this investigation showed that the

increase of uricemia is associated with an enhanced risk of developing diabetes mellitus and metabolic syndrome, at least in the population fraction with age above the median value [65].

5. Xanthine oxidoreductase and metabolic syndrome

The involvement of XOR in the pathogenesis of metabolic syndrome has been indirectly demonstrated in both animal models and clinical studies through the administration of drugs that inhibit the enzyme activity.

In a murine model of metabolic syndrome, the inhibition of XOR with allopurinol lowered the infiltration of macrophages in adipose tissue, decreased the production of pro-inflammatory monocyte chemotactic protein-1, reduced insulin resistance and increased the production of adiponectin, thus contrasting the inflammatory condition of obese mice [66].

Increased XOR activity in macrophages with consequent ROS production has been reported to be essential in the formation of experimental atherosclerotic plaque in the aorta of ApoE-/- mice. The process began when cholesterol crystals stimulated XOR expression and was inhibited by febuxostat, which also attenuated the release of pro-phlogistic cytokines by macrophages [67].

The role of XOR in high fat diet-induced obesity and osteoarthritis in mice has been investigated by comparing febuxostat-treated to control animals. Three months of diet significantly increased mouse body weight, articular cartilage damage in knee joints and XOR activity in various fat depots. The treatment with the XOR inhibitor significantly reduced the joints alterations as well as the expression of inflammatory cytokines/adipokines in fat depots, suggesting that XOR activity contributes to the development of metabolic arthritis [68]. In a rat model of metabolic syndrome, XOR inhibition with allopurinol reversed hypertension and proteinuria, without modifying body weight gain, hyperinsulinemia and fasting hyperglycemia, which were induced by a diet with high levels of fructose, fat and salt. In the kidney, XOR inhibition also reversed the increment of transforming growth factor-beta (TGF-β), collagen deposition, expression of angiotensin II and angiotensin receptor type 1 that could be responsible for hypertension and proteinuria [69].

The level of XOR activity in human plasma, determined by a novel high sensitive assay, showed a positive correlation with insulin resistance, body mass index and subclinical inflammation even in 26 healthy young subjects [70]. In addition, allopurinol treatment

lowered serum uric acid and improved insulin resistance and systemic inflammation in 73 subjects with asymptomatic hyperuricemia [71].

Women with polycystic ovary syndrome (PCOS) show a high incidence of metabolic syndrome. In a study concerning 45 patients with PCOS, the serum level of XOR activity was significantly higher than that of control women and positively correlated with high serum levels of C-reactive protein, triglyceride/HDL cholesterol ratio, fasting glycemia, fasting insulinemia and insulin resistance index. These results suggest a role for XOR activity in the pathogenesis of these metabolic alterations [72].

Although a strong association has been reported between hyperuricemia and hypertension, hypertriglyceridemia, non-alcoholic fatty liver disease, obesity and type 2 diabetes, the question of whether the development of metabolic syndrome may be more coupled to the production of ROS or uric acid is still a matter of dispute (reviewed in [73]).

Increased activity of endothelium-linked XOR may promote high blood pressure through different mechanisms including: (i) the endothelial dysfunction generated by ROS, RNS and uric acid-derived free radicals, (ii) the arteriolar remodeling induced by monocyte activation and myocyte proliferation, (iii) the up-regulation of the renin/angiotensin pathway and (iv) the phlogistic reaction caused by the precipitation of monosodium urate crystals ([74]; reviewed in [19,75]). Increased XOR activity could induce oxidative stress through ROS and uric acid production, thus impairing NO-mediated vasodilation, whereas XOR inhibition by allopurinol counteracted vascular dysfunction and improved myocardial function and ejection fraction in some clinical trials (reviewed in [76]).

A prospective cohort study performed on 503 patients evaluated the outcome 12 months after an ischemic stroke in relation to four levels of serum uric acid. Patients in both the lower and the higher quartiles showed poor outcomes indicating a U-shaped relationship between uricemia and functional upshot [77]. In a clinical study, enrolling 270 patients with cardiac diseases, a positive correlation was observed between the plasma level of XOR activity and the level of aminotransferases, glycated hemoglobin and B-type natriuretic peptide, as well as with body mass index, left ventricular hypertrophy and low left ventricular ejection fraction [78]. The direct correlation reported for heart failure severity and level of serum uric acid may be justified by the increased activity of XOR as a result of increased substrate supply in conditions of hypoxia, catabolism, cell death and insulin resistance. In this case, the consequent production of ROS has been claimed as the main

pathogenic XOR-derived mechanism, while hyperuricemia has been considered a marker more than a player (reviewed in [79]).

A high-fat diet in rats induced obesity associated with hypertension, hyperinsulinemia, hyperglycemia and hypercholesterolemia. In addition, a reduction was reported in NO-dependent arteriolar dilation that was normalized by allopurinol, but not by the NAD(P)H oxidase inhibitor apocynin. The altered vascular dilation corresponded to an increased XOR activity and ROS production in the endothelial lining, suggesting a causal relationship between XOR-generated ROS and the endothelial dysfunction leading to features of metabolic syndrome [80].

In mice, diet-induced obesity was associated with hyperuricemia that was dependent on XOR activity, as it was controlled by the administration of febuxostat. Adipose tissue had a very high XOR expression, comparable to that of the liver and small intestine. Moreover, XOR activity was higher in the fat tissue of obese mice than in control animals, although no variation was detected in XOR mRNA or protein levels. The increased XOR activity in obese adipose tissue could result from: (i) a post-translational regulation, possibly as a consequence of the hypoxic conditions or (ii) the increased substrate availability caused by the high cAMP turnover consequent to elevated lipolysis [81]. The treatment of human mesenchymal stem cell-derived adipocytes with fructose increased their adipogenesis, XOR expression and amount of uric acid. The effect was inhibited by allopurinol. Enhanced adipogenesis was also obtained by directly treating adipocytes with uric acid. This outcome was abolished by an NADPH oxidase inhibitor. These results suggest a causal role for ROS-derived oxidative stress in both fructose and uric acid-mediated adipogenesis [82]. XOR activity has been described as implicated in pre-adipocyte differentiation and adipogenesis in experiments carried out in cultured cells and in XOR gene-knockout mice (reviewed in [16]).

On the other hand, a dietary nitrate load lowered the blood pressure of hypertensive rats and patients, possibly through the NO produced by the nitrate reductase activity of erythrocytic XOR [83]. Accordingly, liver XOR activity, uricemia and blood pressure were more elevated in endothelial NO synthase-deficient than in wild type mice. In deficient mice, the generation of NO was ensured by up-regulation of XOR reductase activity and the nitrate-nitrite-NO pathway. Nitrate supplementation in the diet of deficient mice further up-regulated XOR and was associated with a decrease in both ROS generation and blood pressure, whereas febuxostat administration worsened hypertension [84].

A hypothesis has been formulated about the protective role of XOR in fat tissue when the conditions allow it to function as a nitrate reductase (reviewed in [85]). The dietary nitrate, which is a constituent of vegetable food, had shown anti-diabetic and anti-obesity properties that appear due to its ability to stimulate the expression of adipocyte genes essential for the transformation of adipose tissue from white to brown. The process was promoted by hypoxia in the rat and required the reduction of nitrate to nitrite and then to NO by the nitrate reductase activity of XOR. These results provide a possible explanation for why a vegetable diet gives protection from metabolic diseases, and they also suggest a beneficial role for XOR as an adaptive response to obesity-consequent hypoxia in adipose tissue by activating the reprogramming that leads to browning of the white fat tissue (reviewed in [86]).

Main pro and cons of XOR activities on vasculature and adipose tissue are schematized in Fig. 5.

Meta-analyses of prospective cohort studies show a significant association between metabolic syndrome and malignancies of the liver, colorectal tract and bladder in men, as well as endometrial, pancreas, breast postmenopausal, rectal and colorectal cancers in women.

Hyperuricemia has been suggested as representing the factor linking obesity, diabetes and metabolic syndrome with chronic inflammation and cancer by leading to excessive intracellular concentration of uric acid. The pro-inflammatory action of uric acid may promote cell transformation through ROS/RNS generation. Moreover, intracellular uric acid may contribute to lowering the level of XOR expression in transformed cells with a consequent increase of purine salvage pathway and cell proliferation. Reduced XOR expression increases matrix metalloprotease and COX-2 expression and is related to aggressive breast cancer, with poor cell differentiation and increased metastatic ability (reviewed in [87]).

The etiology of colon cancer is multifactorial and includes genetic predisposition, dietary factors, microbiota alteration, obesity and chronic inflammation. The initiation process is often mediated by oxidative and nitrosative cellular damage in part dependent on XOR activity (reviewed in [88]).

The development and progression of cancer in the liver is associated with a decreased expression of XOR (reviewed in [18]) and this XOR downregulation promotes cancer cell

migration and invasion by increasing the expression of genes responsible for epithelial-mesenchymal transition and activating TGF-β signaling [89].

In high XOR-expressing tissues, XOR activity has been associated with tumor prevention, since it can promote cell differentiation and inhibit angiogenesis by modulating the expression of genes with anti-tumorigenic and anti-proliferative activity (reviewed in [18]).

Conclusions

Metabolic syndrome is characterized by obesity, dyslipidemia, hypertension and diabetes. Both oxidative stress and chronic inflammation have a prominent role in the pathogenesis of metabolic syndrome's main features. Several pathogenic mechanisms of metabolic syndrome involve the enzyme XOR. In mammalians, XOR has the important regulatory function of producing ROS, secondary messengers mediating signal transduction during inflammation and repair. Moreover, XOR is one of the enzymes that modulate the NO endothelial availability both directly by producing it and indirectly by interfering with NADPH oxidase and NO synthase activities, thus contributing to the regulation of both endothelial function and vascular tone. In addition, XOR activity is implicated in adipogenesis and in the browning of white fat tissue.

XOR produces uric acid, which is a two-faced molecule since it may behave as either an oxidant or an anti-oxidant agent. Hyperuricemia has a pathogenic role in fructose-induced metabolic syndrome in animal models that suggests a similar relationship for increased consumption of fructose-containing beverages in the incidence of metabolic syndrome in western countries. A reciprocal correlation has been observed with insulin resistance and hyperuricemia that could explain the interrelation between the serum level of uric acid and the subsequent development of type 2 diabetes. The serum level of uric acid has been thought to ensure correct blood pressure, but its increase is probably responsible for hypertension and kidney disease. Moreover, hyperuricemia is often associated with hypertriglyceridemia, non-alcoholic fatty liver disease and diet-induced obesity.

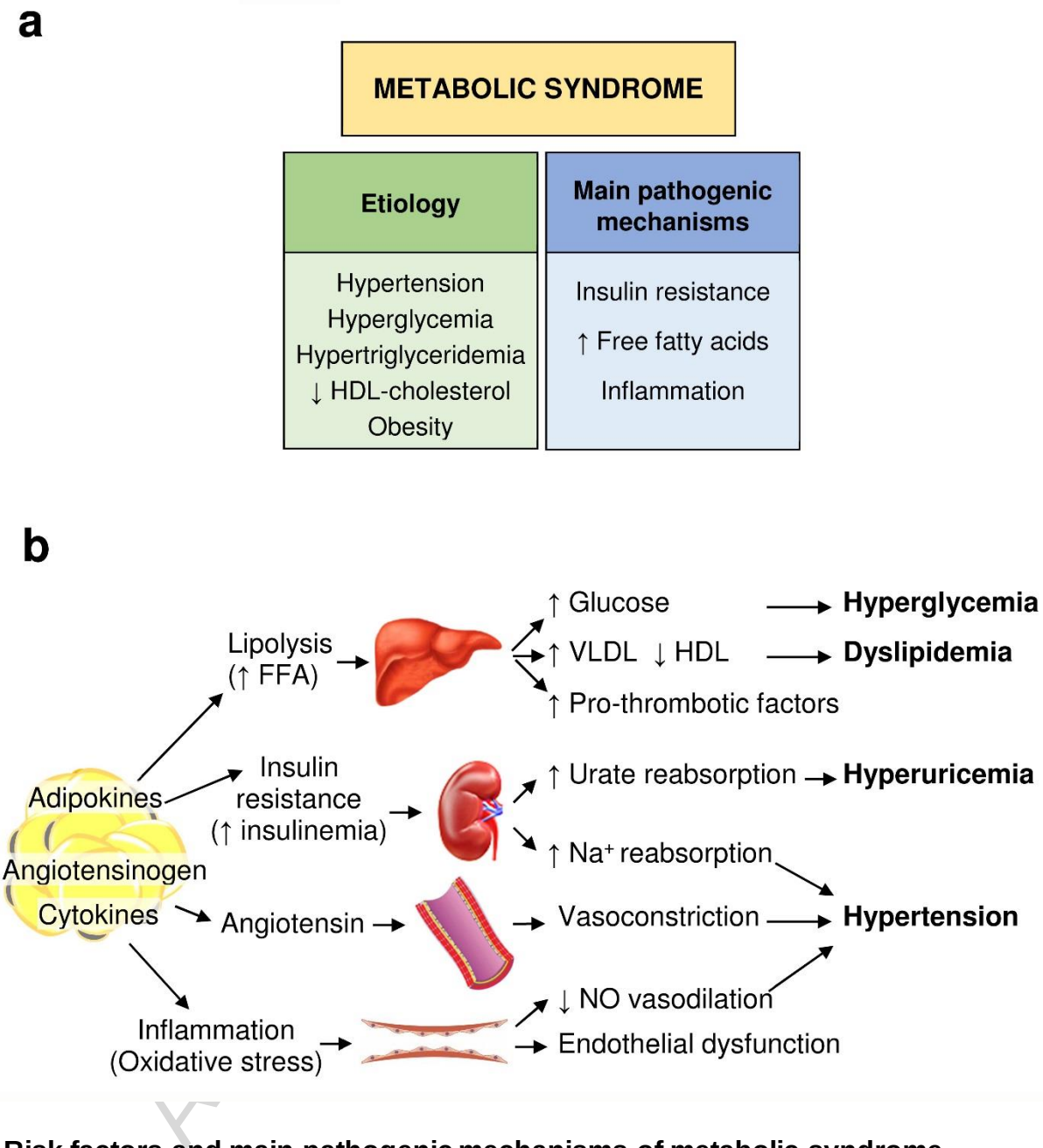
Patients with metabolic syndrome have an increased risk of malignancies including liver, colorectal, bladder, endometrial, pancreas and breast postmenopausal cancers. XOR activity and uric acid play a role in cell initial transformation and proliferation as well as in the progression and ensuing metastatic process.

A huge amount of evidence suggests a pathogenic role for XOR and its products in the development of metabolic syndrome. Although some available XOR inhibitors have received pharmacologic approval, their use at the moment should be limited to

symptomatic hyperuricemia. Indeed, opposite results have been obtained in large cohort studies showing adverse outcomes at both low and high levels of uricemia, possibly because XOR and its products may modulate the redox equilibrium through an intricate interplay with key physiological and pathological cell pathways. Anyway, recently published prospective studies, involving general Japanese and Italian population, suggest to carefully monitor the level of uricemia, particularly in aged subjects with prehypertension, or impaired fasting glycemia, or initial hypertriglyceridemia.

Figures and Legends

Figure 1

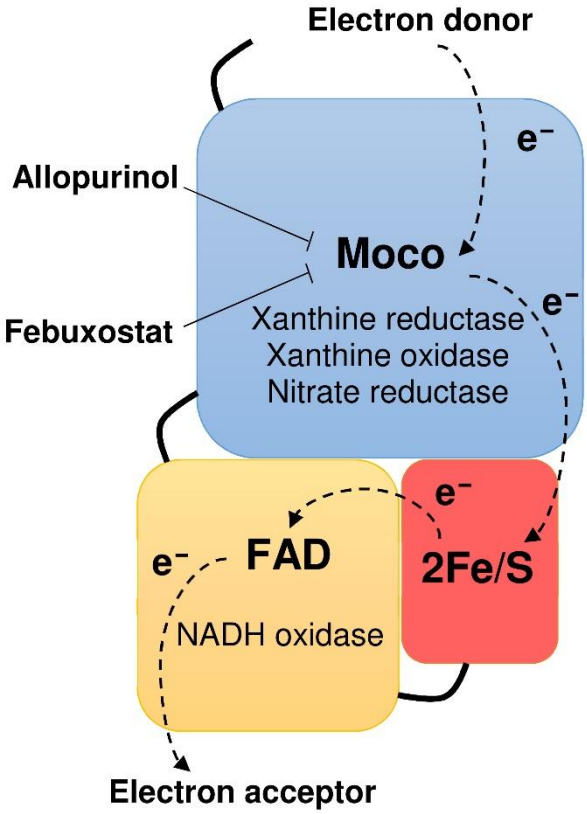


a – Risk factors and main pathogenic mechanisms of metabolic syndrome
b – Pathogenesis of dyslipidemia, hyperglycemia and hypertension in metabolic syndrome

The altered adipokine balance that is reported in visceral obesity consists of increased resistin and decreased adiponectin production and results in insulin resistance and lipolysis, which, in turn, are responsible for the metabolic derangement of liver and kidney leading to the characteristic feature of metabolic syndrome. Dyslipidemia is mainly generated by liver accumulation of free fatty acids deriving from insulin resisting adipose tissue. Hyperglycemia originates both from increased liver gluconeogenesis and reduced muscle utilization of glucose, as a consequence of increased free fatty acids in the blood. Various factors contribute to the elevation of blood pressure: (i) kidney increased reabsorption of Na^+ and urate that are elicited by hyperinsulinemia; (ii) up-regulation of the

renin/angiotensin pathway deriving from enhanced angiotensinogen production by adipocytes and the increased cyclooxygenase-2 (COX-2) expression induced by hyperuricemia; (iii) the impaired NO-dependent vasodilation caused by oxidative stress resulting from the increased production of inflammatory cytokines as well as from urate oxidative products and free fatty acid-induced endothelial dysfunction.

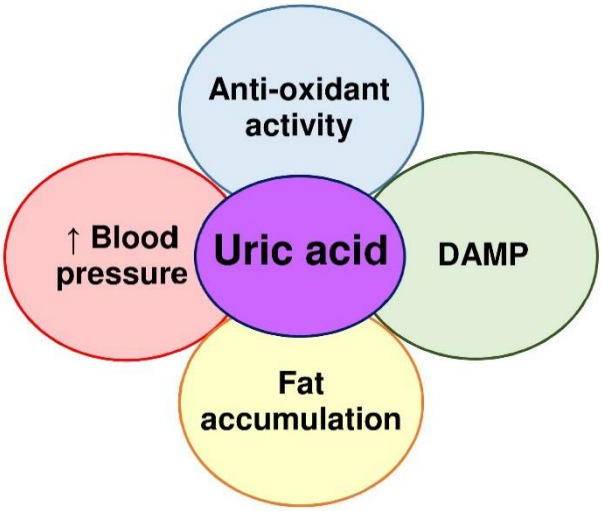
Figure 2



Structure and enzymic activities of xanthine oxidoreductase (XOR)

Each monomer of eukaryotic XOR protein consists of three domains linked through linker peptides plus a short peptide at the C end of the chain that is involved in intermediate dehydrogenase/oxidase activity. The C-terminal domain (blue box) includes a molybdenum-containing molybdopterin cofactor (Moco) that allows both purine oxidative hydroxylation and nitrate reductase activities. These activities can be inhibited by allopurinol or febuxostat in a competitive or non-competitive way, respectively. The intermediate domain (yellow box) has one flavin adenine dinucleotide (FAD) cofactor, where nicotinamide adenine dinucleotide (NAD^+) or oxygen are reduced and also NADH oxidase activity occurs. The N-terminal domain (red box) has two unequal iron-sulfur redox centers (Fe_2/S_2 I and Fe_2/S_2 II), which transfer the electrons (e^-) from Moco to FAD.

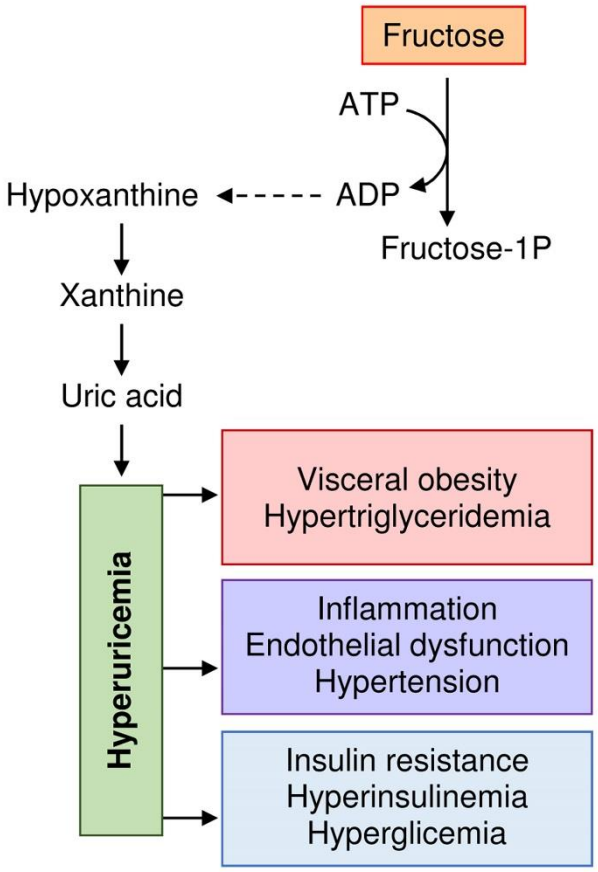
Figure 3



Survival advantages for uricothelic primates deriving from uricase gene loss

The uric acid serum level consequent to mutations leading to uricase gene loss brings various positive outputs. First, it exerts an extracellular anti-oxidant activity that reduces neoplastic transformation, thus exerting a protective role against cancer. Second, a normal uricemic range supports blood pressure, even in the absence of an adequate dietetic salt supply. Third, fructose-dependent increased uric acid production favors both fat storage, which can help to overcome periods of food shortage, and hepatic gluconeogenesis that provides fuel for the brain. Fourth, when urate is released from dead cells it acts as a pro-inflammatory signal like other danger-associated molecular patterns (DAMPs).

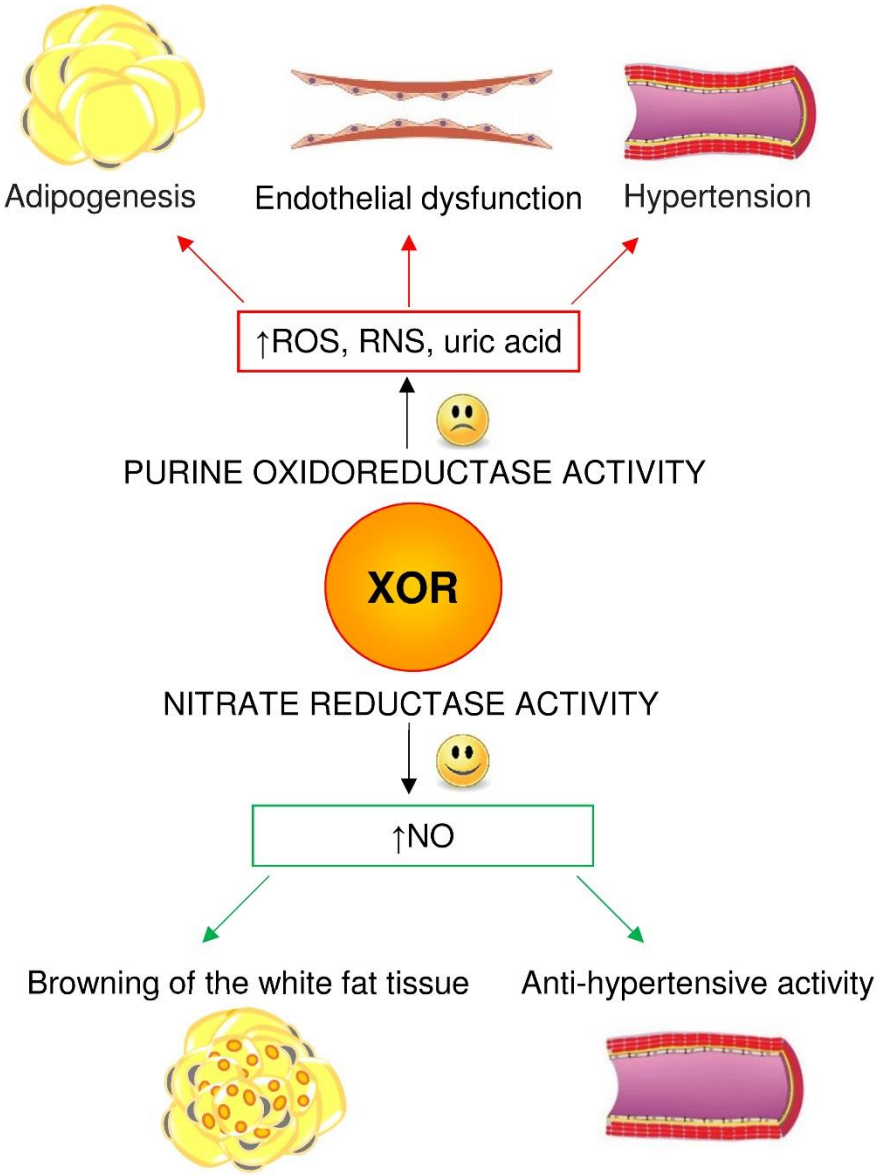
Figure 4



Role of hyperuricemia in fructose-induced metabolic syndrome

The elevation of serum uric acid after the assumption of fructose in the diet depends on the phosphorylation of fructose by hepatic fructokinase that is not limited by a negative feedback, thus inducing ATP depletion and excessive purine degradation. The consequent hyperuricemia may cause the following alterations that are characteristic of metabolic syndrome: (i) visceral obesity and hypertriglyceridemia; (ii) inflammation, endothelial dysfunction and hypertension; (iii) insulin resistance, hyperinsulinemia and hyperglycemia.

Figure 5



Effects of xanthine oxidoreductase (XOR) activities on vasculature and adipose tissue

Negative effects of XOR-purine oxidoreductase activity are adipogenesis, inflammation and hypertension. Positive effects of XOR-nitrate reductase activity are browning of the white fat tissue and anti-hypertensive activity.

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Potential conflicts of interest do not exist for any of the authors, including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

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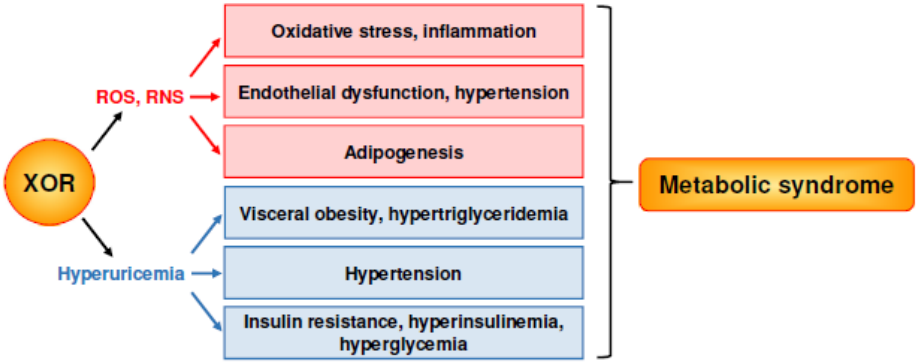


Graphical abstract

HIGHLIGHTS:

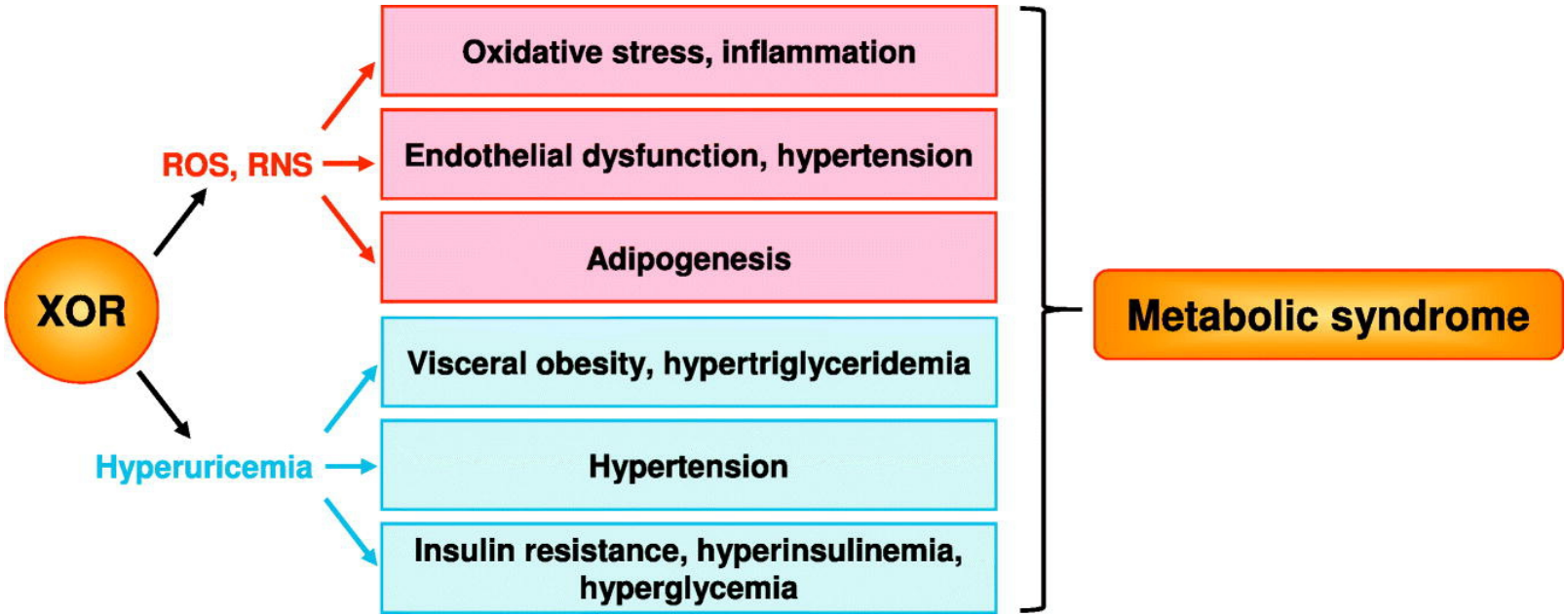
Obesity, oxidative stress and endothelial dysfunction induce metabolic syndrome

Xanthine oxidoreductase activity promotes adipogenesis and fat over-accumulation

Xanthine oxidoreductase products can bring on oxidative stress and inflammation

Xanthine oxidoreductase contributes to cancer initiation and progression

The nitrate reductase activity of xanthine oxidoreductase has protective outcomes



Graphics Abstract

a

METABOLIC SYNDROME

Etiology	Main pathogenic mechanisms
Hypertension Hyperglycemia Hypertriglyceridemia ↓ HDL-cholesterol Obesity	Insulin resistance ↑ Free fatty acids Inflammation

b

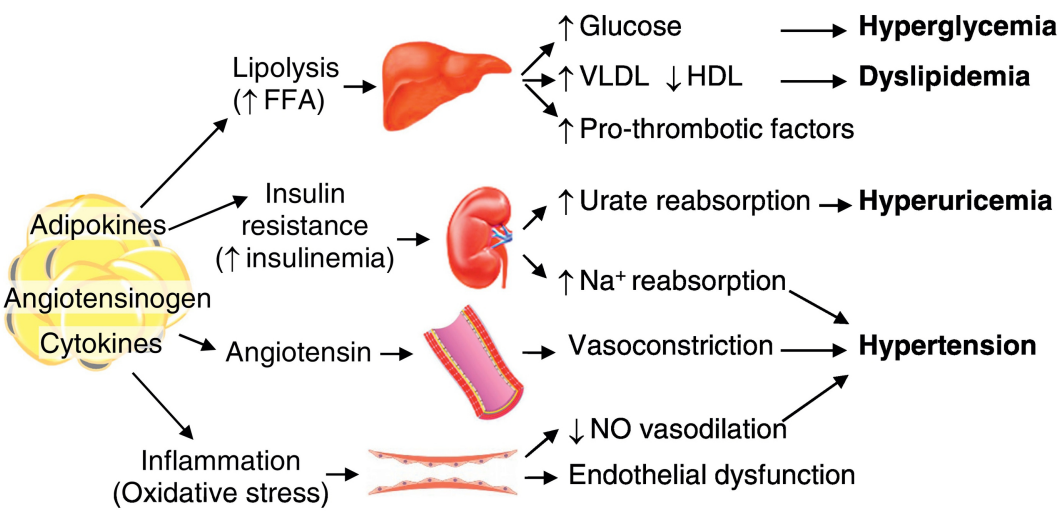


Figure 1

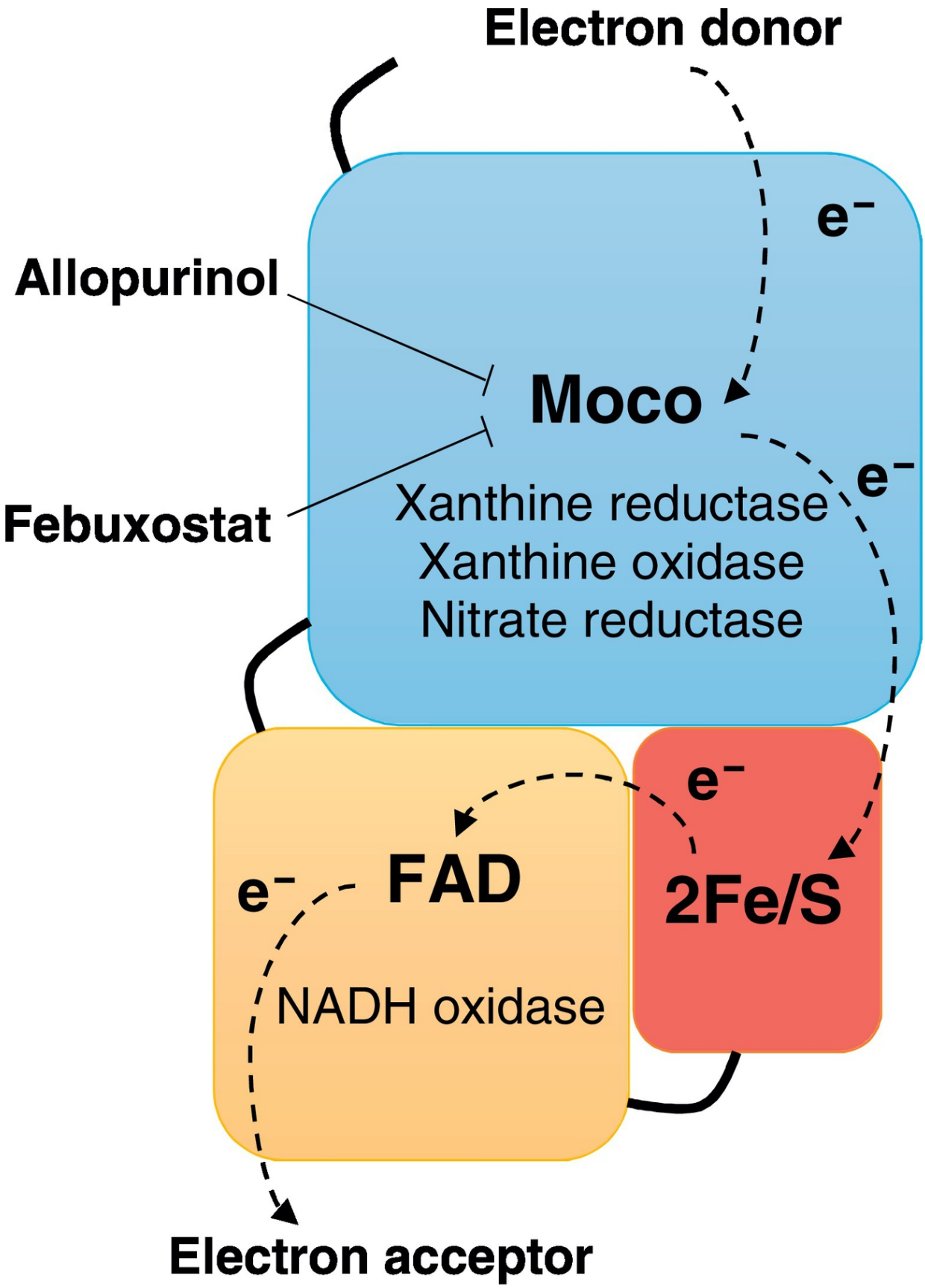

Electron donor
e⁻
Allopurinol
Moco
Xanthine reductase
Xanthine oxidase
Nitrate reductase
e⁻
Febuxostat
e⁻
FAD
e⁻
2Fe/S
NADH oxidase
Electron acceptor

Figure 2

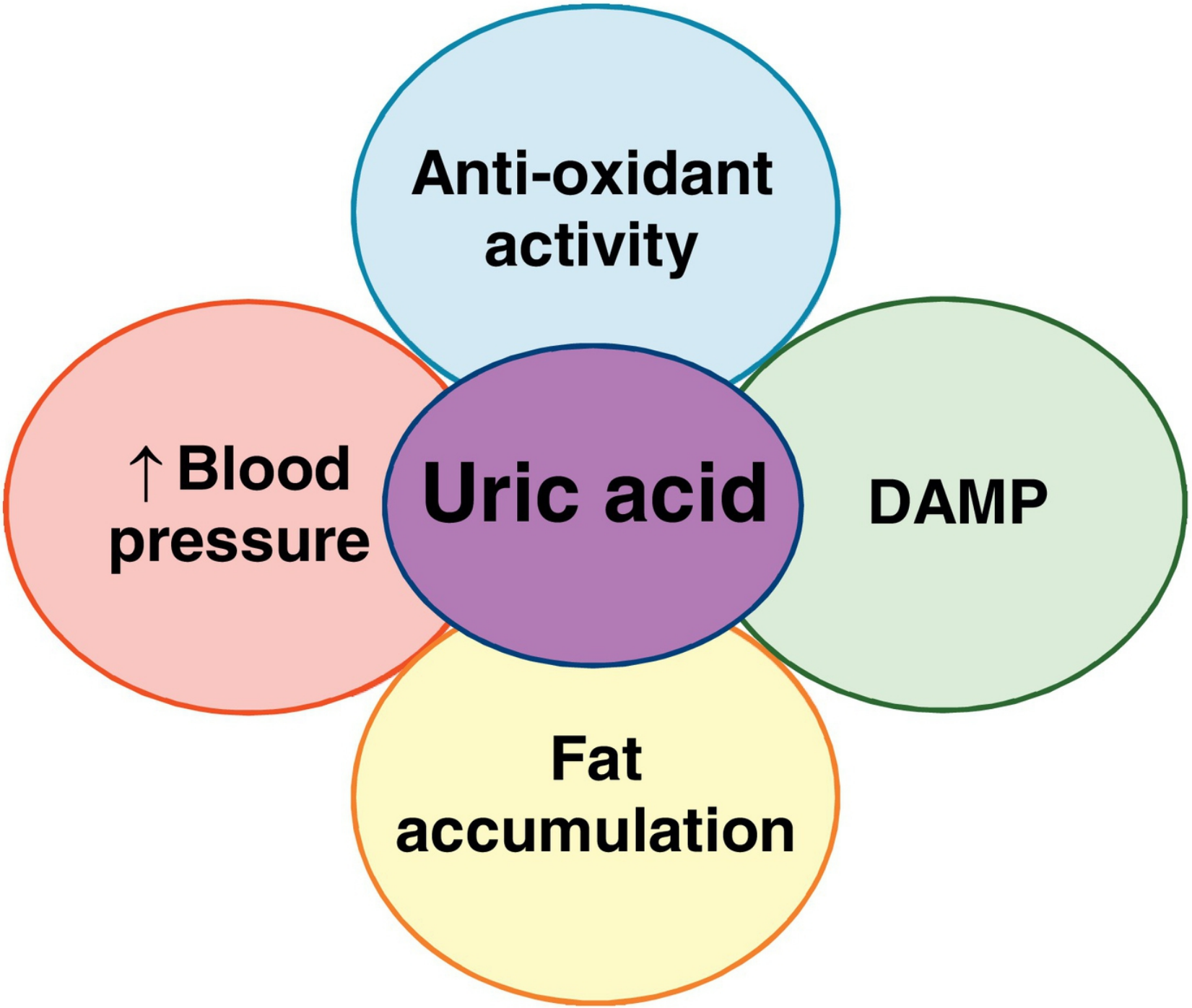

Anti-oxidant activity
↑ Blood pressure
Uric acid
DAMP
Fat accumulation

Figure 3

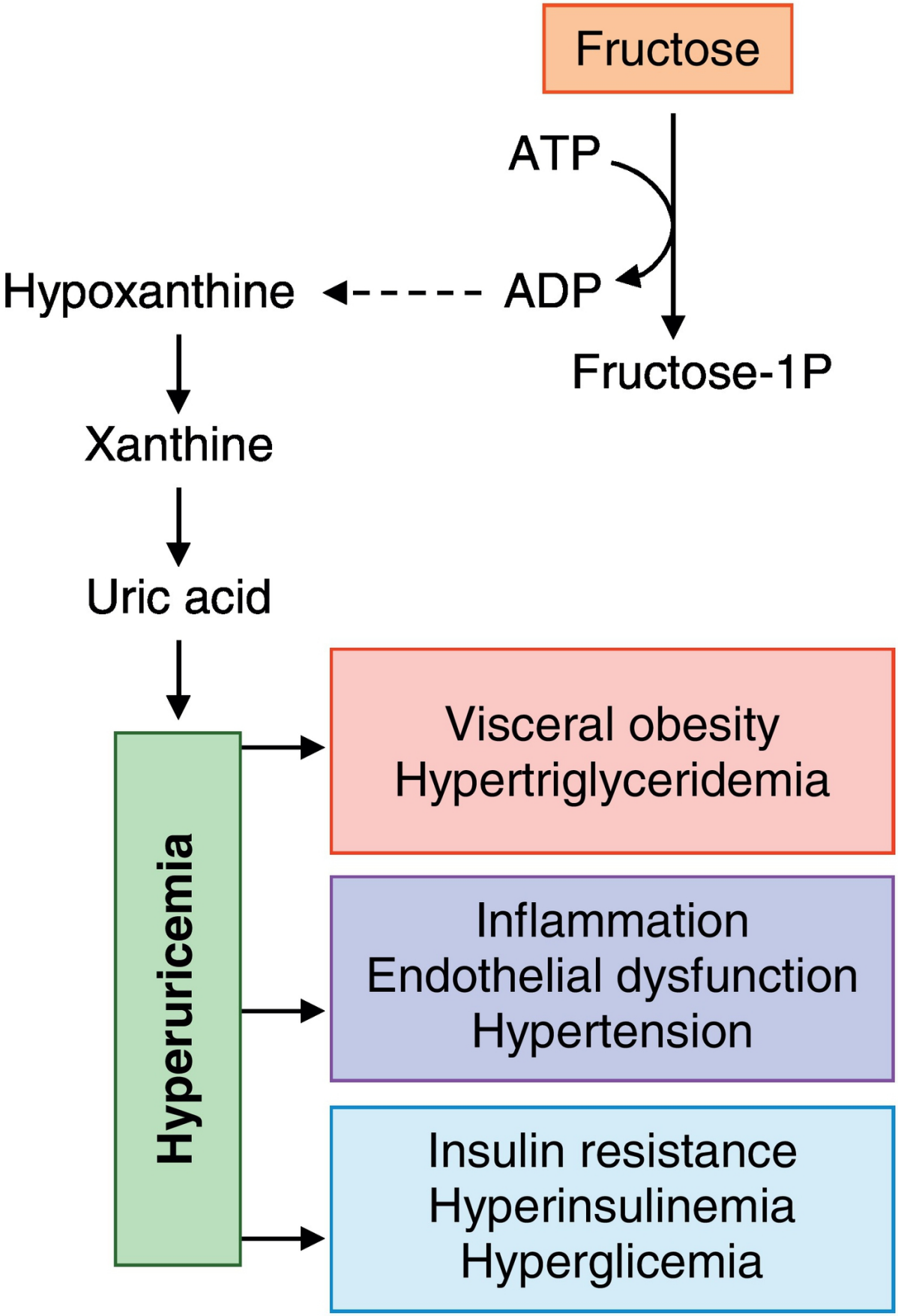

Fructose
ATP
ADP
Hypoxanthine
Fructose-1P
Xanthine
Uric acid
Hyperuricemia
Visceral obesity
Hypertriglyceridemia
Inflammation
Endothelial dysfunction
Hypertension
Insulin resistance
Hyperinsulinemia
Hyperglicemia

Figure 4

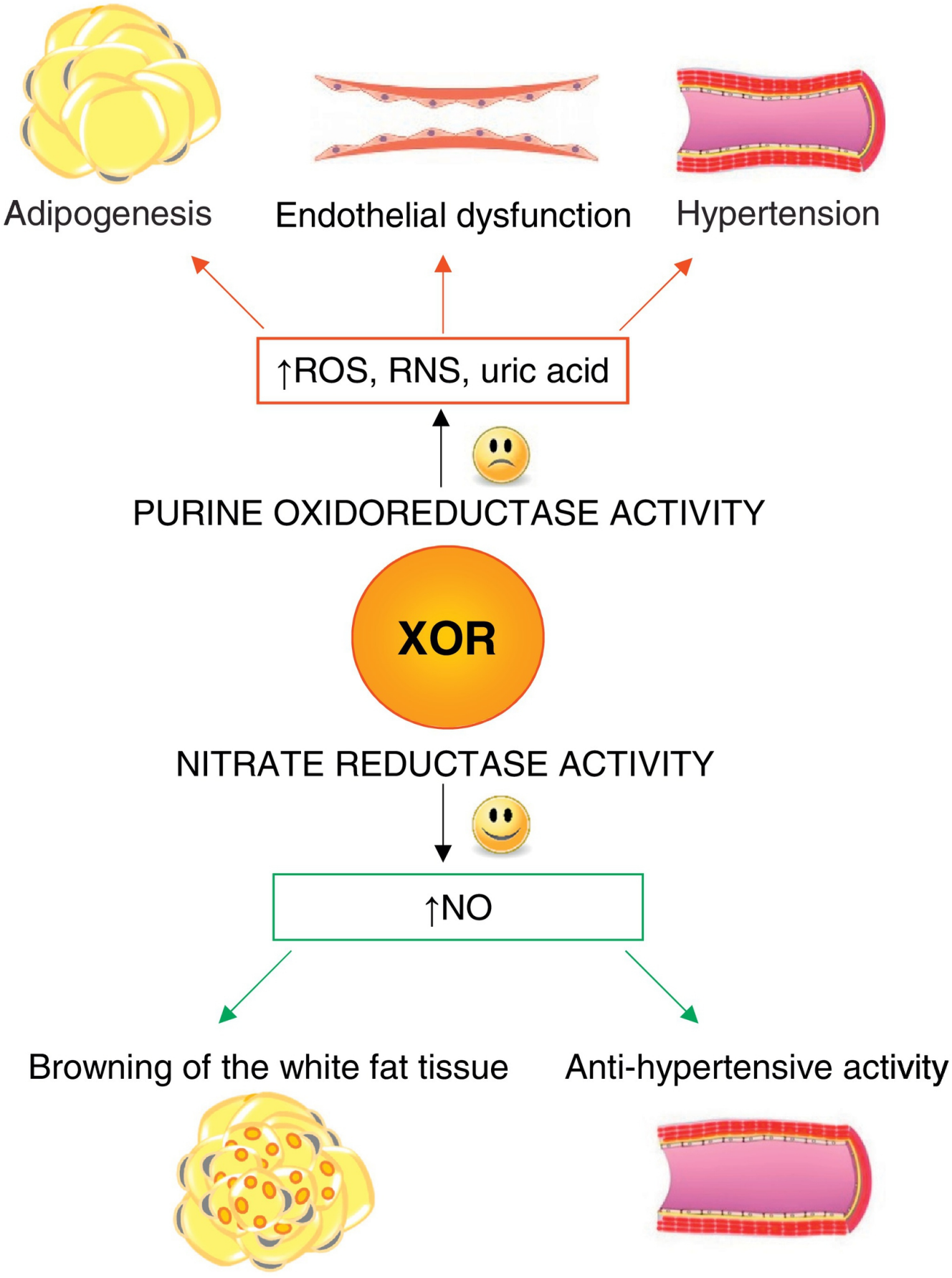

Adipogenesis
Endothelial dysfunction
Hypertension
↑ROS, RNS, uric acid
PURINE OXIDOREDUCTASE ACTIVITY
XOR
NITRATE REDUCTASE ACTIVITY
↑NO
Browning of the white fat tissue
Anti-hypertensive activity

Figure 5