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INVITED REVIEW

Hyperuricemia-induced endothelial insulin resistance: the nitric oxide connection

Zahra Bahadoran[1] · Parvin Mirmiran[1] · Khosrow Kashfi[2,3] · Asghar Ghasemi[4]

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Abstract

Hyperuricemia, defined as elevated serum concentrations of uric acid (UA) above 416 μmol L^{-1}, is related to the development of cardiometabolic disorders, probably via induction of endothelial dysfunction. Hyperuricemia causes endothelial dysfunction via induction of cell apoptosis, oxidative stress, and inflammation; however, it's interfering with insulin signaling and decreased endothelial nitric oxide (NO) availability, resulting in the development of endothelial insulin resistance, which seems to be a major underlying mechanism for hyperuricemia-induced endothelial dysfunction. Here, we elaborate on how hyperuricemia induces endothelial insulin resistance through the disruption of insulin-stimulated endothelial NO synthesis. High UA concentrations decrease insulin-induced NO synthesis within the endothelial cells by interfering with insulin signaling at either the receptor or post-receptor levels (i.e., proximal and distal steps). At the proximal post-receptor level, UA impairs the function of the insulin receptor substrate (IRS) and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) in the insulin signaling pathway. At the distal level, high UA concentrations impair endothelial NO synthase (eNOS)-NO system by decreasing eNOS expression and activity as well as by direct inactivation of NO. Clinically, UA-induced endothelial insulin resistance is translated into impaired endothelial function, impaired NO-dependent vasodilation, and the development of systemic insulin resistance. UA-lowering drugs may improve endothelial function in subjects with hyperuricemia.

Keywords Endothelial insulin resistance · Hyperuricemia · Nitric oxide · Uric acid

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✉ Asghar Ghasemi
Ghasemi@endocrine.ac.ir; Ghasemi.asghar@gmail.com

[1] Nutrition and Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2] Department of Molecular, Cellular and Biomedical Sciences, Sophie Davis School of Biomedical Education, City University of New York School of Medicine, New York, NY 10031, USA

[3] Graduate Program in Biology, City University of New York Graduate Center, New York, NY 10016, USA

[4] Endocrine Physiology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, No. 24, Parvaneh Street, P.O. Box: 19395-4763, VelenjakTehran, Iran

Abbreviations

ABC	ATP-binding cassette transporter
Ang-II	Angiotensin II
AP-1	Activator protein-1
BCRP	Breast cancer resistance protein
CI	Confidence interval
eNOS	Endothelial nitric oxide synthase
ENPP1	Ectonucleotide pyrophosphatase/phosphodiesterase 1
ERK	Extracellular signal-regulated kinase
ET-1	Endothelin-1
GLUT	Glucose transporter
HPX	Hypoxanthine
HUVEC	Human umbilical vein endothelial cell
IRS	Insulin receptor substrate
JNK	C-Jun N-terminal kinase
MAPK	Mitogen-activated protein kinase
MCT	Monocarboxylate transporter
MRP	Multidrug resistance-associated protein
NF-κB	Nuclear factor kappa-B
NO	Nitric oxide

OAT	Organic anion transporter
PI3K	Phosphatidylinositol 3-kinase
PKC	Protein kinase C
ROS	Reactive oxygen species
RR	Relative risk
SLC	Solute carrier family
T2DM	Type 2 diabetes mellitus
UA	Uric acid
UAT	Uric acid transporter
URATv1	Voltage-driven urate transporter 1
VCAM-1	Vascular cell adhesion molecule-1
XDH	Xanthine dehydrogenase
XO	Xanthine oxidase
XOR	Xanthine oxidoreductase

Introduction

Uric acid (UA), the end product of purine catabolism in humans, is synthesized from xanthine through the action of the xanthine oxidoreductase (XOR) enzyme system [63]. In addition to being the primary cause of gout [64], hyperuricemia is a risk factor for cardiometabolic disorders [33, 48, 55, 99] and mortality [52, 100]. Meta-analyses of cohort studies report a 24% attributable risk of high-serum UA for incidence of type 2 diabetes mellitus (T2DM) with each 59.48 μmol L^{-1} (1 mg dL^{-1}) increase in circulating UA concentration increases the risk of T2DM by 6–17% [50, 60]. Although still controversial, increased circulating levels of UA are considered to be a causative factor for developing T2DM [50, 60].

High UA concentrations can be a predisposing factor in the onset of T2DM. This is potentially due to induction of pancreatic β-cell death and impairment of insulin secretion [31, 59] and/or blunting of insulin signaling in various cells, including cardiomyocytes [115], skeletal muscle cells [109], adipocytes [9], hepatocytes [116], and endothelial cells [20] that is consequently reflected as systemic insulin resistance [2, 65].

Hyperuricemia induces endothelial dysfunction primarily by decreasing nitric oxide (NO) bioavailability [66], which is considered to be the primary factor coupling endothelial dysfunction with insulin resistance [19]. Hyperuricemia inhibits insulin-induced activation and expression of endothelial NO synthase (eNOS) and therefore decreases NO production in the endothelial cells, resulting in endothelial insulin resistance [20, 77, 97]. The critical role of endothelial-derived NO in insulin homeostasis is greatly supported by experiments in which eNOS-deficient animals display insulin resistance [18, 25].

This review aims to elaborate on how hyperuricemia induces endothelial insulin resistance by disrupting the endothelial NO system.

UA metabolism

Uric acid (C5H4N4O3, 7,9-dihydro-1 H-purine2,6,8(3 H)-trione, molecular mass 168 Da) is a weak hydrogenated organic acid with pKa_1 of 5.75 and pKa_2 of 10.3. Under physiological conditions (i.e., pH 7.4 and 37 °C), UA predominantly circulates (~ 98–99%) in the plasma and synovial fluid in its mono-deprotonated ionic form (urate anion) [72]. Figure 1 summarizes the biosynthesis and catabolism of UA, indicating how an imbalance in UA metabolism leads to hyperuricemia and contributing to the development of gout and cardiometabolic disorders. The whole-body homeostasis of UA depends on the balance between its production and catabolism [91]. UA is originated from the catabolism of adenine- and guanine-based purines arising from endogenous (i.e., de novo purine biosynthesis and cell and tissue turnover) and exogenous (i.e., dietary purines occurring in the seafood, meats, and legumes) sources [40, 102, 103]. The liver is the major site of UA production, while other organs such as the intestine, myocardium, kidney, and endothelium also synthesize UA to a lesser extent [26]. About two-thirds of UA is eliminated by the kidneys in the urine [92] and approximately one-third to one-fourth is eliminated via the gastrointestinal tract [14, 63].

Many enzymes are involved in metabolizing purines (adenine and guanine) to UA; adenosine monophosphate (AMP) is converted to inosine via nucleotidase and adenosine deaminase, whereas guanine monophosphate (GMP) is converted to guanosine by nucleotidase [63]. Both nucleosides (inosine and guanosine) are subjected to further processes to convert to hypoxanthine (HPX) and guanine, respectively, by the act of purine nucleoside phosphorylase [63]. The guanine is then deaminated to form xanthine via guanine deaminase [63]. The XOR is the key and rate-limiting enzyme in purine metabolism [63] that converts HPX to xanthine and then to UA [63]. Mammalian XOR has two interconvertible forms, a dehydrogenase form (XDH, EC 1.17.1.4) and an oxidase form (XO, EC 1.17.3.2) [36]. The XDH-XO transition occurs either irreversibly via partial proteolysis or reversibly via the chemical or enzymatic oxidation of thiol groups [12]. The XDH is predominantly the intracellular form, whereas XO is the post-transcriptionally modified circulating form and is highly expressed in pathological conditions (e.g., hypoxia and ischemia [119]) that generate toxic levels of superoxide anion and hydrogen peroxide [3, 11]. NO can modify XOR activity; exogenous NO and also NO produced by XOR-induced reduction of nitrite to NO inactivate XOR by NO-induced conversion of XO to its desulfo-form [32, 39].

Normal plasma concentrations of UA are 155–357 μmol L^{-1} in women and 208–428 μmol L^{-1} in men [23]. A

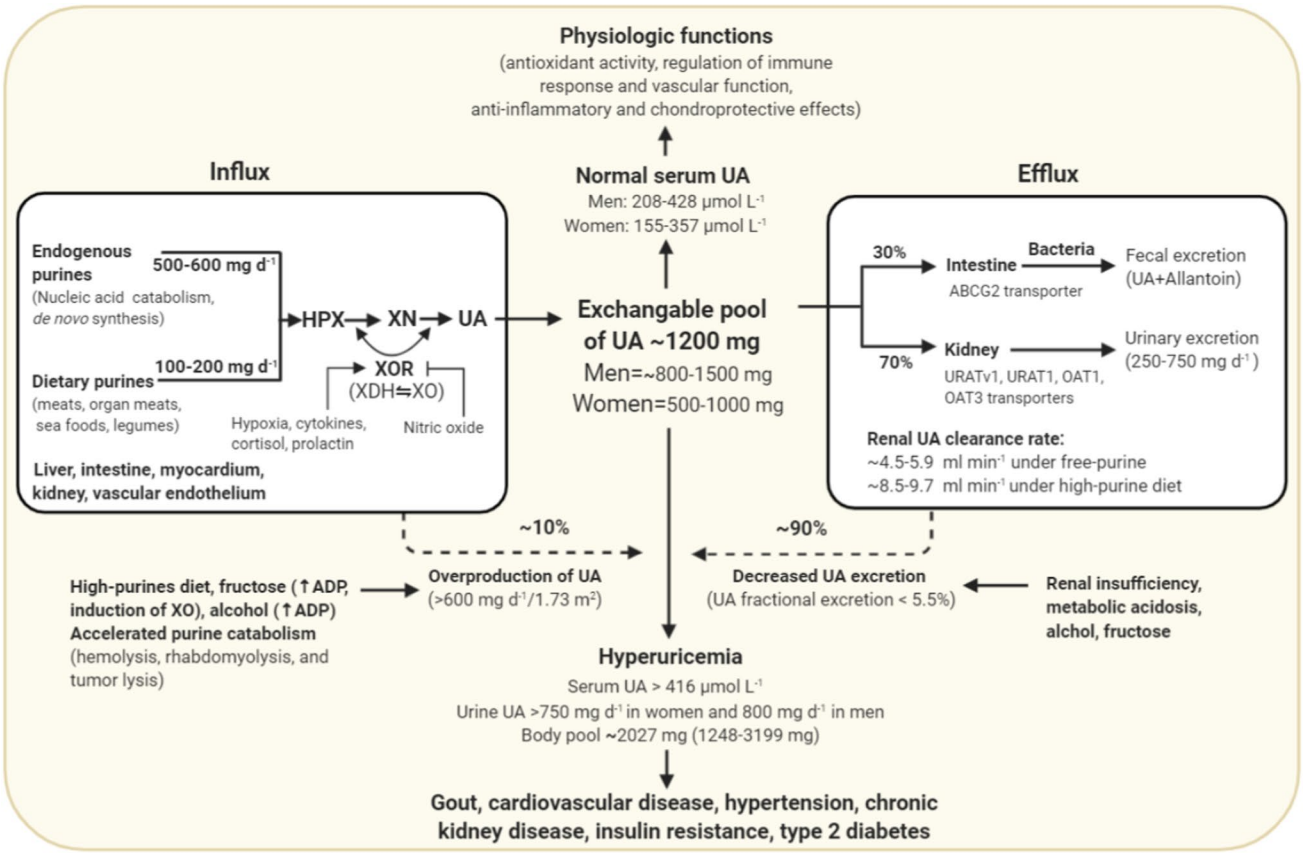

Fig. 1 Uric acid (UA) biosynthesis/catabolism pathways in humans and determinants of its whole-body homeostasis. The xanthine oxidoreductase (XOR) is the key and rate-limiting enzyme in the biosynthesis of UA that converts hypoxanthine (HPX) to xanthine (XN) and UA. Mammalian XOR has two interconvertible forms: dehydrogenase (XDH) and oxidase (XO) forms. The kidneys eliminate about two-thirds (62.8–69.8%) of UA in urine, and one-third to one-fourth (16–22%) is eliminated via the gastrointestinal tract and excreted in the feces as intact UA and allantoin (i.e., produced by bacterial uricase activity). The voltage-driven urate transporter 1 (URATv1), working together with URAT1, organic anion transporter 1 (OAT1), and OAT3, regulates renal urate handling, and ATP-binding cassette G2 (ABCG2) is known as the main one for intestinal UA transport regulation. Serum UA in humans is regulated mainly by ABCG2 (a secretion transporter) and URAT1 and URATv1 (urate reabsorption transporters). About 10% of hyperuricemia is attributed to UA overproduction, more than 80% to decreased UA renal excretion, and 10% to combined overproduction-underexcretion

threshold level of < 360 μmol L^{-1} has been suggested to be a cut-off value to identify healthy subjects [23]; however, hyperuricemia is commonly defined as plasma UA concentration of greater than 416 μmol L^{-1}, which is related to an increased size of exchangeable UA pool by about twofold (from 1200 to 2027 mg) and hyperuricosuria (urinary excretion of UA > 800 mg day^{-1} in men and > 750 mg day^{-1} in women) [14, 102].

Physiological functions of UA

Although physiological functions of UA have been poorly documented, both in vitro and in vivo studies indicate that physiological concentrations of UA can exert antioxidant [13], anti-inflammatory, and chondroprotective effects [54]. UA is also essential for endothelial function (see the "Physiologic functions of UA in the endothelial cells" section), immune response, and defense against neurological and autoimmune diseases [13, 26]. As discussed by Johnson et al. [42], UA may act as a "physiological alarm signal" in response to modern lifestyle. The lack of uricase is responsible for a higher level of UA in human blood (180–720 μmol L^{-1}) compared to other mammals that have uricase (30–120 μmol L^{-1}) [42]. It has been hypothesized that uricase mutation (occurred in early hominoid evolution) led to higher serum UA concentrations, might have been a compensatory response to the loss of *L*-gluconolactone oxidase (the enzyme responsible for ascorbic acid synthesis) that acted as an antioxidant system, improved innate immune function, maintained blood pressure during periods of environmental stress, and increased life span [5, 41].

Emerging high UA levels in modern humans have been interpreted as an adaptive response. UA retained in the circulation in an attempt to offset disease-associated oxidative

stress [15]. Uric acid is as effective as ascorbate at inhibiting lipid peroxidation [5] or more effective than ascorbate at neutralizing peroxynitrite [53]. The higher circulating level of UA compared to ascorbate (300 vs. 60–90 μmol L^{-1}) makes it the major antioxidant in humans. About half of the plasma total antioxidant capacity in humans has been attributed to circulating UA [5, 13]; UA comprises ~ 10–15% of hydroxyl radical-scavenging capacity and 30–65% of the peroxyl radical-scavenging capacity of plasma [13]. The oxidative damage of biological molecules (i.e., protein, DNA, and lipids), induced by 2,2′-azobis-(2-amidinopropane)-dihydrochloride, is effectively prevented by UA [71]. Physiological concentrations of UA inhibit the oxo-heme oxidant formed by peroxide reaction with hemoglobin, and protect erythrocyte membrane against lipid peroxidation, and erythrocytes from peroxidative damage and lysis [5, 46]. Uric acid also dose-dependently inhibits oxidation of human low-density lipoprotein at concentrations of 5–100 μmol L^{-1} [88]; at a concentration of 100 μmol L^{-1}, UA reduces consumption of other antioxidants (i.e., α-tocopherol and β-carotene), by ~ 50% and effectively suppresses oxidation of polyunsaturated fatty acids [88].

At physiologic concentrations (15–60 μg/ml), UA inhibits activator protein-1 (AP-1) and extracellular signal-regulated kinase (ERK) signaling pathways as well as expression of tumor necrosis factor-α- and interleukin-induced inducible NOS, cyclooxygenase-2, and matrix metalloproteinase-13 in joint tissues [54].

Pathological effects of high concentrations of UA

Epidemiological evidence indicates that hyperuricemia is associated with incidence of cardiovascular diseases [16, 27] and development of atherosclerosis [34]. A meta-analysis of prospective cohort studies showed that hyperuricemia was related to the risk of major adverse cardiovascular events [relative risk (RR) = 1.72, 95% confidence interval (CI) = 1.28–2.33) [112]. The pooled estimated effect size of hyperuricemia for the risk of coronary heart disease mortality and all-cause mortality was 1.14 (95% CI = 1.06–1.23) and 1.20 (95% CI = 1.13–1.28), respectively. Each 59.48 μmol L^{-1} increase in serum UA concentration increased risk of coronary heart disease and all-cause mortalities by 20% and 9%, respectively [118]. A meta-analysis of 11 studies indicated that each 59.48 μmol L^{-1} increase in serum UA increases risk of metabolic syndrome and non-alcoholic fatty liver disease by 30% and 21%, respectively [110]. High-serum UA levels also contribute to the development of hypertension and can lead to renal dysfunction by increasing renal vascular resistance and decreasing renal blood flow [86, 87]. High UA concentration induces vascular dysfunction, by activating the nuclear factor kappa-B (NF-κB) signaling pathway [57], as well as decreases cell viability, by activating NF-κB and ERK signaling pathways [58], inducing oxidative stress, and activating renin-angiotensin system [108].

Endothelial insulin resistance

The endothelium is an important insulin target tissue [10]; despite not regulating metabolism, insulin regulates endothelial cell homeostasis [82] via two main signaling pathways [47]. First, the phosphatidylinositol 3-kinase (PI3K)-protein kinase B (Akt) pathway, and second, the Ras/Raf/mitogen-activated protein kinase (MAPK) pathway (Fig. 2).

Through the PI3K-Akt pathway, insulin stimulates endothelial NO production by inducing eNOS phosphorylation at Ser^{1177} (as stimulatory site) and eNOS dephosphorylation at Thr^{495} (as inhibitory site), which is constitutively phosphorylated in the endothelial cells [6]. In addition, insulin increases eNOS gene expression and transcription via PI3K-induced binding of transcriptional factors Sp1 (specificity protein 1) and AP-1 to the eNOS gene [28]. Insulin can also suppress inflammation in the endothelial cells, probably through the PI3K-Akt pathway, as loss of insulin signaling in the endothelial cells (induced by endothelial-specific elimination of the insulin receptor) leads to increased inflammation and expression of the vascular cell adhesion molecule-1 (VCAM-1) [83]. Furthermore, through induction of the PI3K-Akt pathway and phosphorylation of caspase-9, insulin suppresses caspase-9-induced endothelial cell apoptosis [35]. Insulin also inhibits NADPH oxidase-dependent superoxide production in the endothelial cells, probably via the PI3K-Akt pathway [24].

Through the Ras/Raf/MAPK pathway, insulin regulates mitogenesis, growth, and differentiation of the endothelial cells. Also, it mediates vasoconstrictor actions of insulin by stimulating the production of endothelin-1 (ET-1) and angiotensin II (Ang-II) [68, 73, 79]. In the hyperinsulinemic or insulin resistance states, insulin promotes VCAM-1 expression in the endothelial cells by activating the p38-MAPK pathway, an effect that is intensified by blocking the PI3K-Akt pathway [61]. Insulin signaling in the endothelial cells may be complicated by a network of multiple feedback loops and cross-talk between two major pathways [69]; for example, inhibition of the PI3K-Akt pathway leads to enhanced mitogenic action of insulin [68].

Although the concept of endothelial insulin resistance is not clinically established nevertheless, at the cellular level, it has been characterized as an impaired responsiveness of the cell to insulin's actions through inactivation of both PI3K-Akt and MAPK pathways. This notion is supported by using the endothelial cell insulin receptor knockout mouse model, where both eNOS and ET-1 were observed to be decreased [98]. However, some evidence emphasizes

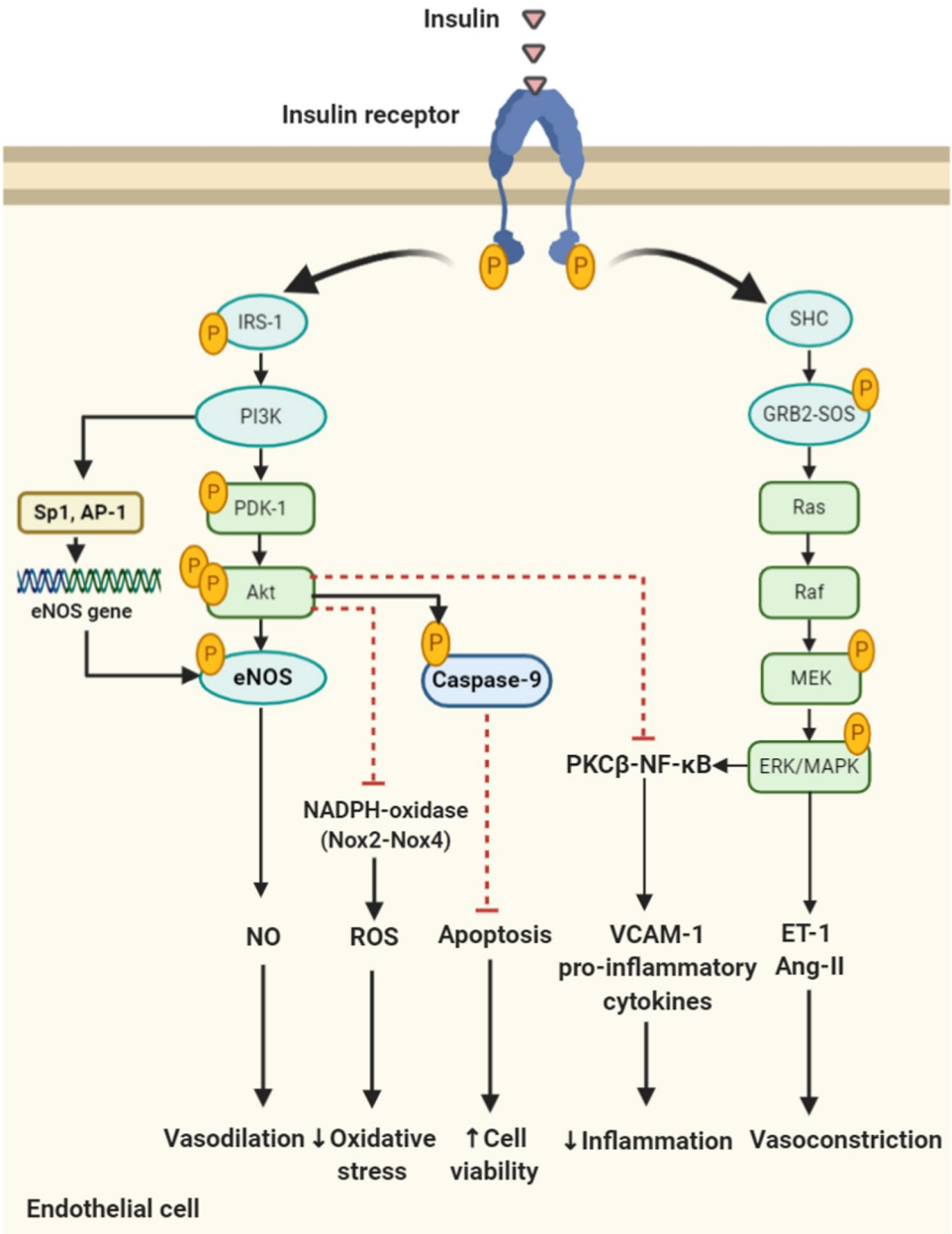

Fig. 2 Insulin signaling pathways in the endothelial cells. Insulin regulates endothelial cell homeostasis via two main signaling pathways: (1) phosphatidylinositol 3-kinase (PI3K)-protein kinase B (Akt) pathway and (2) Ras/Raf/mitogen-activated protein kinase (MAPK) pathway. IRS, insulin receptor substrate; PDK, phosphoinositide-dependent kinase; eNOS, endothelial nitric oxide (NO) synthase; ROS, reactive oxygen species; NADPH, the reduced form of nicotinamide adenine dinucleotide phosphate; PKC, protein kinase C; NF-κB, nuclear factor kappa-B; Ang-II, angiotensin II; ET-1, endothelin1; VCAM-1, vascular cell adhesion molecule-1; GRB2, growth factor receptor binding protein-2; SHC, Src (sarcoma) homology collagen-like-1; SOS, son of sevenless; Ras, rat sarcoma; Raf, rat fibrosarcoma; MAPK, MEK, mitogen-activated ERK kinase; ERK, extracellular-regulated kinase; MAPK, mitogen-activated protein kinase. Sp1, specificity protein 1; AP-1, activator protein 1

that endothelial insulin resistance in the PI3K-Akt pathway does not necessarily coincide with resistance in the other signaling pathway [22, 111] and a selective reduction in the ability of insulin to stimulate the PI3K-Akt pathway alongside with augmented insulin-induced MAPK pathway occurs in endothelial insulin resistance [69]. In support, both in vitro and in vivo models of endothelial insulin resistance (i.e., induced by high-fat diet and high-glucose concentrations, respectively) indicate decreased insulin-stimulated NO production with increased Ang-II concentrations [111]. In addition, in a high-glucose-induced model of endothelial insulin resistance, insulin cannot activate the PI3K-Akt-eNOS pathway. In contrast, the Ras/Raf/MAPK pathway responds to insulin through up-regulation of extracellular signal-regulated kinase-1/2 (ERK1/2), p38, and JNK (c-Jun N-terminal kinase) phosphorylation [22].

Impaired insulin-stimulated NO synthesis has been suggested to be the hallmark of endothelial insulin resistance [70, 89]. Following exposure to insulin, freshly isolated peripheral venous endothelial cells obtained from patients with T2DM displayed decreased Ser^{1177} eNOS phosphorylation (which increases eNOS activity) and increased Thr^{495} eNOS phosphorylation (which decreases eNOS activity) when compared to the cells obtained from healthy subjects [94].

UA and the endothelial cells

Uric acid enters into the endothelial cells via uric acid transporters (UAT) and is also synthesized from HPX within the cells. The major physiological NO-related function of UA in the endothelial cells seems to be increased NO availability.

Uric acid transporters in the endothelial cells

Uric acid transporters are classified as reabsorbing and excretory transporters; URAT1 (SLC22A12, solute carrier family 22, member 12) is a reabsorbing transporter, expressed in both the luminal and basolateral membranes of the renal proximal tubular cells [105]. The organic acid transporter 1 (OAT1/SLC22A6), OAT3 (SLC22A8), multidrug resistance-associated protein 4 [(MRP4); also called ATP-binding cassette transporter C4 (ABCC4)], ABCG2, and voltage-driven urate transporter 1 [(URATv1); also called glucose transporter 9 (GLUT9) or SLC2A9] are excretory transporters [105].

Expression of UAT has been widely reported in the kidneys and intestine, however, little is known about their distribution in other tissues. Among the known UAT, mRNA expressions of MCT9 (monocarboxylate transporter 9)/SLC16A9, URATv1, BCRP (breast cancer resistance protein; also called ABCG2), MRP4, and OAT10 have been documented in the human umbilical vein endothelial cells (HUVECs) [51, 58, 67, 93]. In addition, expression of URAT1 has also been reported in the HUVEC cells [58] and in the human vascular smooth muscle cells, where it enters UA into the cells [80]. However, others have reported that URAT1, OAT1, OAT3, NPT1 (sodium-dependent phosphate cotransporter), and NPT4 are not expressed in the HUVEC cells [67, 93]. To the best of our knowledge, there is no report to address the distribution of UAT in the endothelial cells of different vascular beds and this issue needs further investigation.

Among UAT in the endothelial cells, URATv1 (GLUT9) and MCT9 are involved in the entry of UA into the cells; in the presence of high UA concentrations, they act as influx transporters [67], and BCRP and MRP4 act as efflux UA transporters [51]. High UA concentration disturbs UA efflux in the HUVECs; UA (595 and 892 μmol L^{-1} vs. 300 μmol L^{-1}) decreases Akt phosphorylation and therefore inhibits intracellular BCRP translocation to the cell surface, resulting in intracellular accumulation of UA [51]. It has been suggested that hyperuricemia-induced activation of URATv1 (GLUT9) contributes more to UA-induced impaired NO production in the endothelial cells [67] (Fig. 3).

Uric acid synthesis in the endothelial cells

In addition to its entry into the endothelial cells via UATs [58, 67, 93], UA is also synthesized in the endothelial cells from its precursor, HPX, via XOR activity [76] (Fig. 3). Hypoxanthine enters into the endothelial cells via a nucleoside transporter, characterized as nitrobenzylthioinosine-insensitive equilibrative nucleoside transporter (NBMPR-insensitive transporter with a medium affinity for the purine, with a K_m 320 ± 10 μmol L^{-1}) [74]; HPX influx is saturable and Na^+-independent [74]. XOR is located both within the cytoplasm of the endothelial cells (with higher intensity in the perinuclear region) and on the outside surface of the endothelial cell membrane [84]. Circulating XO released from XO-rich tissues under pathophysiological conditions interacts with glycosaminoglycans on the surface of the endothelial cells and is endocytosed into intracellular compartments [38]. Extracellular UA negatively regulates XOR activity, as blockage of UA transporters (due to mutations or inhibitors, e.g., probenecid) promotes XOR activity [29, 81]. Moderate hypoxia and inflammatory cytokines induce XOR expression and activity in the endothelial cells [45, 78]; conversion of XOR to XO, in response to inflammatory conditions, leads to superoxide anion and hydrogen peroxide production, which negatively impact endothelial function by decreased NO bioavailability [4, 8].

Physiologic functions of UA in the endothelial cells

Although UA's physiologic functions in the endothelial cells have not been fully understood [66], some evidence indicates that normal concentrations of UA in the endothelial cells can preserve NO-dependent endothelial function by increasing NO availability. UA increases NO availability by increasing eNOS expression and NO production in HUVECs [37] and also by decreasing oxidative stress–induced NO inactivation [21, 37, 93]; the latter is probably done by preventing eNOS uncoupling, reacting with peroxynitrite, and preventing oxidant-induced inactivation of extracellular superoxide dismutase [30, 63].

In support of this notion that normal levels of UA help NO-dependent endothelial function, it has been reported that mutations in the URAT1, encoded by the SLC22A12 gene, are associated with lower flow-mediated dilation, which is an index of endothelium-dependent vasodilatation [93]. Extremely low levels of serum UA (< 47.5 μmol L^{-1}), observed in subjects who were homozygote and compound-heterozygous for URAT1 mutations, are related to decreased flow-mediated dilation (homozygous = 2.7 ± 2.3%, compound-heterozygous = 4.7 ± 2.8%, heterozygous = 9.3 ± 7.2%, and mutation free = 7.0 ± 2.3%). In contrast, nitrate-mediated dilation remained unchanged [93], indicating the normal

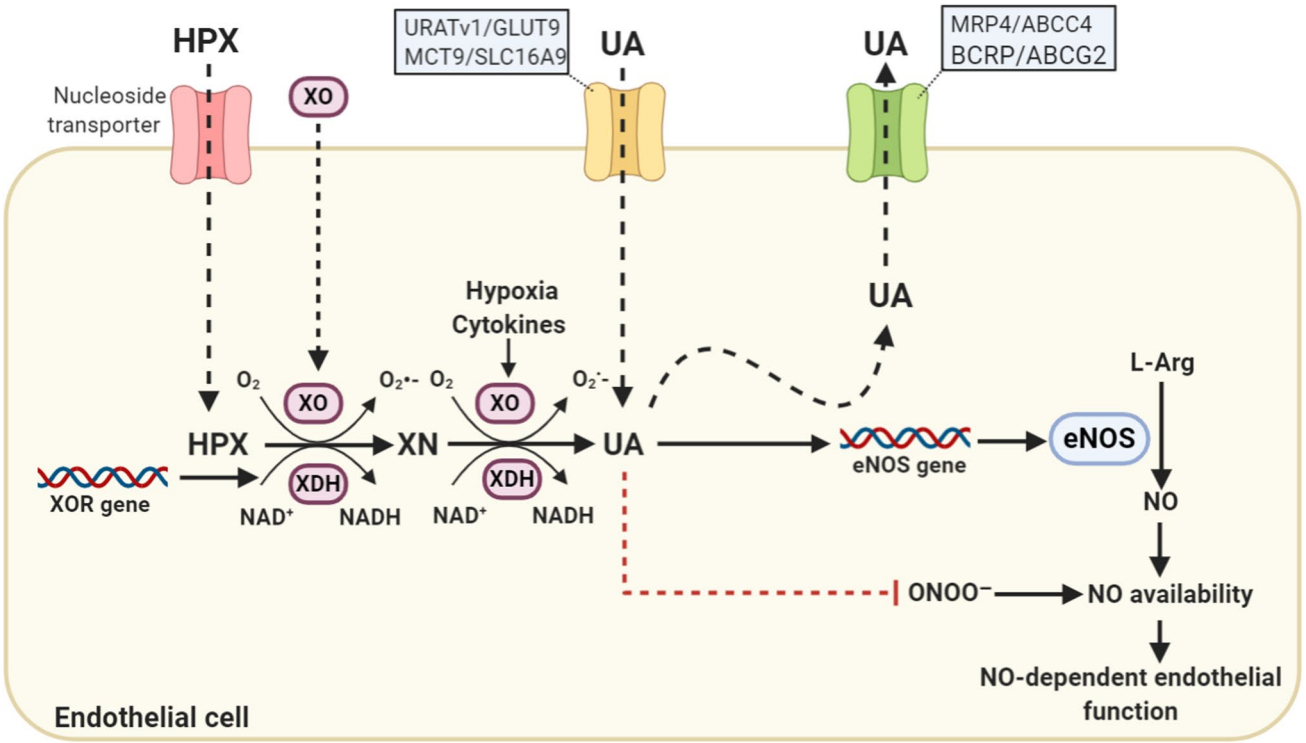

Fig. 3 Intracellular source of uric acid (UA) in the endothelial cell. Uric acid enters into the endothelial cells via uric acid transporters (UAT); UA is also synthesized in the endothelial cells from its precursor, hypoxanthine (HPX) by xanthine oxidoreductase (XOR), which exist in two interconvertible forms: dehydrogenase (XDH) and oxidase (XO) forms. eNOS, endothelial nitric oxide (NO) synthase; ONOO-, peroxynitrite; for details and abbreviations of UA transporters, see the "Uric acid transporters in the endothelial cells" section

response of vascular smooth muscle to NO. Furthermore, in type 1 diabetic patients with low-serum UA levels (264 vs. 322 µmol L^{-1} compared to controls), impaired acetylcholine-induced forearm blood flow response was restored following intravenous infusion of 1000 mg UA [101].

UA has an inhibitory feedback effect on XOR activity (*K*i UA for XOR = 70 µM, in the presence of 50 µM xanthine and 210 µM oxygen) and therefore regulates XOR-induced reactive oxygen species (ROS) production [81, 95]. It is therefore tempting to assume that in a similar way to plasma, normal levels of UA suppress oxidative stress in the endothelial cells; in human plasma, UA at concentrations of 150 and 300 µmol L^{-1} decreases the oxidation of xanthine to UA and formation of superoxide anion (37.5 ± 5.6 and 48.9 ± 6.1%, and 23.2 ± 1.9 and 32.0 ± 2.3%, respectively) [95]. Indeed, moderate and severe short-term hypouricemia (plasma UA ~ 126 and 18 µmol L^{-1}), induced by administration of febuxostat per se and febuxostat + rasburicase, increases lipid peroxidation in healthy humans [21].

To sum up, at concentrations near to normal human plasma levels (< 300 µmol L^{-1}), UA seems to be essential for NO-dependent endothelial function.

Uric acid and endothelial insulin resistance

Both clinical and experimental studies indicate that exposure of the endothelial cells to high UA concentrations may cause endothelial dysfunction. In clinical studies, endothelium-dependent vasodilation was inversely related to serum UA levels [44, 117]; for each 59.48 µmol L^{-1} increase in serum UA concentration, there was a 41% higher risk of endothelial dysfunction [117]. The reactive hyperemia index, considered an index of endothelial function of the microvasculature, was negatively associated with serum UA concentrations [75]. Flow-mediated dilation but not nitrate-mediated dilation was significantly impaired in subjects with serum UA levels of 488 ± 11.9 µmol L^{-1} compared with those who had UA levels of 357 ± 11.9 µmol L^{-1}; similarly, acetylcholine-induced but not nitrate-induced forearm blood flow was impaired in subjects with UA levels greater than 327 µmol L^{-1} [117]. Such data may imply that a selective impairment of the endothelial NO-dependent vasodilation in the absence of overt structural vascular disease occurs in hyperuricemic subjects [44].

Table 1 Mechanisms by which high uric acid concentrations cause endothelial dysfunction

Study	UA concentration (μmol L^{-1})	Effects	Underlying mechanisms
Kang et al. [43]	535	↑ mRNA and protein expression of C-reactive protein	Activation of p38 and ERK44/42 MAPK signaling pathway
Yu et al. [108]	357, 535, and 714	↑ Cell senescence, ↓ cell viability	↑ Intracellular ROS and activation of the renin-angiotensin system, and ↑ Ang-II levels
Sánchez-Lozada et al. [85]	714	↑ Intracellular ROS generation (by 2.5-fold)	Activation of NADPH oxidase
Liang et al. [57]	119, 357, 714, and 1070	↑ mRNA expression of MCP-1, ICAM-1, VCAM-1, and IL-8 at a dose of 714 μmol L^{-1} Induction of cell apoptosis at a dose of 1070 μmol L^{-1}	Activation of NF-κB signaling pathway
Xie et al. [104]	476	↑ mRNA expression of IL-6, ICAM-1, TNF-α, and MCP-1 ↑ Intracellular ROS (by ~ 3.3-fold)	↑ Expression of NF-κB p65 ↑ Notch-1 expression and activation of NOTCH signaling ↑ Expression of Hes1, Hes5, Hey1
Li et al. [56]	119, 357, 714, and 1070	↑ Cell apoptosis, dose-dependently	↑ Intracellular ROS concentration and ER stress
Liu et al. [58]	197, 595, and 892	↑ mRNA levels of MCP-1, ICAM-1, VCAM-1, and IL-1β, dose-dependently ↓ Cell viability, dose-dependently, reached up to 60% (at a dose of 892 and time of 96 h)	↑ Phosphorylation of NF-κB and ERK ↑ Nuclear translocation of NF-κB p65
Cai et al. [17]	1190	↑ TNF-*α*, IL-6, ICAM-1, VCAM-1	↑ Expression of HMGB1 and its interaction with RAGE Activation of NF-κB signaling pathway
Zhen et al. [114]	197, 595, and 892	↑ IL-6, IL-8 and TNF-α	Activation of NF-κB signaling pathway
Komori et al. [51]	197, 595, and 892	↓ Cell viability by 20% at doses of 595 and 892 μmol L^{-1} (time of 12 h) not 197 μmol L^{-1}	↑ Intracellular ROS concentration
Otani et al. [75]	1000	↓ Cell viability by 40% at hypoxic condition	Probably via increased intracellular ROS production
Ko et al. [49]	535	↑ Intracellular ROS generation (by fourfold)	Activation of membranous and mitochondrial NADPH oxidase
Yang et al. [106]	50, 100, and 300 (MAECs)	↑ Cell apoptosis, in a dose- and time-dependent manner	↓ miR-214 mRNA expression ↑ Bax, caspase-3, and COX-2 expression ↑ PGE2 levels

All experiments were done on HUVECs, unless stated otherwise

MAECs, mouse aorta endothelial cells; *Bax*, Bcl-2 (B cell lymphoma protein2) associated X-protein; *COX-2*, cyclooxygenase-2; *Hes*, hairy and enhancer of split related protein1; *Hey*, Hes with YRPW motif; *NADPH*, reduced form of nicotinamide adenine dinucleotide phosphate; *Notch*, *Drosophila*, notched wing; *PGE2*, prostaglandin E2; *RAGE*, receptor for advanced glycation end-products; *ROS*, reactive oxygen species; *NF-κB*, nuclear factor kappa-B; *Ang-II*, angiotensin II; *HMGB*, high-mobility group box protein-1; *ICAM-1*, intercellular adhesion molecule-1; *VCAM-1*, vascular cell adhesion molecule-1; *ER*, endoplasmic reticulum; *MCP-1*, monocyte chemoattractant protein-1; *MAPK*, mitogen-activated protein kinase; *ERK*, extracellular signal-regulated kinase

Table 1 summarizes the underlying mechanisms (i.e., inducing cell apoptosis, increasing oxidative stress, and inflammation) by which high UA levels induce endothelial dysfunction. In brief, high UA concentrations (300–900 μmol L^{-1}), occurring by either induction of intracellular XO or hyperuricemia, result in endothelial dysfunction and higher concentrations of UA (~ 1070–1190 μmol L^{-1}) cause endothelial cell death.

Among the underlying mechanisms explaining endothelial dysfunction induced by high UA concentrations, impaired insulin-stimulated PI3K-Akt-eNOS pathway, and decreased endothelial NO availability, resulting in the development of endothelial insulin resistance, may be the most important ones. This notion is supported by the in vivo evidence indicating hyperuricemia (induced by the uricase inhibitor, allantoxanamide, in rats) disrupts the

insulin-stimulated but not acetylcholine-stimulated eNOS phosphorylation in endothelium-intact aortic rings and NO-dependent vasodilation [20]. In the following sections, we focus on the UA-induced mechanisms targeting insulin signaling and NO bioavailability in the endothelial cells.

Underlying mechanisms of UA-induced insulin resistance

A high UA concentration interferes with insulin signaling in the endothelial cells at the receptor and post-receptor levels; at the post-receptor level, both proximal (IRS and PI3K-Akt components) and distal (eNOS-NO system) steps within the insulin signaling pathway are affected by UA (Fig. 4). Other mechanisms summarized in Table 1, including high UA-induced oxidative stress, inflammation, and cell apoptosis, may also contribute to the development of insulin resistance in the endothelial cells.

Insulin receptor level

Uric acid increases recruitment and binding of ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), a plasma membrane enzyme that regulates nucleotide metabolism, to α-subunit of the insulin receptor in HUVECs; this binding impairs tyrosine-kinase activity and autophosphorylation of the β-subunit, which results in the inhibition of insulin signaling [1]. Through this inhibition, the Ser^{473} phosphorylation of Akt and the Ser^{1177} phosphorylation of eNOS is decreased in the endothelial cells [97]. Inhibition of UA entry into the cell (using probenecid at a dose of 1 mmol L^{-1} for 30 min) restored these effects [97]. In addition, exposing HUVECs to UA at a dose of 200 µmol L^{-1} decreases tyrosine phosphorylation of the β-subunit in the

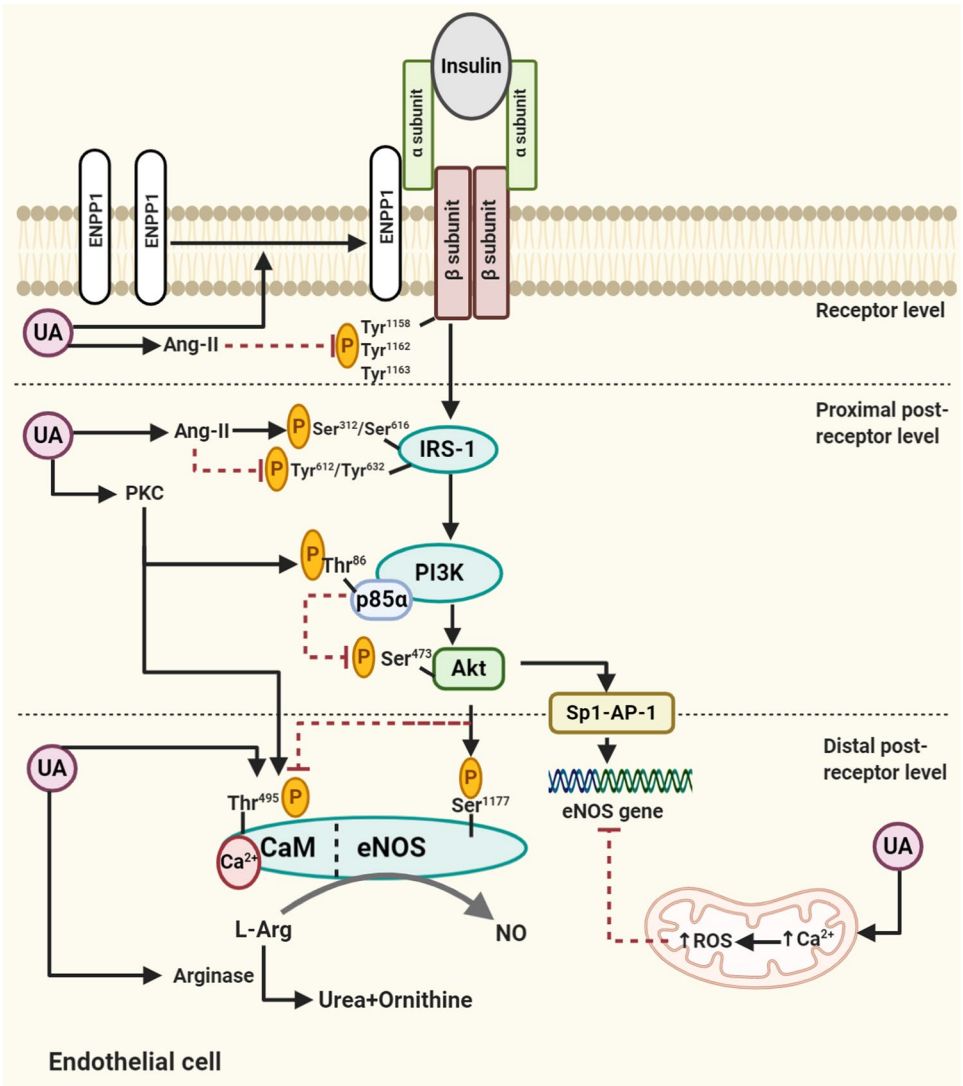

Fig. 4 Interfering of high uric acid (UA) levels with insulin signaling at the receptor and post-receptor levels in the endothelial cells; at the post-receptor level, both proximal (IRS and PI3K-Akt components) and distal (eNOS-NO system) steps within the insulin signaling pathway are affected by UA. ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; Ang-II, angiotensin II; IRS, insulin receptor substrate; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; Sp1, specificity protein 1; AP-1, activator protein 1; eNOS, endothelial nitric oxide (NO) synthase; ROS, reactive oxygen species; CaM, calmodulin; PKC, protein kinase C

insulin receptor and decreases insulin-induced PI3K/Akt/eNOS-mediated NO production [20].

High UA concentrations may also interfere with insulin signaling at the receptor level by increasing Ang-II levels in the endothelial cells. This notion is supported by evidence indicating that UA is a potent activator of the renin-angiotensin system in endothelial cells [107, 108]. At a dose of 535 μmol L^{-1}, intracellular concentrations of Ang-II increased by about threefold in HUVECs over a 24-h period; this increase was due to up-regulation of the pro-renin receptor [107], increased mRNA expressions of angiotensin-converting enzyme, and angiotensinogen [108]. Ang-II inhibits insulin-stimulated tyrosine phosphorylation of the insulin receptor at its β-subunit [7]. Exposing HUVECs to Ang-II at a dose of 200 nM had shown to decrease insulin-stimulated Tyr phosphorylation (Tyr^{1158}/Tyr^{1162}/Tyr^{1163}) of the receptor by 65% [7].

To sum up, these data indicate that in the endothelial cells, high concentrations of UA can directly interfere with the insulin signaling pathway at the receptor level and can contribute to the development of endothelial insulin resistance.

Post insulin receptor level

Proximal signaling pathway (IRS and PI3K-Akt components)

Exposing HUVECs to UA at a dose of 200 μmol L^{-1} decreases the percent of p-IRS-1/IRS-1 [20]. It has been shown that UA can cause oxidase stress–induced activation of protein kinase C (PKC) in HUVECs [56]. PKC activation inhibits the PI3K-Akt signaling pathway of insulin in bovine aortic endothelial cells; this effect is partly due to inhibition of insulin-induced Tyr phosphorylation of IRS2 [62] but not IRS1, which is functionally more important in the endothelial cells [62]. PKC phosphorylates Thr^{86} on p85α subunit of PI3K and therefore decreases binding of p85α to IRS1, resulting in a decrease in the insulin-induced activation of PI3K activity [62]. UA also interferes with the insulin signaling pathway at the IRS-1 level in the endothelial cells by increasing intracellular levels of Ang-II [108], which increases phosphorylation of Ser^{312} and Ser^{616} (as negative regulatory sites) at IRS-1, leading to decreased ability of IRS-1 to be phosphorylated on Tyr^{612} and Tyr^{632} (i.e., essential sites for engaging the p85 subunit of PI3K) [7]. Quantitatively, Ang-II (at a dose of 100 nM) reduces insulin-stimulated binding of IRS-1 to the p85 subunit of PI3K by about 30%, resulting in decreased insulin-induced Akt-Ser^{473} and eNOS-Ser^{1177} phosphorylation in HUVECs by 60% and 45%, respectively [7]. This effect is mediated by increasing JNK and ERK 1/2 activity [7]. Ang-II also induces Ser/Thr phosphorylation of p85α/β subunit of PI3K, through the activation and translocation of PKCα/β/δ, from the cytosol to the membrane. The predominant effect of Ang-II is on the PKCα isoform, which effectively phosphorylates Thr^{86} of p85/ PI3K [62].

In HUVECs, UA (50–200 μmol L^{-1}) inhibits insulin-stimulated eNOS phosphorylation at Ser^{1177} (IC_{50} of 51.0 μmol L^{-1}) by inhibiting insulin-stimulated Akt phosphorylation (IC50 = 21.97 μmol L^{-1}), as transfection of the cells with p110, a class I PI3K catalytic subunit, restored the inhibitory effects of UA on Akt and eNOS phosphorylation [20]. UA can also trigger disruption of the PI3K-Akt pathway by increasing PKC phosphorylation and activity [56]. Activated PKC phosphorylates Thr^{86} of p85 subunit of PI3K, resulting in decreased p-Akt at Ser^{473} and p-eNOS at Ser^{1177} [62]. At a dose of 714 μmol L^{-1}, UA increases intracellular p-PKC/PKC ratio, resulting in phosphorylation of eNOS at Thr^{495} and decreased production of NO [56].

High UA concentrations are also able to counteract PI3K-Akt activity through the induction of oxidative stress and inflammation. UA (at concentrations of 357 and 535 μmol L^{-1}) increases intracellular levels of C-reactive protein (by 7.2-fold at 1 h, and 6.5-fold at 3 h) through activation of p38 and ERK44/42 MAPK signaling pathways, leading to decreased NO production in HUVECs by 80% [43]. High-C-reactive protein levels in the endothelial cell blunt insulin-induced Akt phosphorylation, via the immunoreceptor tyrosine–based inhibition motif of FcγRIIB and SHIP-1 (Src homology 2 domain-containing inositol 5′-phosphatase 1) [96].

Distal signaling pathway (eNOS-NO system)

High UA concentrations can impair the eNOS-NO system by decreasing eNOS expression, reducing eNOS activity, and by direct inactivation of NO. UA-induced decrease in eNOS activity is achieved in several ways: (1) diminishing the insulin-induced Ser^{1177} phosphorylation of eNOS, (2) reducing insulin-induced Thr^{495} dephosphorylation of eNOS, (3) decreasing interaction between eNOS and calmodulin, and (4) reducing the availability of substrate for eNOS via (a) decreased intracellular *L*-arginine concentrations and (b) increased arginase activity.

Incubation of HUVECs with a high dose of UA (1190 μmol L^{-1}) decreases eNOS expression and the amount of NO released by HUVECs (by threefold, from ~ 30 to 10 μmol L^{-1}) [28]. Incubation of HUVECs with high UA concentrations (≥ 600 μmol L^{-1}) switches the direction of mitochondrial Na^+/Ca^{2+} exchanger, resulting in an influx of calcium into the mitochondria, causing an overload in mitochondrial calcium [37]. Elevated mitochondrial calcium levels upregulate mitochondrial ROS production and therefore increased intracellular ROS, which decreases eNOS protein expression and NO synthesis [37]. Blockage of mitochondrial Na^+/Ca^{2+} exchanger inhibits UA-induced reduction in

eNOS protein expression and NO production [37]. These effects are against the actions of insulin, which stimulates eNOS gene expression and transcription via PI3K-induced binding of transcriptional factors, Sp1 and AP-1, to the eNOS gene [28].

In HUVECs, UA at concentrations ranged 50–200 μmol L^{-1} had neither an effect on the expression nor the phosphorylation of Ser^{1177} within eNOS, meanwhile insulin-stimulated eNOS phosphorylation was blunted by the same doses (with an IC_{50} of 51.0 μmol L^{-1}) [20]. This data indicates that the effects of UA on eNOS expression/phosphorylation in the endothelial cells, at least in part, are mediated by the insulin signaling pathway. Indeed, UA causes ROS-induced PKC activation, which increases eNOS phosphorylation at Thr^{495} and decreases eNOS activity by decreasing calmodulin binding to eNOS [56]. On the other hand, insulin through the PI3K-Akt pathway dephosphorylates eNOS at Thr^{495} and increases eNOS activity [6]. UA (at a dose of 714 μmol L^{-1} for 24 h) can also decrease eNOS activity and NO production by reducing the interaction of eNOS with calmodulin (as an eNOS activator) [77].

UA (at concentrations of 297 and 446 μmol L^{-1}) decreases stimulated NO production in pig pulmonary arterial endothelial cells by increasing arginase activity; this effect is due to an increase in affinity of arginase for *L*-arginine (K_m = 1.1 mmol L^{-1} vs. 0.6 mmol L^{-1} in the presence of 446 μmol L^{-1} UA) without neither affecting V_{max} of the enzyme not changing the gene expression of arginase II (as predominant endothelial isoform of arginase) [113]. Furthermore, UA suppresses eNOS activity via decreasing cellular *L*-arginine uptake; this effect is not mediated through manipulating the *L*-arginine transporter (cationic amino acid transporter-1) content or affecting the post-translational modification by PKCa [90].

Uric acid can also react directly with NO (in both human plasma and aortic endothelial cell lysates) through a rapid, irreversible reaction leading to the formation of 6-aminouracil and depletion of NO [30].

Conclusion and future perspective

Uric acid can act as a Janus-faced molecule in the endothelial cells because of its highly contrasting features at varying concentrations. At low concentration, UA is essential for eNOS expression, NO synthesis and availability, and NO-dependent endothelial functions. Meanwhile, at high concentrations, UA can cause endothelial dysfunction. This is so because high-intracellular UA concentrations decrease the responsiveness of the endothelial cells to insulin, resulting in the development of endothelial insulin resistance. Intracellular high UA targets the IRS-PI3K-Akt-eNOS pathway at different steps, including the insulin receptor binding capacity to its downstream signaling events, finally translating to decreased eNOS expression and activity. As a caution, it should be noted that most data that associate hyperuricemia and endothelial insulin resistance are from in vitro studies and needs to be verified through in vivo models. In addition to interfering with insulin signaling pathways and NO synthesis, other unknown mechanisms may also be involved in the development of hyperuricemia-induced endothelial insulin resistance.

Current data provides not only new insights into the complex mechanisms of endothelial insulin resistance in relation to hyperuricemia but also addresses potential therapeutic targets. Since hyperuricemia-induced endothelial insulin resistance is a risk factor for developing systemic insulin resistance, T2DM, and cardiovascular diseases, treating asymptomatic patients with hyperuricemia and maintaining their serum UA within the normal range could potentially protect against cardiometabolic disorders. However, well-designed clinical trials are needed to confirm this assumption.

Author contribution Idea and conceptualization: Asghar Ghasemi and Zahra Bahadoran

Writing, reviewing, and editing: Zahra Bahadoran, Asghar Ghasemi, Khosrow Kashfi, Parvin Mirmiran

Literature research: Zahra Bahadoran, Asghar Ghasemi, Khosrow Kashfi, Parvin Mirmiran

Figure conceptualization and design: Zahra Bahadoran and Asghar Ghasemi

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Declarations

Conflict of interest The authors declare no competing interests.

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